Antineoplastic Therapy and Immunotherapy Course

UPMC Hillman Cancer Center

UPMC
LIFE CHANGING MEDICINE

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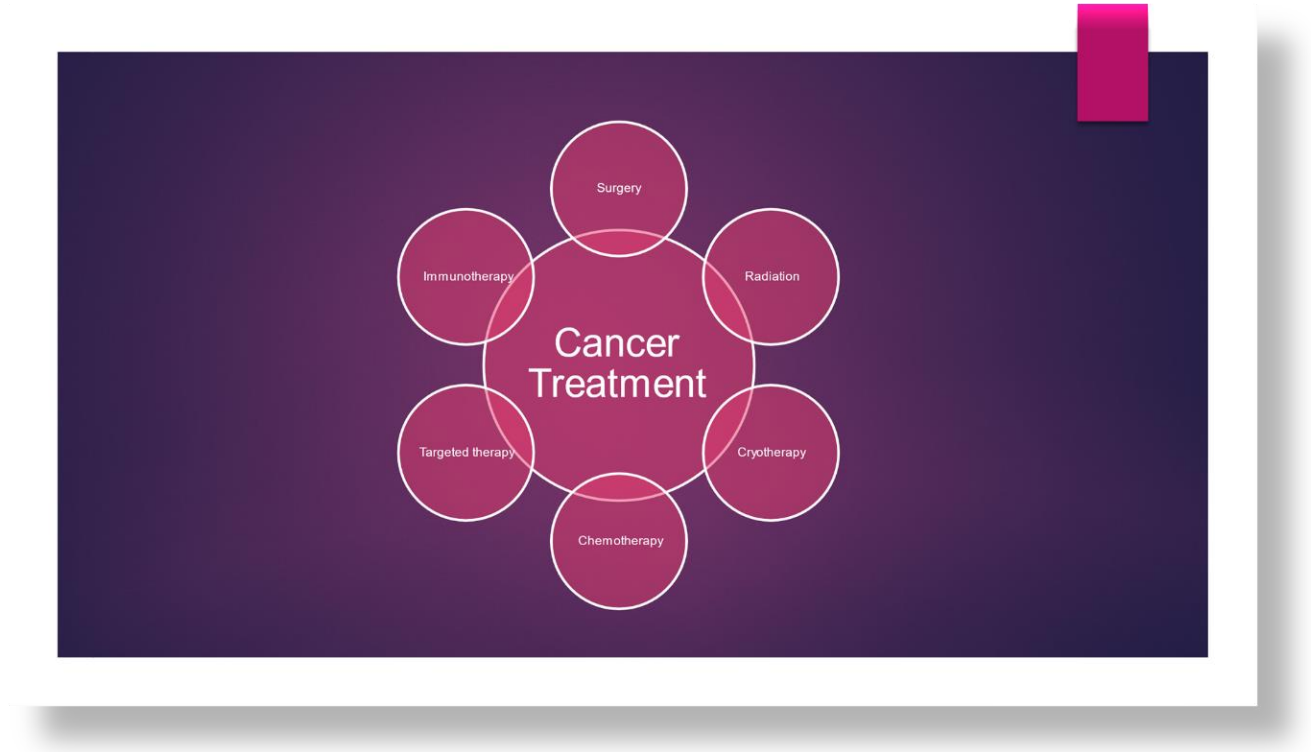
Adoptive Cellular Therapy and BiTEs



Immunotherapy

- Strong relationship between immune system evasion and cancer cell proliferation
- Aim to modulate the patient's immune system against malignant cells
- Rationale
    - Reduced toxicity, increased specificity, and improved outcomes compared to traditional chemotherapy

Immunotherapies	
Cancer Vaccines	▪ Gp100:209-217(210M) peptide vaccine ▪ sipuleucel-T
Adoptive Cellular Immunotherapy	▪ Chimeric antigen receptor (CAR)-T cells ▪ Tumor infiltrating lymphocytes (TIL)
Immune Checkpoint Blockade	▪ Anti-CTLA-4 antibody ▪ Anti-PD1 antibody ▪ Anti-PD-L1 antibody
Oncolytic Viruses	▪ talimogene laherparepvec (T-VEC)
Bispecific T-cell engagers (BiTE)	▪ blinatumomab ▪ tebentafusp ▪ teclistamab ▪ talquetamab ▪ epcoritamab ▪ elranatamab ▪ glofitamab

Adoptive Cellular Immunotherapy

- Utilizes natural anti-tumor properties of lymphocytes
- Autologous lymphocyte re-infusion following lymphodepleting chemotherapy
- Shown to have activity in both hematologic and oncologic malignancies

CAR T Therapy

- Immunotherapy comprised of genetically altered T cells that can recognize malignant cells
- T cells are derived from the blood and must be genetically altered to elicit their effect
- Comprised of two primary components
    - Chimeric antigen receptor (CAR)
    - Patient-specific T-lymphocytes

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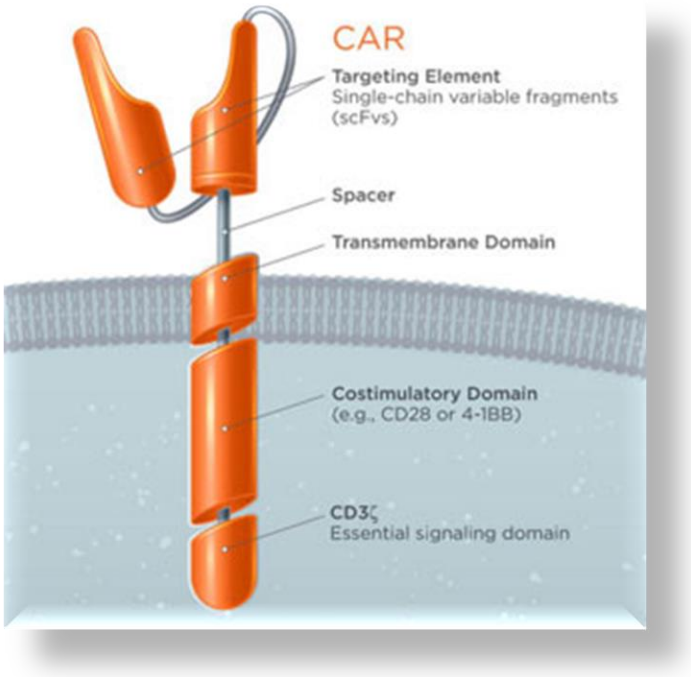
Chimeric Antigen Receptor: CAR

- Receptor comprised of
  - Specific binding domains from tumor targeting antibody
  - T cell signaling domains
- Allows targeted antibody redirected T cell activation

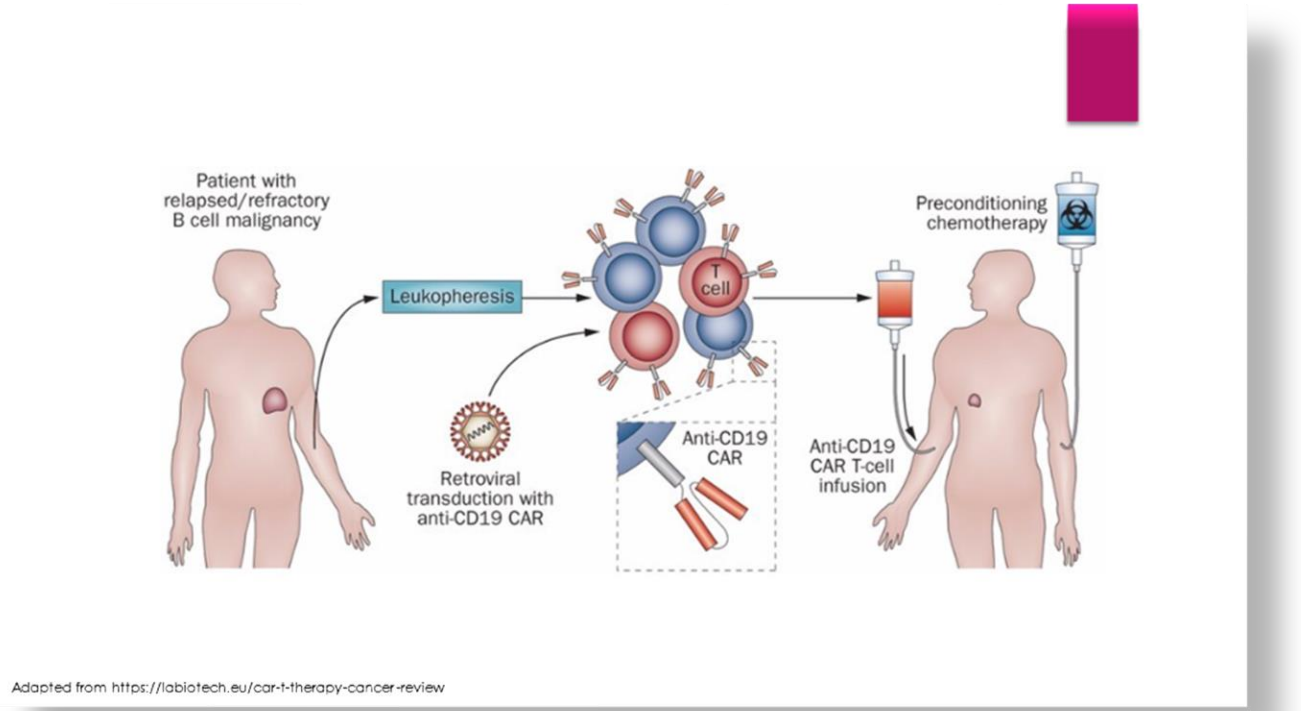


CAR T-Cells

- Once the CAR has been created, T cells can be engineered to express CAR by gene transfer
  - Utilizes retroviral vectors
- CAR T-Cell Mechanism of Action
  - Recognize their target antigen
  - Result in T cell activation towards specific target antigen (located on malignant cells, e.g. CD19)

CAR T Manufacturing Process

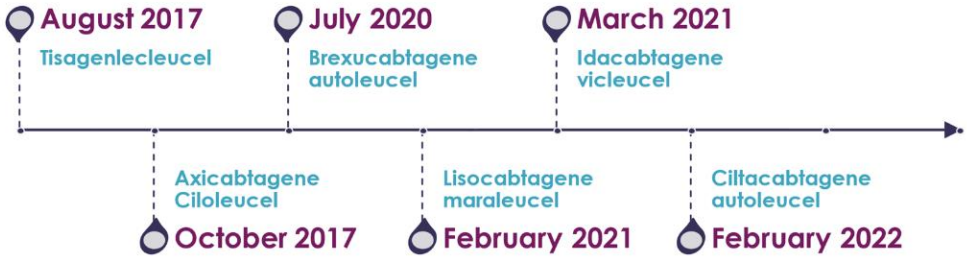
- Patient deemed eligible for CAR T therapy
- T-cells are extracted from the patient's blood
- T-cells engineered to express CAR and replicated
- Patient receives T-cell depleting chemotherapy (LDC)
- CAR T-cells reinfused into patient



CAR T Overview

- Cell utilized: T-lymphocytes
- Patient-specific
- Genetic alteration
- Conditioning therapy/lymphodepletion (LDC)
  - Fludarabine/cyclophosphamide (Flu/Cy)
- Timeframe
  - Three to four weeks
- FDA approved indications
- Relapsed / refractory large B-cell lymphoma
- Relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)
- Relapsed/refractory multiple myeloma

FDA-Approved CAR-T Products



Available CAR-T Indications

	tisagenlecleucel	axicabtagene ciloleucel	lisocabtagene maraleucel	idecabtagene vicleucel	Brexucabtagene autoleucel	Ciltacabtagene autoleucel
MOA	Anti-CD19	Anti-CD19	Anti-CD19	Anti-BCMA	Anti-CD19	Anti-BCMA
FDA-approved indication(s)	1. B-cell ALL in children and young adults 2. R/R lymphoma, including DLBCL and follicular	R/R lymphoma, including large B-cell and follicular	R/R aggressive B-cell non-Hodgkin lymphoma R/R CLL/SLL	R/R multiple myeloma	1. R/R mantle cell lymphoma 2. R/R B-cell ALL in adults	R/R multiple myeloma

CAR T: Warnings and Common Adverse Effects
Boxed Warnings: All products

- Cytokine release syndrome (CRS)
- Neurotoxicity
    - Including immune effector cell–associated neurotoxicity syndrome (ICANS)
- REMS programs
- Incidence of toxicities vary amongst products
- Most product labels recommend inpatient administration
- Other unique toxicities are product specific
- Infection
- Renal/hepatic impairment
- Cytopenia

CAR T Administration Pearls

- Must be REMS certified to prescribe, dispense, or administer product
- Product must be thawed prior to infusion
    - Tisagenlecleucel: Stable for 30 minutes at room temperature
    - Axi-cel: Stable for 3 hours at room temperature
    - Liso-cel: Administer within 2 hours of initiation of thawing
    - Ide-cel: Infuse within 1 hour of initiation of thawing
    - Brexucabtagene autoleucel: Stable for 3 hours at room temperature
    - Ciltacabtagene autoleucel: Administer within 2.5 hours of completion of thawing

- Premedicate 30-60 minutes prior to infusion
    - Acetaminophen
    - Diphenhydramine (or other H1-antihistamine)
    - Do not use corticosteroids unless life-threatening adverse reaction
    - Follow universal precautions and local biosafety guidelines for handling and disposal

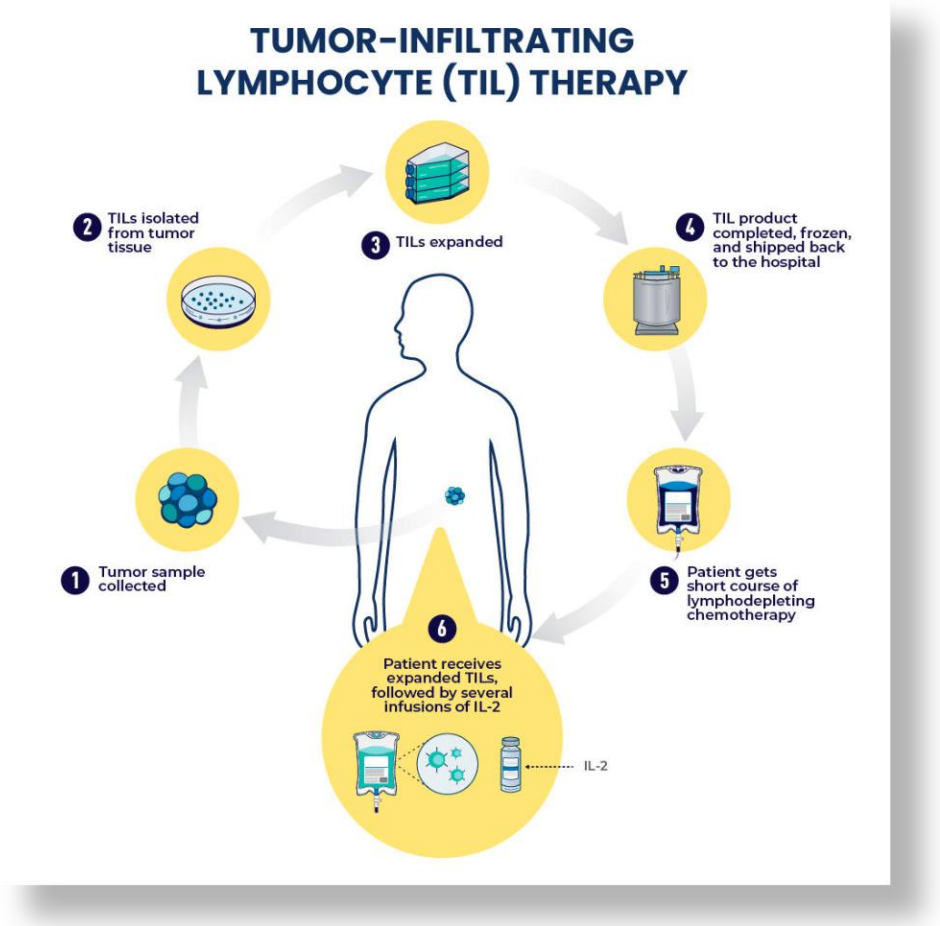
CAR T Treatment Costs

- Tisagenlecleucel (Kymriah®): $475,000
- Axicabtagene ciloleucel (Yescarta®): $373,000
- Lisocabtagene maraleucel (Breyanzi®): $428,400
- Idecabtagene vicleucel (Abecma®): $419,500
- Brexucabtagene autoleucel (Tecartus®): $373,000
- Ciltacabtagene autoleucel (Carvykti®): $490,000
- Stem cell transplant: Variable
    - Autologous: Median ~$100,000
    - Allogeneic: Median ~$200,000

TIL Therapy

- Immunotherapy comprised of T-cells that are derived from the tumor
- T-cells are not engineered before being expanded
- During manufacturing, IL2 is added to help expansion into billions of cells

- To enhance the TILs ability to attack the cancer and their overall potency
    - Patients receive lymphodepletion with fludarabine/cyclophosphamide
    - After TIL infusion, patients receive IL-2



FDA-Approved TIL

- Lifileucel
- Indication: Unresectable or metastatic melanoma in adults after PD-1 monoclonal antibody and BRAF inhibitor with or without a MEK inhibitor (if BRAF V600 mutated)
- Cost: $515,000

TIL Administration

- Premedicate 30-60 minutes prior to infusion
    - Acetaminophen
    - Diphenhydramine or other H1-antihistamine
    - Do not use corticosteroids unless life-threatening adverse reaction
- Follow universal precautions and local biosafety guidelines for handling and disposal
- Must be administered within 3 hours of thawing

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- Review package insert to see details of administration

Common Adverse Effects of TIL

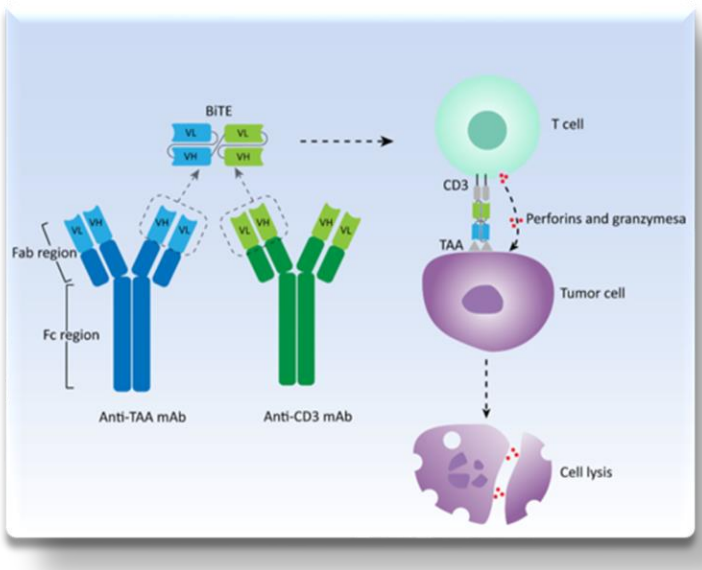
- Black box warning: Treatment related mortality, prolonged severe cytopenia, severe infection, cardiopulmonary, and renal impairment
- Capillary leak syndrome: Edema, hypotension, weight gain, tachycardia, dyspnea, hypoxia
- Skin rash/pruritis
- Cytopenias
- Encephalopathy
- Acute kidney injury
- Fever

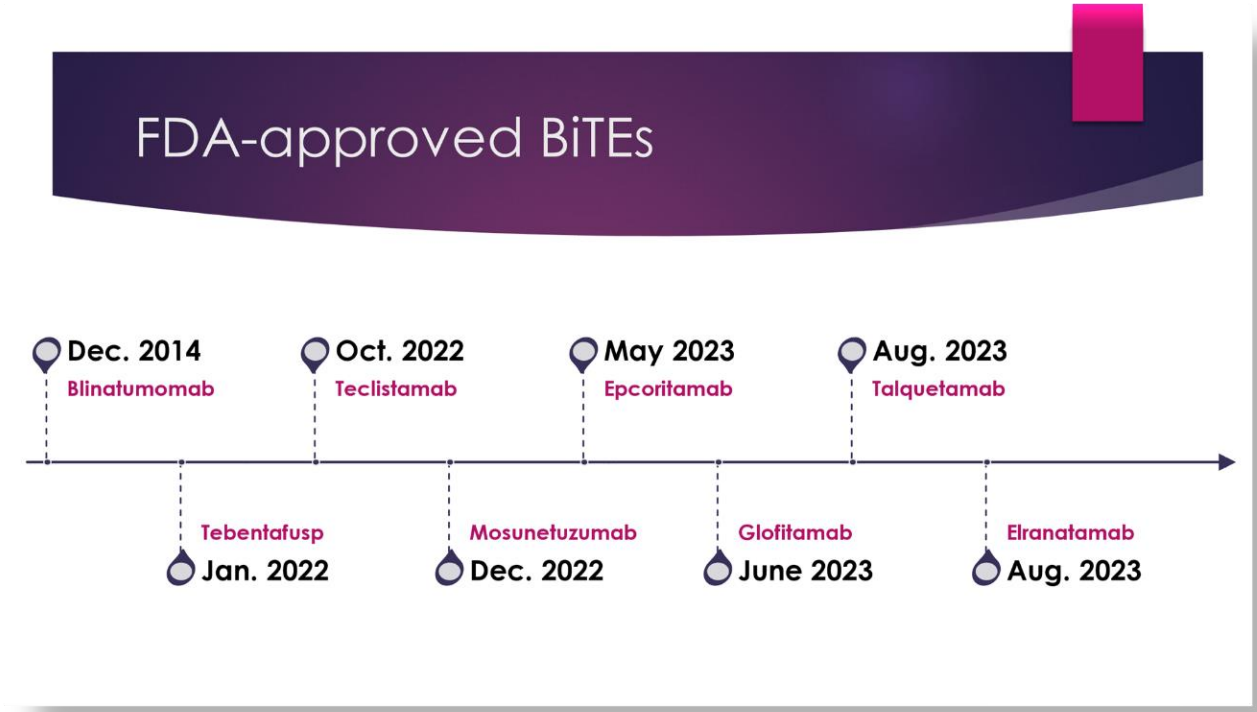
Ongoing TIL Trials

- Uveal melanoma
- Cholangiocarcinoma
- Cervical cancer
- Colon cancer
- Non-small cell lung cancer
- Breast cancer

BiTEs: Bridging The Gap Between T-cells and Cancer Cell

- Class of targeted immunotherapy designed to harness the body's own immune system to fight cancer
  - Relies on endogenous T-cells for efficacy
- Construct: Bispecific antibodies with two antigen binding domains that are connected by a flexible peptide linker
  - One side binds to a tumor-associated antigen (TAA) on the surface of a cancer cell, while the other binds to a T-cell receptor (usually via the CD3 co-receptor)[1,2]
- Mechanism of Action
  - BiTE creates a link between the T-cell and cancer cell
  - Linked T-cell is activated and releases cytotoxic enzymes and cytokines (immune response)
  - Targeted lysis of cancer cell while sparing nearby healthy cells
- Elicits a T-cell response that is not affected by cancer cell escape mechanisms, potentially targeting cancers that are "invisible" to the immune system



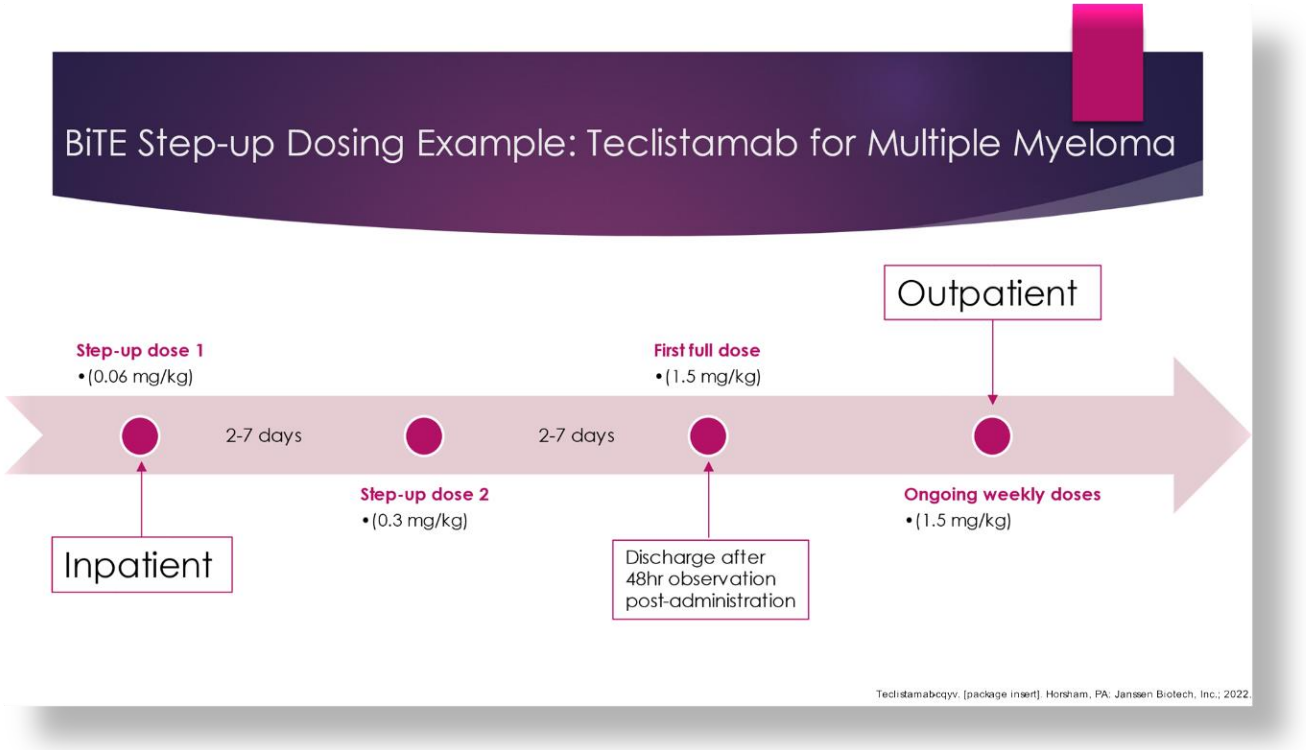


Why BiTEs?

- Ready-to-Use Availability
  - Come in formulations that allow for immediate use – unlike other T-cell therapies (e.g., CAR-T)

- Engineered Targeting
  - Target antigens expressed on leukemia, lymphoma, and myeloma cells
  - Also used in uveal melanoma
- Engagement with Cancer Cells
  - Given via IV or SQ route and acts on circulating cancer cells in blood and lymphatic system
- Used in Refractory Disease:
  - Offers an effective treatment option for patients who have relapsed or are refractory to traditional treatments
- Deep Remission
  - Capable of inducing a sustained remission

BiTE Step-up Dosing Example: Teclistamab for Multiple Myeloma



The First BiTE: Blinatumomab

- FDA approved in December 2014 for relapsed or refractory Ph(-) B-cell acute lymphoblastic leukemia (B-ALL) based on the TOWER trial
  - Improved median overall survival over physician's choice of salvage chemotherapy [7.7 months vs 4 months (p=0.01)] [1]
- Name derived from "**B-lin**eage-specific **a**nti**tum**or m**o**use **m**onoclonal **a**nti**b**ody"
- Indications (Both adults & pediatrics)
  - CD19+ B-cell ALL in first or second complete remission with MRD greater than or equal to 0.1%

- Relapsed or refractory CD19+ B-cell ALL
- Independent of Philadelphia chromosome status

- Target
  - CD19 on B-cells
  - CD3 on T-cells

Blinatumomab: Not So Simple

	MRD+ B-ALL		**R/R B-ALL**	
Dosing	≥45 kg	<45 kg	≥45 kg	<45 kg
	28 mcg/day CIVI	15 mcg/m^2/day (max 28 mcg/day)	Cycle 1: - 9 mcg/day x7 days - 28 mcg/day x21 days Cycle 2 and on: - 28 mcg/day	Cycle 1: - 5 mcg/m^2/day x7 days (max 9 mcg/day) - 15 mcg/m^2/day x21 days (max 28 mcg/day) Cycle 2 and on: - 15 mcg/m^2/day (max 28 mcg/day)
	28 days on (CIVI), 14 days off		- Induction/consolidation: 28 days on (CIVI), 14 days off - Continued therapy: 28 days on (CIVI), 56 off	
Duration	One induction cycle (42 days) Up to 3 consolidation cycles		- Up to 2 cycles of induction (42 days) - 3 cycles for consolidation (42 days) - Up to 4 additional cycles of continued therapy (84 days)	
Setting	**Hospitalization recommended**: - First 3 days of cycle 1 - First 2 days of cycle 2 - Any interruption of ≥ 4 hours		Hospitalization recommended: - First 9 days of cycle 1 - First 2 days of cycle 2	
Premedication	- Dexamethasone		- Dexamethasone	

Other Available BiTEs

Lymphoma

- Mosunetuzumab
- Glofitamab
- Epcoritamab

Multiple Myeloma

- Teclistamab

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- Talquetamab
- Elranatamab

Uveal Melanoma
- Tebentafusp

Bites: Lymphoma

Agent	Target	FDA Indication	Considerations
Mosuntezumab	Targets CD20 on B-cells and CD3 on T-cells	R/R follicular lymphoma (FL) after 2+ lines of systemic therapy	- Given IV - Step-up dosing on days 1, 8, and 15 - Premedication: corticosteroid, antipyretic, antihistamine - No inpatient treatment/monitoring required - Given for 8-17 cycles (fixed)
Epcoritamab		R/R DLBCL not otherwise specified, including LBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after 2+ lines of systemic therapy	- Given SQ - Step-up dosing on days 1, 8, and 15 - Premedication: corticosteroid - Inpatient treatment/monitoring recommended - Given until progression or unacceptable toxicity
Glofitamab			- Given IV - Step-up dose 1: patients receive obinutuzumab (lowers rate/grade of CRS) - Subsequent step-up doses with glofitamab on days 8 and 15 - Premedication: corticosteroid, antipyretic, antihistamine - Inpatient treatment/monitoring recommended - Given for 12 cycles (fixed)

BiTEs: Multiple Myeloma

Agent	Target	FDA Indication	Considerations
Talquetamab	Targets G-protein coupled receptor, family C, group 5D (GPRC5D) on MM cells and CD3 on T-cells	R/R multiple myeloma after 4 lines of therapy including an immunomodulator a proteasome inhibitor, and an anti-CD38 mAb	- Given SQ - Weekly or biweekly dosing schedule options - Step-up dosing days depends on dosing schedule - Premedication: corticosteroid, antipyretic, antihistamine - Inpatient treatment/monitoring recommended - Unique ADRs includes skin, nail, and oral toxicity (on-target/off-target effects) - REMS requirement - Given until progression or unacceptable toxicity
Elranatamab	Targets B-cell maturation antigen (BCMA) on MM cells and CD3 on T-cells		- Given SQ - Weekly or biweekly dosing schedule options - Step-up dosing days 1, 4, 8 - Premedication: corticosteroid, antipyretic, antihistamine - Inpatient treatment/monitoring recommended - REMS requirement - Given until progression or unacceptable toxicity
Teclistamab			- Given SQ - Step-up dosing on days 1, 4, 7 - Premedication: corticosteroid, antipyretic, antihistamine - Inpatient treatment/monitoring recommended - REMS requirement - Given until progression or unacceptable toxicity

BiTE Treatment Costs

- Teclistamab: $6691/weekly
- Talquetamab: $12432/weekly
- Elranatamab : $8243/weekly
- Epcoritamab: $18544/dose (number of doses varies per cycle)
- Glofitamab: $3678/every 3 weeks
- Blinatumomab: $172872/cycle (28 days)
- Tebentafusp: $24312/weekly

BiTEs: Boxed Warning

- Cytokine release syndrome (CRS)
- Neurotoxicity
  - Including immune effector cell–associated neurotoxicity syndrome (ICANS)
- REMS programs
- Most approved BiTEs carry both boxed warnings
- All approved BiTEs carry risk of CRS
- Incidence of toxicities vary amongst products
- Most product labels recommend inpatient administration and monitoring for initial or step-up dosing before they can be given in the ambulatory setting
- Other unique toxicities are product specific

Cytokine Release Syndrome (CRS)

What is CRS?

- Acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction

How does it happen?

- T-cell activation and proliferation leads to high levels of cytokines being released into the bloodstream
- T-cell activation and proliferation leads to high levels of cytokines being released into the bloodstream

Clinical Manifestations

- Fever, headache, nausea, hypoxia, weakness, hypotension, increase in liver enzymes

Considerations

- Frequent monitoring is required
- Early interventions may prevent progression to severe/refractory CRS
- Step-up dosing method can decrease rate and severity of CRS
- Frequency rate and severity varies by product

Cytokine Release Syndrome

- Caused by excessive inflammatory cytokine release from high-level immune system activation
- Immune system activation is necessary for efficacy
- Multiple cytokines involved, but primarily IL-10, IL-6, and IFN-γ with CAR-T therapy
- IL-6 thought to be a central mediator of toxicity in CRS

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Therapies Associated with CRS: Multiple different immunotherapies

- Monoclonal antibodies
  - Rituximab
  - Alemtuzumab
  - Blinatumomab
- Adoptive cellular immunotherapy
- BiTEs
- Others

CRS Signs and Symptoms

- Collection of various inflammatory symptoms
  - Fevers
  - Myalgia
  - Hypotension
  - Coagulopathy
  - Pulmonary edema
- Can be mild, flu-like, or life-threatening

CRS Risk Factors

- High pre-infusion tumor burden
- Greater than 50% blasts in bone marrow
- Uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy
- Active infections
- Active inflammatory processes

CRS Management

- Supportive care
  - Vasopressors, fluids, antipyretics, etc.
- Corticosteroids
  - Compromise efficacy of CAR-T therapy.
- IL6 inhibitors
  - Tocilizumab
  - Siltuximab (off-label)

Tocilizumab: Recombinant humanized monoclonal antibody

- Substantially decreases cytokine production through IL-6 receptor antagonism

Dosing and administration

- Weight < 30 kg: 12 mg/kg/dose
- Weight $\geq$ 30 kg: 8 mg/kg/dose
- Maximum dose: 800 mg/dose
- Administered every 8 hours IV over 1 hour
- Max of three doses in 24 hours, four doses total

Neurotoxicity: Symptoms

- Peripheral neuropathies, headaches, and cognitive disturbances
- Generally, less severe than those seen with ICANS
- Unlike ICANS this form of neurotoxicity is not exclusively associated with cytokine storms
- Can be a direct or indirect effect of the therapy (e.g. immune mediated damage)

ICANS

- Characterized by neurologic deficits, often concurrent with CRS
- Deficits can be serious and progressive
- Symptoms
- Aphasia, altered mental status, weakness, reduced cognition, motor dysfunction, seizures, and/or cerebral edema

Proposed Mechanism

- Peripheral immune overactivation and endothelial activation
- Blood brain barrier dysfunction
- CNS inflammation

Assessment for Grading ICANS

- Immune Effector Cell-Associated Encephalopathy (ICE) score
  - Standardized tool used to assess and grade the severity ICANS
- The ICE score helps clinicians identify onset and progression of neurotoxicity
- Evaluates five neurocognitive functions
  - Score of 10 (maximum) = no impairment
  - Score of 0 (minimum)=unarousable and unable to perform assessment

Neurotoxicity

- May be severe or life-threatening
- Typically occurs within 2-8 weeks of treatment
- Management varies by product: Refer to package insert
- Close monitoring at home after discharge
- No driving or other activities where loss of consciousness can prove to be dangerous in first 2 months after CAR T infusion

REMS Programs

- Required for all CAR T and most BiTE products due to CRS and neurotoxicity risk
- Highlights
  - Certified healthcare facilities must have on-site, immediate access to tocilizumab with at least 2 doses available for administration within 2 hours after infusion start
  - Required REMS participants
    - Providers who prescribe, dispense, or administer product

Logistical Questions

- Efficient large scale manufacturing processes
  - Patient specific products vs. commercialized product
- Billing
  - Drug vs. Procedure
- Affordability
  - Healthcare system and patient

Patient Materials

- Patient wallet cards
- Patient booklet sections
- CRS overview, monitoring and what to do
- ICANS overview, monitoring and what to do

Ongoing Studies

- Over 400 registered clinical trials currently investigating CAR-T, TIL and BiTE therapies around the world
  - Clinicaltrials.gov

- Both oncologic and hematologic malignancies are represented in these studies

Summary

- CAR T therapy involves genetically modified autologous T lymphocytes while TIL therapy involves naturally occurring autologous lymphocytes
- Major adverse effects of CAR-T and BiTE therapy include CRS and neurotoxicity
- Supportive care, tocilizumab, and/or corticosteroids may be used to manage CRS and neurotoxicity
- REMS training must be completed prior to prescribing, dispensing, or administering CAR-T and some BiTE therapy
- Uncertainty remains regarding how both hospitals and patients will afford these new therapies

Alkylating Agents

History of Alkylating Agents
WWI: 1914-1918

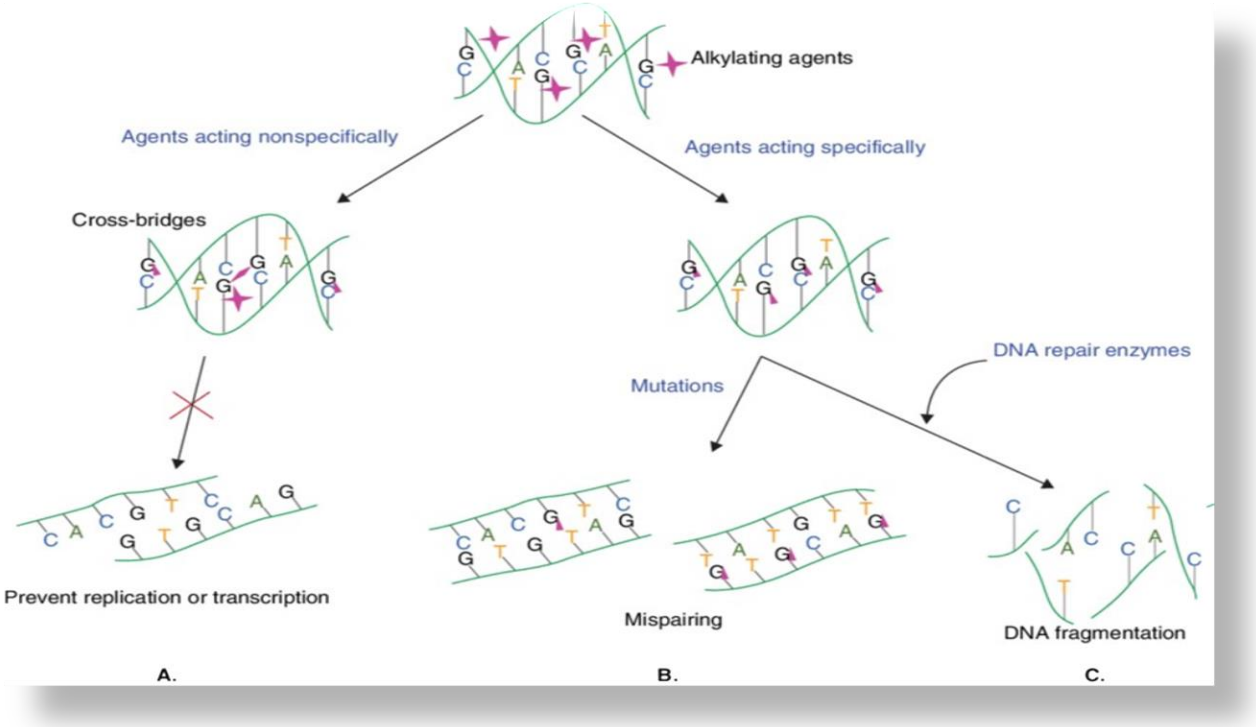
- Sulfur Mustard gas used as military weapons
- Vesicant properties caused skin irritation, blindness and pulmonary damage

WWII: 1939-1945

- Sulfur mustard spill in Bari Harbor, Italy
- Exposed sailors experienced bone marrow depression and lymph node depletion
- Observations led to further study of less toxic nitrogen mustards for cancer treatment
- Among the first antineoplastic drugs developed

Mechanisms of Action

- Cell cycle non-specific
- Exert effects in all phases of the cell cycle
- Work on Dividing and Resting Cells
- Effective in Slow-Growing Tumors
- Effective in Large Tumors that have few Actively Dividing Cells
- These agents are given intermittently, allowing the patient time to recover from toxicities prior to administering the medication again



Alkylating Agents Subclasses

- Nitrogen Mustards
- Alkyl Sulfonates
- Nitrosoureas
- Triazenes and Hydrazines
- Platinum

Toxicities Common to all Alkylating Agents and Dose Limiting Toxicities

- Major toxicities often directly relate to the administered dose
- Nadir 6-10 days after administration with recovery around 14-21 days
- Nitrosoureas Nadir 4-6 weeks after administration
- Bone marrow suppression (thrombocytopenia/risk for bleeding), anemia, neutropenia
- Organ-specific toxicities dependent on medication and dose: Renal, hepatic, pulmonary, cardiac, urotoxicity
- Hemorrhagic cystitis
- Infertility
- Hypersensitivity: Rare

Side Effects

- Gastrointestinal tract: Nausea, vomiting, anorexia, diarrhea, mucositis, stomatitis Emetogenicity varies
- Neurological: Peripheral neuropathy
- Tumor lysis syndrome: Oncologic emergency that occurs when many cancer cells are killed within a short period of time, releasing intracellular contents into the blood
- Risk of developing a new or secondary malignancy
- Other rapidly dividing cells are affected often causing alopecia, rashes, or infertility

Pre-and Post-Administration Considerations

- Monitor blood counts closely and reference treatment parameters
    - Chemotherapy plans may include a colony-stimulating factor (e.g., pegfilgrastim)
    - Blood transfusion replacement may be needed
    - Doses may be held or reduced based on blood counts
    - Urinalysis may be needed based on medication (e.g. Cyclophosphamide, Ifosfamide-monitoring for blood in urine- risk for hemorrhagic cystitis)
    - Negative pregnancy test is required before treatments
- Conduct baseline and symptom assessments to closely monitor for side effects, and report or intervene early
- Aggressive or extensive hydration is required for some alkylating agents because of the risk of hemorrhagic cystitis and nephrotoxicity
- IV site should be assessed prior to chemotherapy administration with special attention to vesicant and irritant precautions
- Reference boxed warnings and drug reference sheets for individual medications.
    - Note- *not all alkylating agents have the same risk for organ toxicity, side effects, or risk for the development of new malignancies and drug interactions*
- Discuss fertility preservation

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Nitrogen Mustards

Methchlorethamine (Valchlor): Indications
- Cutaneous T Cell Lymphoma
- Mycosis fungoides

Route of Administration: Topical
- Apply a thin film topically to affected area
- Apply immediately (or within 30 minutes) after removal from refrigerator; return to refrigerator promptly after each use
- Apply to completely dry skin at least 4 hours before or 30 minutes after showering/washing
- Allow treated area(s) to dry for 5 to 10 minutes after application before covering with clothing
- May apply emollients (moisturizers) to treated area 2 hours before or 2 hours after application
- Do not use occlusive dressings over treatment areas
  Caregivers should wear nitrile gloves when applying to patients
- Wash hands thoroughly with soap and water after handling/application
  If accidental skin exposure occurs, wash thoroughly for at least 15 minutes with soap and water; remove any contaminated clothing

Monitoring Parameters
- Monitor for dermatologic toxicity: Skin ulcers, blistering, dermatitis, secondary skin infection
- Signs and symptoms of nonmelanoma skin cancer or hypersensitivity reactions

Cyclophosphamide (Cytoxan) Indications:
- Breast Cancer
- Non-Hodgkin's Lymphoma
- Chronic Lymphocytic Leukemia
- Sarcoma
- Graft vs Host Disease Prophylaxis
- Multiple Myeloma
- Stem Cell Transplantation Conditioning Regimens
- Autoimmune Disorders
- Acute Lymphoblastic Leukemia

Route of Administration: IV or oral
IV administration
- IRRITANT; Potentially VAPORIZES AT ROOM TEMP
- Moderate or high emetic potential depending on dose, regimen, or administration route; antiemetics prior
- Infusion rate may vary based on protocol
- Administer by direct IV injection, IVPB, or continuous IV infusion

Adverse Reactions

- Leukopenia, neutropenia, thrombocytopenia, and anemia
- Cardiotoxicity: Prolonged QT
- Hepatotoxicity: Hepatic sinusoidal obstruction syndrome
- Bladder toxicity: Risk for hemorrhagic cystitis
    - To minimize bladder toxicity risk, increase normal fluid intake during and for 1 to 2 days after Cyclophosphamide dose. High dose regimens should be accompanied by vigorous hydration with or without Mesna therapy.
    - Morning administration may be preferred to ensure adequate hydration throughout day
    - Most adult patients will require a fluid intake of at least 2 L/day

Oral Administration

- Swallow whole; do not crush or chew; do not open capsules
- If contact with open capsules would occur, wash hands immediately and thoroughly
- Supplied in 25 mg and 50 mg capsules
- Well absorbed orally

Monitoring Parameters: IV and oral

- CBC w/diff, platelets, BUN, electrolytes, Cr, UA, pregnancy status prior to use in patients of childbearing years
- Monitor for secondary malignancies, wound healing impairment
- Metabolized in liver
- Excreted in urine

Ifosfamide: (Ifex): Indications

- Soft tissue sarcoma
- Lymphoma
- Testicular Cancer

Common Regimens

- MAI: Mesna, doxorubicin, ifosfamide
- ICE: Ifosfamide, carboplatin, etoposide
- VIP: Etoposide, ifosfamide, cisplatin

Route of Administration: IV

- Irritant
- SPILL PRECAUTIONS
- IV over at least 30 minutes (infusion times may vary by protocol duration)
- Moderate emetic potential
- To prevent bladder toxicity, Ifosfamide should be given with Mesna and hydration

Monitoring Parameters

- CBC w/diff, liver, renal function tests
- Urine output and UA for erythrocytes prior to each dose

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- Monitor for s/sx neurotoxicity, pulmonary toxicity, hemorrhagic cystitis, secondary malignancies

Ifosfamide Induced Encephalopathy Risk Factors
- Renal dysfunction
- Pelvic Mass
- Low albumin
- Previous nephrectomy
- Previous cisplatin administration

Treatment
- Discontinue Ifosfamide
- Consider methylene blue 50 mg IV every 4-8 hours until resolution
- Supportive care
- Spontaneous resolution usually occurs in 24-72 hours

Mesna Indications
- Urinary tract protectant: Used to decrease the incidence of hemorrhagic cystitis from Ifosfamide and high dose cyclophosphamide

Route of Administration
- IV formulation
- PO formulation 400 mg scored tablets

MESNA dosing
- Standard dose: 2.5 gm/m2/day via short infusion
- Mesna IV total daily dose: 60% of Ifosfamide dose split evenly into 3 doses administered 15 min before, 4 hours after and 8 hours after Ifosfamide
- To substitute oral Mesna tablets for the 2nd and 3rd IV dose, double the dose and give 2 hours before the scheduled IV dose

- IV: Administer as an IV bolus, may also be administered by short infusion or continuous infusion (maintain continuous infusion for 12 to 24 hours after completion of ifosfamide infusion)
- Maintain adequate hydration and urinary output during treatment
- Oral: Administer orally in tablet form
- If patient vomits within 2 hours after taking oral Mesna should repeat the dose or receive IV Mesna
- Oral form may be diluted in syrup, juice, carbonated beverages or milk

Melphalan (Alkeran, Evomela, Hepzato): Indications
- Multiple Myeloma
- Amyloidosis
- Waldenstrom's macroglobulinemia
- Stem cell transplant conditioning regimen

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- Ovarian Cancer
- Melanoma and soft tissue sarcoma

Route of Administration: IV
- IRRITANT and
- High emetic potential
- Evomela is formulated in cyclodextrin so it must be used within 4 hours of preparation
- Infused over 30 min
- Alkeran is also available in IV and is dissolved in propylene glycol so it must be used withing 1 hour of preparation

Oral Administration
- Available in 2 mg tabs
- Taken on empty stomach
- Oral tablets have variable absorption
- Tablets should be stored in refrigerator

Adverse Reactions
- Emetogenicity
  - High dose: IV: Moderate
  - Oral: Minimal-Low
- Myelosuppression
- Mucositis/stomatitis: Cryotherapy prevents mucositis in high dose
- Hypersensitivity: Rare 2% with IV formulation
- High dose therapy: Extravasation, cardiotoxicity, hepatic veno-occlusive disease, pneumonitis, renal toxicity, seizure, paralytic ileus

Monitoring Parameters
- CBC w/diff, platelet count, serum electrolytes, renal/liver function tests, serum uric acid
- Signs and symptoms of hypersensitivity reaction, pulmonary and GI toxicity
- Monitor adherence with oral melphalan

Chlorambucil (Leukeran): Indications
- Chronic Lymphocytic Leukemia (CLL)
- Hodgkin lymphoma
- Non-Hodgkin lymphomas
- Waldenstrom Macroglobulinemia

Route of Administration: Oral
- Single agent chlorambucil often combined with anti-CD20 monoclonal antibody (rituximab, ofatumumab, obinutuzumab)
- Available as a 2 mg tablet only and may be administered as a single daily dose
- Must be stored in refrigerator
- Take on empty stomach (improves absorption)
- Metabolized via liver

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- Half-life approx.1.5 hours
- Excreted in urine
- Dosing:
    - Typical dosing: 0.1 mb/kg/day for 3-6 weeks or 0.4 mg/kg/plus doses administered intermittently, biweekly, or monthly (increase by 0.1 mg/kg/dose until response or toxicity

Adverse Reactions
- Emetogenicity: oral; minimal to low
- Myelosuppression: Weekly CBCs while on therapy
- Seizures: Risk factors: High doses, nephrotic syndrome, history of seizures or head trauma
- Agitation, ataxia, confusion
- Skin reactions: erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis

Monitoring Parameters
- LFTs, CBC w/diff weekly, with WBC monitored twice weekly during the first 3-6 weeks of treatment
- Monitor oral adherence

Alkyl Sulfonates

Bendamustine (Bendeka, Belrapzo, Treanda, Vivimusta): Indications
- CLL
- Non-Hodgkin's Lymphoma
- Multiple Myeloma
- Waldenstrom's Macroglobulinemia
- Hodgkin's Lymphoma, relapsed or refractory

Route of Administration: IV
- Irritant with vesicant like properties
- Premedicate with antihistamines, antipyretics, and corticosteroids for patients with a previous grade 1 or 2 infusion reaction
- Highly protein bound
- Metabolized in the liver
- Excreted in urine and feces
- Extravasation
    - Sodium Thiosulfate 1/6 M solution

Adverse Reactions
- Rash
- Moderate emetogenicity
- Hypersensitivity reactions

Monitoring Parameters

- CBC w/diff and platelets frequently; in clinical trials, blood counts were monitored weekly initially
- Serum creatinine, LFTs (ALT, AST, total Bilirubin) prior to and during tx
- Potassium, uric acid levels in patients at risk for tumor lysis syndrome
- Pregnancy status prior to use
- Monitor signs and symptoms of infusion reactions, anaphylaxis, infection, dermatologic toxicity progressive multifocal leukoencephalopathy
- Monitor IV site during and after infusion
- Monitor for development of secondary malignancies, including dermatologic evaluations, during and after treatment

Thiotepa (Tepadina): Indications

- CNS malignancy
- Stem Cell Transplant for acute leukemias, beta-thalassemia
- Leptomeningeal mets: Intrathecal

Route of Administration: IV

- Irritant
- Moderate emetic potential
- Administer using a 0.2 micron in-line filter
- Crosses blood brain barrier: CSF concentration = plasma concentration
- Metabolized by liver
- Excreted in urine

Adverse Effects

- Emetogenicity: Low
- May be higher with high dose therapy
- Myelosuppression
- Excreted in sweat
- Pruritis and dermatitis
- Skin rashes and irregular skin pigmentation
- Mucositis
- Hypersensitivity
- Dizziness
- Headache
- Sinusoidal obstruction syndrome
- CNS toxicity

Busulfan (Myleran, Busulfex): Indications

- Stem Cell Transplant Conditioning Regimen in CML, and in other malignancies
- Polycythemia vera

Route of Administration: IV

- Crosses blood brain barrier
- Moderate or high emetic potential
- Incompatible with polycarbonate; do not use syringes, filters, or IV tubing containing polycarbonate for preparation or administration
- Stop all acetaminophen 72 hours before busulfan
- Seizure risk-use with caution if predisposed to seizures
    - Prophylactic anticonvulsant beginning 12 hours prior to busulfan and continued until 24 hours after last dose
- Measure Busulfan levels to guide dose adjustments
- Delayed pulmonary fibrosis (Busulfan lung)
- Hepatic Veno-Occlusive disease
- Monitor for signs and symptoms of cardiac tamponade and sinusoidal obstruction syndrome

Nitrosoureas

Carmustine (BiCNU, Gliadel Wafer): Indications

- Glioblastoma multiforme: Wafer or IV
- Lymphoma
- Conditioning regimen prior to autologous stem cell transplant
- Astocytoma
- Brainstem Glioma
- Ependynoma
- Medulloblastoma
- Multiple Myeloma

Route of Administration: IV

- Irritant
- Vaporizers at room temperature
- High emetic potential
- Significant CSF concentration
- Mixed with sterile alcohol, then diluted for administration (alcohol contributes to the side effect profile)
- Infuse through a free-flowing saline or dextrose infusion, or administer through a central catheter to alleviate venous pain/irritation, especially with high doses
- Infuse at least over 2 hours
- High dose carmustine may be fatal if not followed by stem cell rescue; monitor vital signs frequently
- Patients should be supine during infusion and may require Trendelenburg position, fluid support, and vasopressor support
- CBC w/diff, platelet count weekly for 6 weeks after dose
- Liver and renal function tests
- Pulmonary function tests at baseline and frequently during treatment

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Adverse Reactions

- Emetogenicity
  - Dose > 250 mg/m2: High
  - Dose <250 mg/m2: Moderate
- Delayed pulmonary toxicity: High doses
- Prolonged myelosuppression and delayed nadir occurs at 4-5 weeks; dosing is every 6 weeks
- Cardiac arrhythmia: High dose
- Hypotension: Alcohol content
- Flushing: Alcohol content
- Vein irritation: Alcohol content
- Nephrotoxicity

Lomustine (Gleostine): Indications

- Brain tumors
  - Intracranial tumors; Astrocytoma, Glioma, Medulloblastomas, Oligodendrogliomas

Route of Administration: Oral

- 10mg 40mg 100mg capsules
- Prescribe, dispense, and administer only enough capsules for one dose
- Fatal toxicity occurs with overdosage of Lomustine.
  - Both health care provider and pharmacist should emphasize to the patient that only one dose of Lomustine is taken every 6 weeks

Adverse Effects

- Emetogenicity: Moderate/high
- Prophylactic antiemetic indicated
- Myelosuppression: Prolonged and delayed nadir (dose Q 6 weeks), can be dose-limiting
- Pulmonary toxicity: High cumulative dose
- CNS effects
- Renal impairment

Streptozocin (Zanosar): Indications

- Adrenocortical carcinoma, metastatic
- Pancreatic neuroendocrine tumors, metastatic
- Gastrointestinal neuroendocrine tumors
- Thyroid carcinoma, medullary, advanced, or metastatic
- Concentrates in the liver, intestine, pancreas and kidney
- Sugar-containing nitrosourea, high affinity for cells of the islets of Langerhan

Route of Administration: IV

- Irritant with vesicant-like properties
- IV either by IVP or infusion
- Highly emetic potential-antiemetics are recommended

Adverse Reactions
- Decreased glucose tolerance
- Diarrhea
- Nausea, vomiting
- Proteinuria

Triazenes

Temozolomide (Temodar)
- Crosses blood brain barrier
- Can be used alone or with radiation therapy

Indications
- Glioblastoma
- Anaplastic astrocytoma
- CNS mets from solid tumors
- Metastatic melanoma
- Soft tissue sarcoma

Route of Administration: IV or oral
- IV
  - Irritant with vesicant properties
  - Moderate to high emetogenic potential
- Oral
  - 5mg, 20mg,100mg,140mg,180mg,250mg capsules
  - Give on an empty stomach and/or at bedtime to reduce N/V
  - Swallow capsules whole with a full glass of water; do not open or chew

Precautions
- Hypersensitivity to DTIC (dacarbazine)
- Severe renal or hepatic impairment
- May cause secondary malignancies (MDS, AML, CML)

Dacarbazine (DTIC): Indications
- Hodgkin's lymphoma: ABVD-doxorubicin, bleomycin, vinblastine, dacarbazine
- Metastatic melanoma

Route of Administration: IV
- Irritant
- Infuse over 15-60 minutes, rapid infusion may cause severe venous irritation

Adverse Reactions
- High emetic potential
- Hepatotoxicity
- Seizure
- Infiltration: Irritant

- Photosensitivity
- Flu-like symptoms
- Metallic taste in mouth
- Alopecia
- Leukopenia, thrombocytopenia

Platinums

Cisplatin (Platinol): Indications
- Testicular cancer
- Ovarian cancer
- Bladder cancer
- Head and neck cancer
- Esophageal cancer
- Lung cancer
- Non-Hodgkin's lymphoma
- Trophoblastic neoplasm

Route of Administration: IV
- Vesicant
- High emetic potential
- Administer appropriate pretreatment hydration and maintain adequate hydration and urinary output for 24 hours following cisplatin administration
- Cisplatin has been infused over 30 minutes to 4 hours, at a rate of 1 mg/min or as a continuous infusion; rates vary based on protocol
- Do not administer as a rapid IV injection
- Needles or IV administration sets that contain aluminum should not be used in the preparation or administration; aluminum may react with cisplatin resulting in precipitate formation and loss of potency
- Radio sensitizing agent
- Administer after Taxol, which prevents delayed Taxol excretion and increased toxicity
- To prevent nephrotoxicity, administer pretreatment hydration with 1-2 liters of IV saline solution
- Risk of ototoxicity is increased when combined with aminoglycosides and loop diuretics

Adverse Effects
- Nephrotoxicity
- Peripheral Neuropathy
- Ototoxicity (audiometric testing recommended)
- Nausea/vomiting-: Highly emetogenic
- Hypersensitivity reactions within minutes of 1st infusion, and in pts treated with more than 5 cycles continuous treatment
- Ocular toxicity
- Metallic taste of foods

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- Extravasation
  - Sodium Thiosulfate: Antidote
  - Elevate the extremity
  - Cold application immediately
  - Vesicant potential when more than 20 ml of concentrated solution has extravasated.

Carboplatin (Paraplatin): Indications
- Ovarian cancer
- Germ cell tumors
- Head and neck cancers
- Lung cancer
- Bladder cancer
- Non-Hodgkin lymphoma
- Cervical cancer
- Testicular cancer
- Malignant pleural mesothelioma
- Breast cancer

Dosing: Calculated to a target "area under the curve"
- AUC based on the glomerular filtration rate (GRF)
- AUC represents total drug exposure
- Calvert formula is used to calculate dose
  - Target AUC x (GFR + 25)=dose in mg
- Usual target AUC range is 5-7
- May be lower for weekly doses, or radio sensitizing doses
- Refer to published regimen for specific targets
- If patient has been previously treated, AUC 4-6

Rout of Administration: IV
- Irritant
- Infuse over at least 15 minutes; usually infused over 15-60 minutes, varies by regimen
- Needles or IV administration sets that contain aluminum should not be used in preparation or administration, could result in precipitate formation and loss of potency

Adverse Effects
- Myelosuppression
- Nausea/vomiting
- Renal toxicity: Mild
- Peripheral neuropathy: Mild
- Hypersensitivity

Oxaliplatin (Eloxatin): Indications
- In combination with 5FU/leucovorin or capecitabine (FOLFOX, FLOX,CAPEOX)
- Adjuvant: Stage III colorectal cancer

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- Palliative: Metastatic/advanced colorectal cancer
- Relapsed/refractory non-Hodgkins and Hodgkins lymphoma
- Cholangiocarcinoma
- Esophageal/gastric cancer
- Pancreatic cancer

Route of Administration: IV
- IRRITANT w/vesicant like properties
- Administer over 2 hours, extend infusion time to 6 hours for acute toxicities
- Moderate emetic potential and is known to cause delayed nausea and vomiting
- Use D5W: Not compatible with NSS
- Avoid ice chips, exposure to cold temperatures, or consumption of cold food/beverages during or within hours after oxaliplatin infusion (may exacerbate acute neurological symptoms
- Do not use needles or administration sets containing aluminum

Adverse Effects
- Neurotoxicity: Dose-limiting
- Myelosuppression
- Nausea/vomiting : Moderate emetogenicity
- Diarrhea
- Hypersensitivity/anaphylactic reactions
- Cold sensitivity

Monitoring Parameters
- EKG monitoring is recommended in patients at risk for QT prolongation, heart failure, brady arrhythmias, and electrolyte abnormalities, and in patients taking medications known to cause QT prolongation
- Perform neurologic evaluation prior to each dose and periodically thereafter
- Monitor for hypersensitivity signs and symptoms, pulmonary toxicity, posterior reversible encephalopathy syndrome (diagnosis confirmed w/ MRI), neuropathy, bleeding, and GI toxicity

Lurbinectedin (Zepzelca): Indications
- Small cell lung ca stage IV metastatic
- Administered once q21 days until disease progression or unacceptable toxicity

Route of Administration: IV
- VESICANT
- Administer over 60 min
- Moderate emetic potential, premedicate with dexamethasone & antiemetic
- Avoid grapefruit and Seville oranges while receiving Zepzelca

Adverse Effects
- Bone marrow suppression

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- GI toxicities
- Hepatotoxicity

Trabectedin:(Yondelis): Indications

- Unresectable or metastatic liposarcoma or leiomyosarcoma in patients who have received a prior anthracycline containing regimen
- Ovarian cancer: Relapsed, platinum sensitive

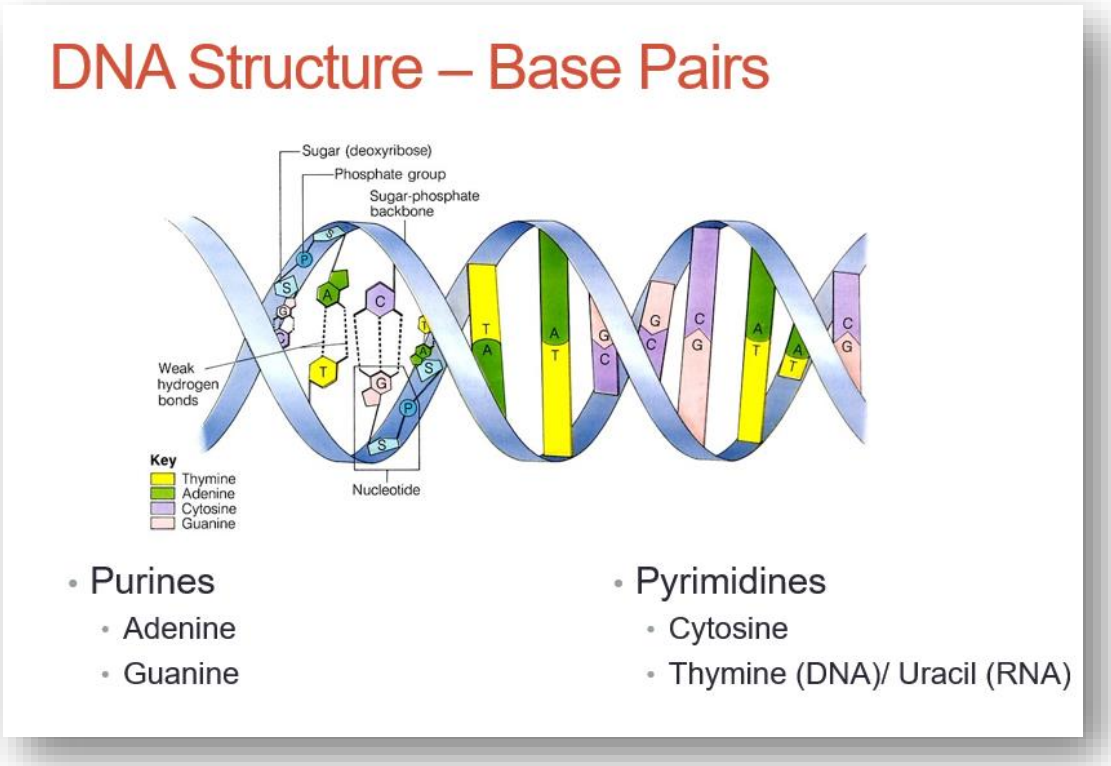
Route of Administration: IV

- VESICANT
- Cycle length 3 weeks
- Infuse through a central line with a 0.2 micron filter
- Infusion must be completed within 30 hours of reconstitution
- Premedicate with corticosteroid 30 minutes prior to treatment; additional antiemetics may be needed
- For soft tissue sarcoma: Single-agent therapy; Infuse as a continuous infusion over 24 hours

Adverse Events

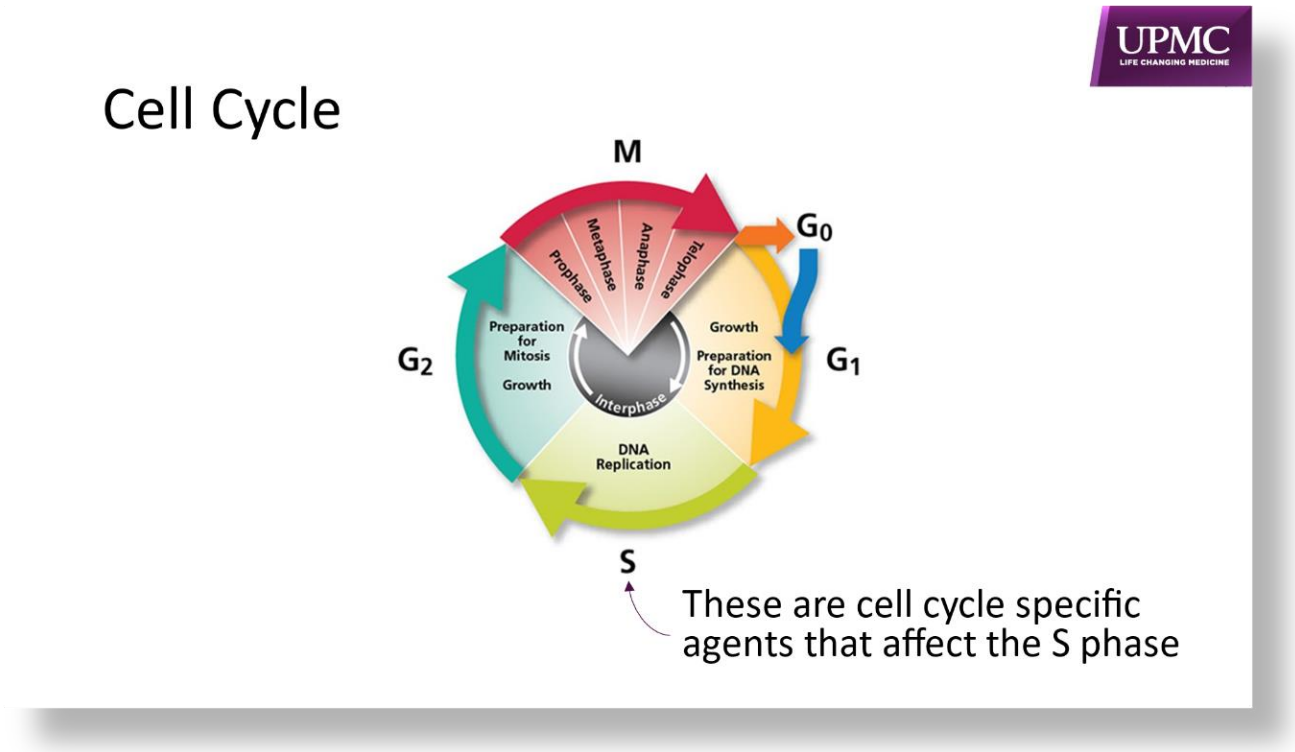
- Cardiomyopathy
  - Monitor EF
- Moderate emetic potential

Antimetabolites



What is an antimetabolite?

- Structurally related to compounds found in the body: Proteins, DNA, RNA
- Compete for binding sites on enzymes
    - Inhibit nucleotide synthesis
- Incorporate directly into DNA or RNA
    - Act as “false” nucleotides



Antifolates

- Folic acid analogs
  - Methotrexate
  - Pemetrexed
  - Pralatrexate

Pyrimidine Antimetabolites

- Fluoropyrimidines (uracil analogs)
- 5-Fluorouracil (5-FU)
- Capecitabine
- Trifluridine/tipiracil
- Floxuridine (FUDR)

Purine Antimetabolites

- Thiopurines (Guanine analogs)
- 6-mercaptopurine (6-MP)
- 6-thioguanine (6-TG)

Guanosine Analog

- Nelarabine

Adenosine Analogs

- Fludarabine
- Pentostatin
- Cladribine
- Clofarabine

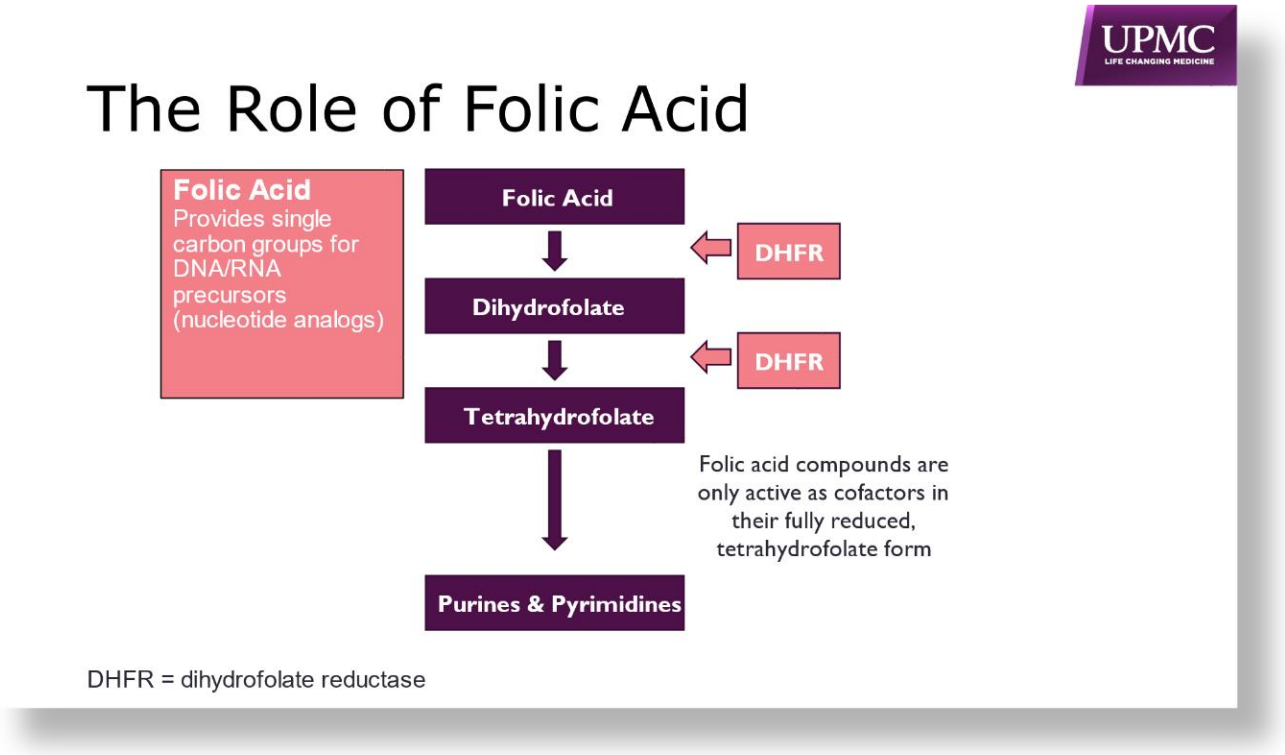
Cytosine Analogs

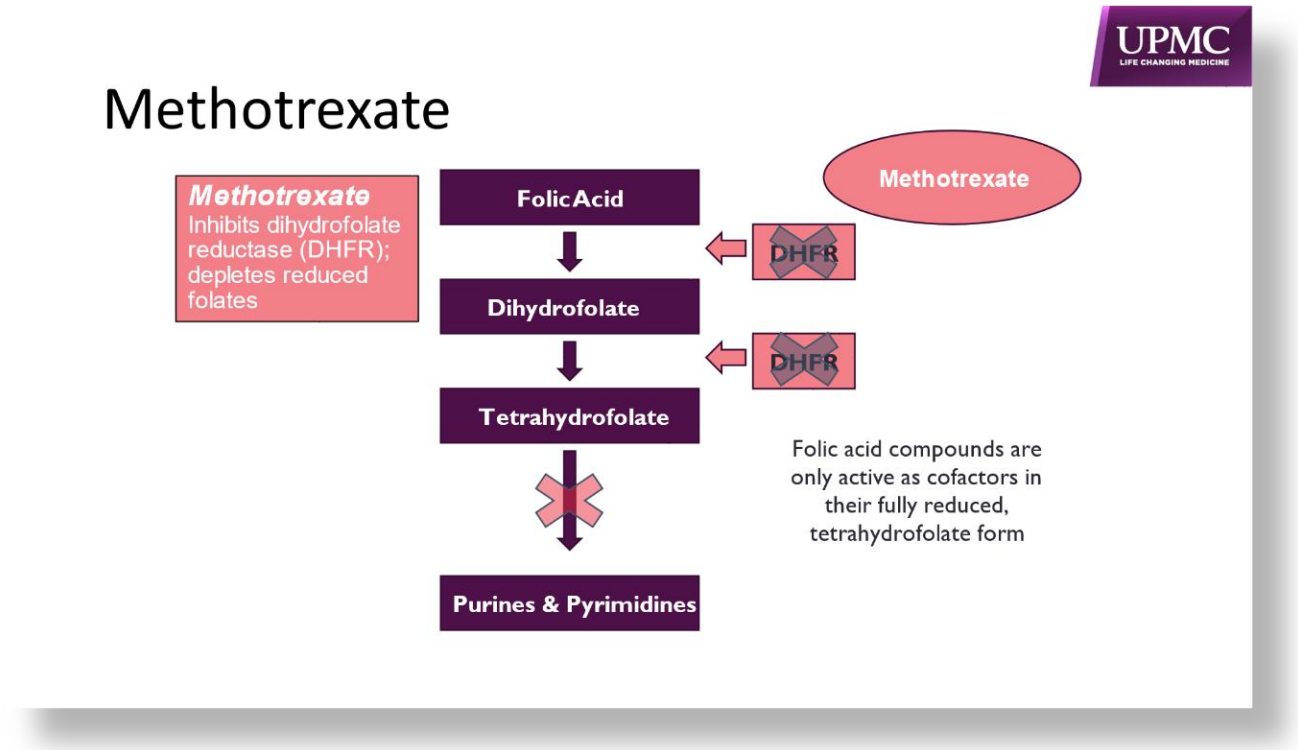
- Cytarabine (Ara-C)
- Gemcitabine
- Azacytidine
- Decitabine

Miscellaneous

- Hydroxyurea

Folate Antagonists

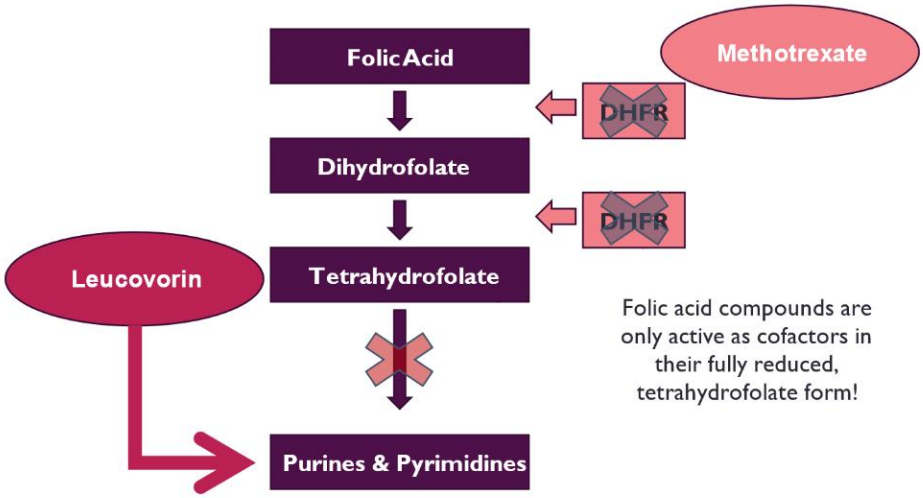




Methotrexate (MTX)

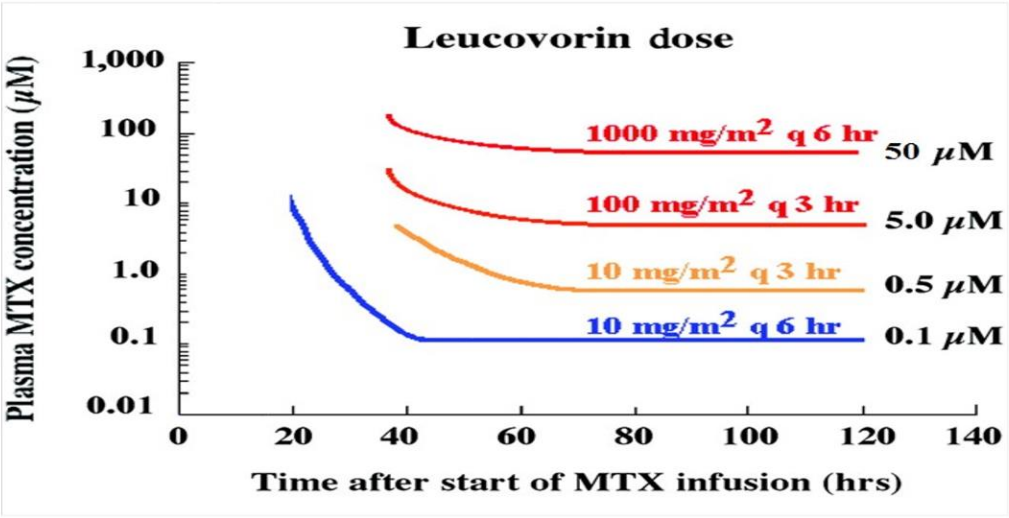
- Indication
  - Breast cancer and head and neck cancer
  - Mycosis fungoides
    - Cutaneous T-cell lymphoma
  - Osteosarcoma
  - CNS lymphoma and prophylaxis in high-risk leukemia and lymphoma patients
- Administration: Intravenous (IV), Intrathecal (IT), and Oral (PO)
- Toxicity
  - Mucositis
  - Myelosuppression
  - Increase in liver function tests (LFTs)
  - Decrease in renal function
  - Pneumonitis
  - Neurotoxicity: Leukoencephalopathy
  - Radiation recall

Folinic Acid (Leucovorin) Rescue



Folic acid compounds are only active as cofactors in their fully reduced, tetrahydrofolate form!

Methotrexate – Leucovorin Rescue



- Drug interactions
    - Drugs that may increase MTX levels/delay clearance
        - Nonsteroidal anti-inflammatory drugs
        - Drugs that are highly protein bound: Salicylates, phenytoin, sulfonamides
    - Penicillin
    - Aminoglycosides (and other nephrotoxins)
    - Tetracyclines
    - Proton-pump inhibitors

- General Dose Adjustments
    - Renal
        - Creatinine clearance (CrCl) ≥ 50 mL/min: Full dose; CrCl 10-50 mL/min: 50% dose reduction; CrCl < 10 mL/min: Avoid use
    - Avoid high-dose methotrexate to patients with abnormal renal function
        - High dose is > 500 mg/m^2
    - Liver: Bilirubin < 3.1mg/dL: Full dose; Bilirubin 3.1-5 mg/dL: 25% dose reduction; Bilirubin > 5 mg/dL: Avoid use

Clinical Pearls for MTX

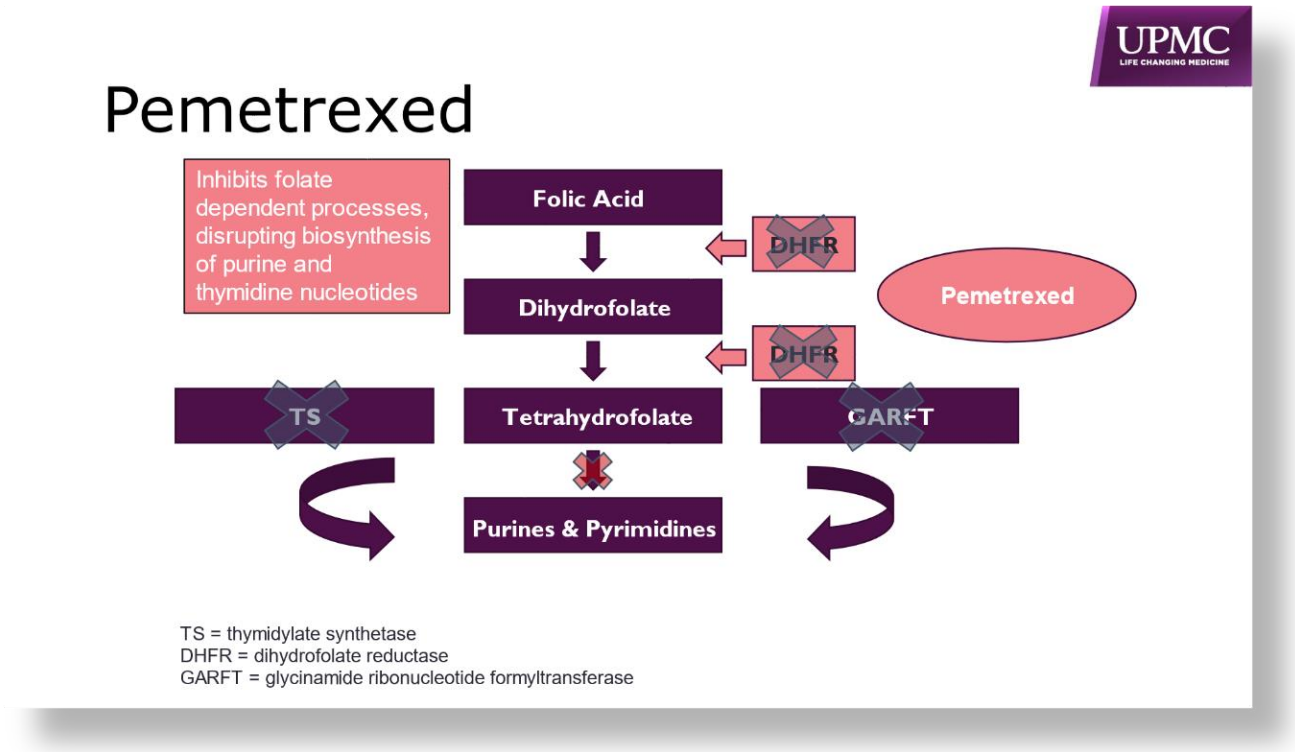
- Monitor plasma concentrations (patients receiving high-doses)
    - Samples should be drawn in a red-top vial and wrapped in foil light degrades MTX
    - Samples should be drawn daily until level ≤ 0.05μM
    - Leucovorin rescue begins ~24 hours after the end of MTX infusion
- Patients receiving high-dose MTX require alkaline urine
    - Do not administer until urine pH ≥ 7
        - Sodium bicarbonate: Available in both PO and IV formulations
- Methotrexate accumulates in fluid collections: Drain pleural effusions, ascites, etc. before giving high dose methotrexate

Your patient with CNS lymphoma who received high dose methotrexate yesterday is too nauseous to take her oral leucovorin pills. You should

A. Omit the dose and mark “patient refused” in the medical record
B. Insert an NG tube, crush tablets, and administer through the NG tube
C. Administer ondansetron and try again in an hour
D. Request an order for IV leucovorin

Glucarpidase

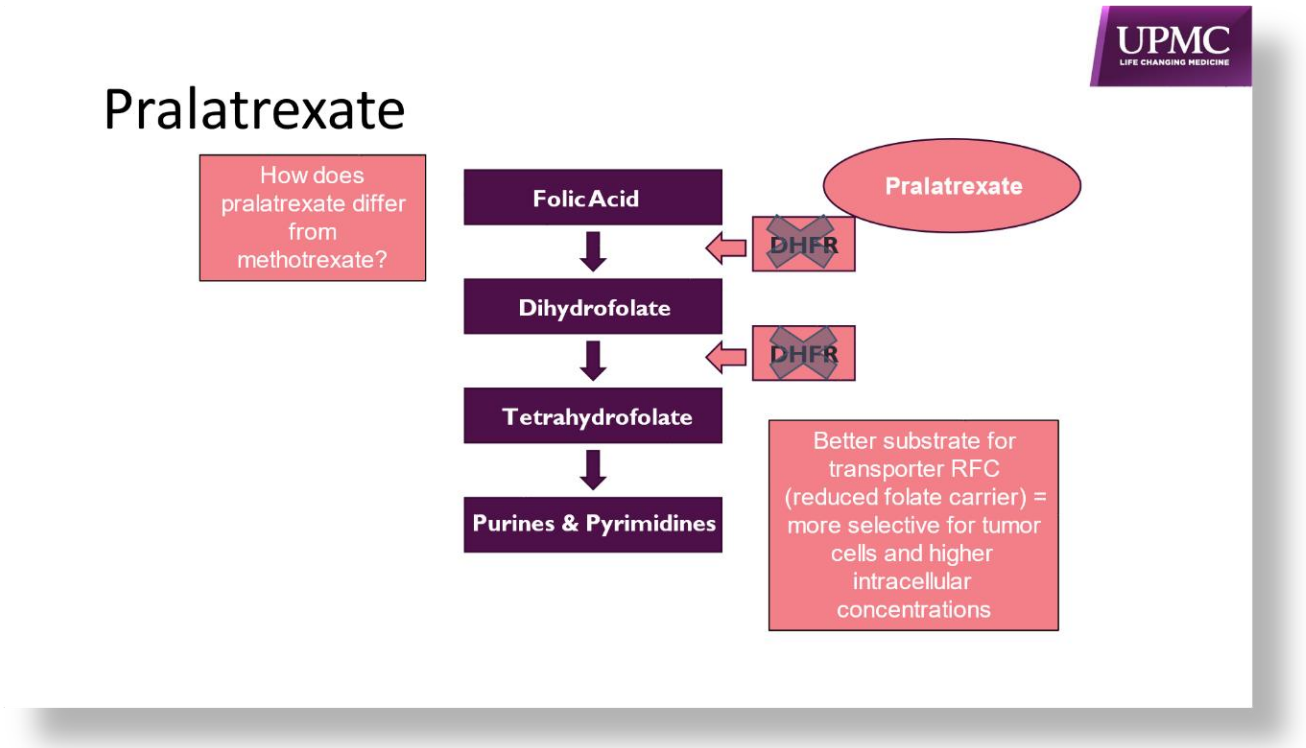
- Recombinant enzyme (carboxypeptidase)
- Indication
    - Treatment of toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function



Pemetrexed (Alimpta)

- Indication
  - Locally advanced or metastatic non-squamous non-small cell lung cancer
    - Initial treatment with platinum agent or as maintenance chemotherapy
  - Mesothelioma
    - In combination with platinum agent
- Often combined with checkpoint inhibitor monoclonal antibodies
- Administration
  - IV: 500mg/m2 q 21 days infused over 10 minutes
- Toxicity
  - Myelosuppression
  - Fatigue
  - Nausea/vomiting
  - Stomatitis/pharyngitis
  - Rash: Premedicate
- Clinical Considerations
  - Premedication
    - Folic acid: Take folic acid 400 mcg to 1000 mcg orally once daily beginning seven days before the first dose; Continue throughout therapy and for 21 days after the last dose

- Vitamin B12: Administer vitamin B12 1 mg intramuscularly 1 week prior to the first dose of pemetrexed and every 3 cycles thereafter
- Corticosteroids: Take dexamethasone 4 mg orally twice daily for three days

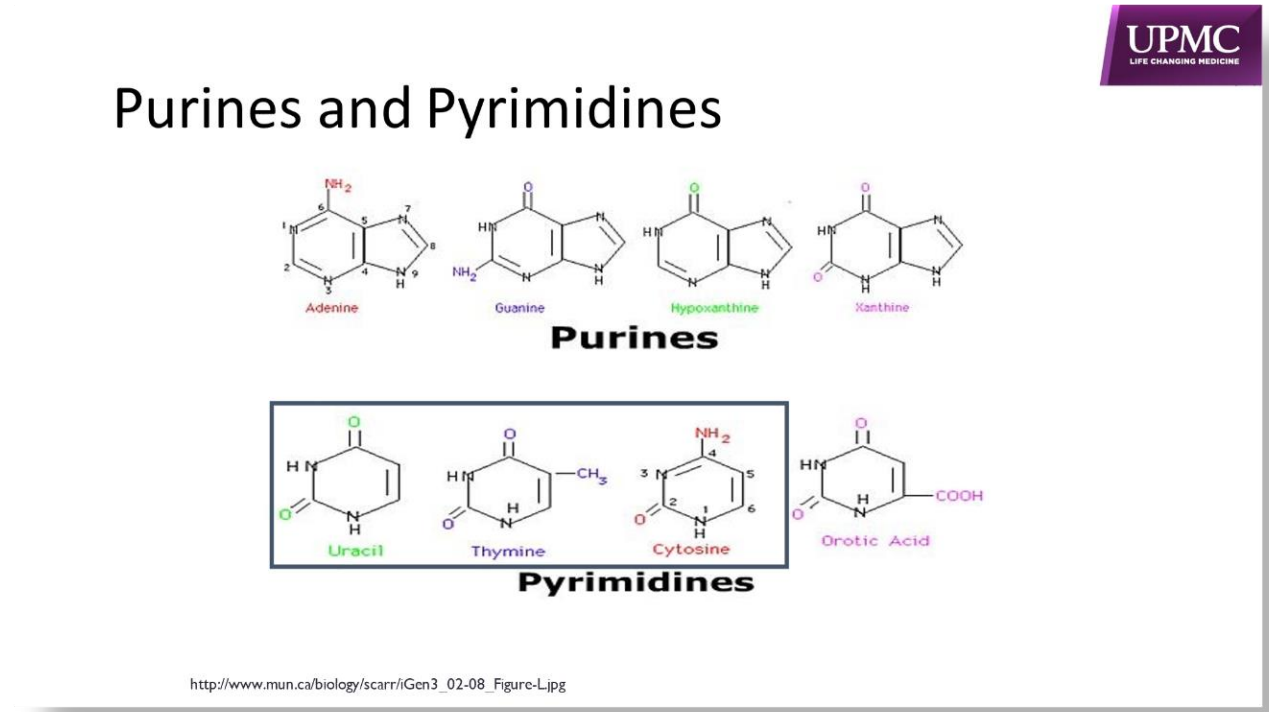


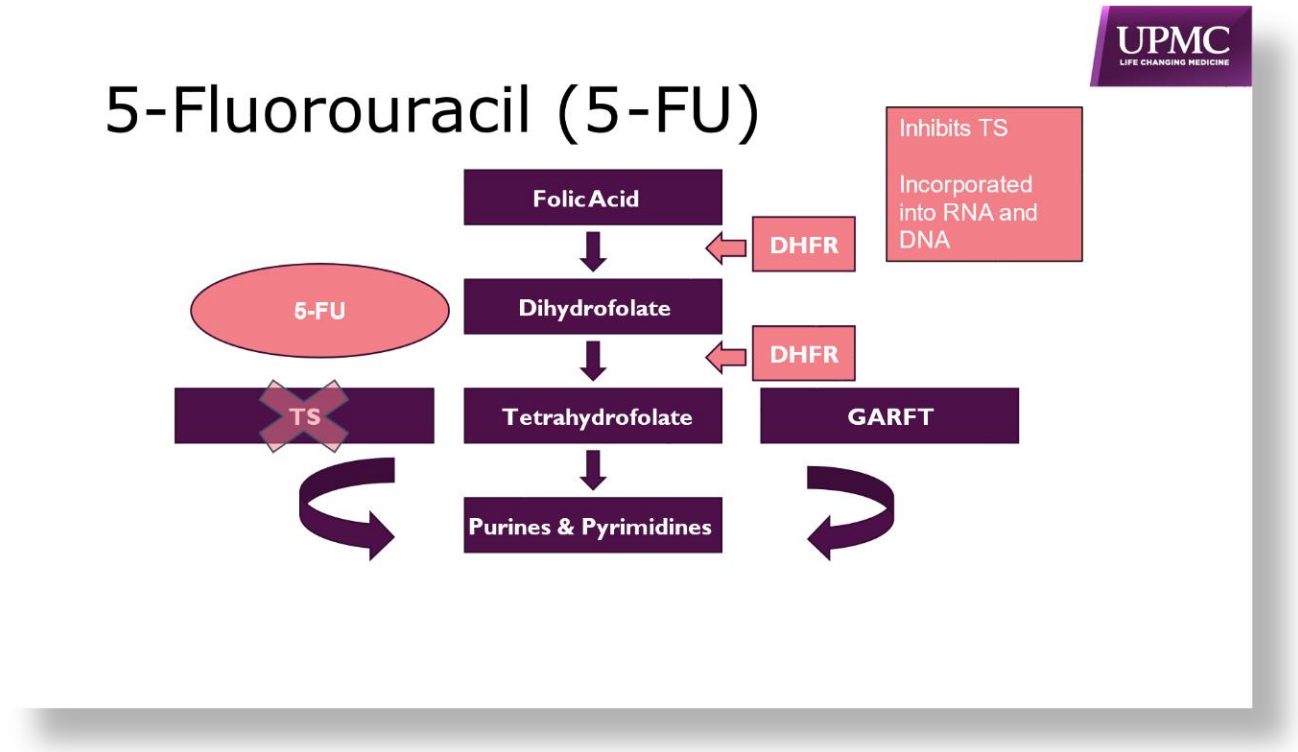
Pralatrexate

- Indication
  - Relapsed or refractory peripheral T-cell lymphoma (PTCL)
  - Administration: IV push 30mg/m^2 q week for 6 weeks in a 7-week cycle
- Toxicity
  - Myelosuppression
  - Mucositis
  - Rash
  - Hepatic toxicity
- Dose Adjustments
  - Renal or hepatic dysfunction
    - May be necessary to decrease dose to 20 mg/m^2 (also for grade 2-3 toxicity)
  - Patients should not begin a new cycle of treatment until
    - Mucositis should be ≤ grade 1
    - ANC is ≥ 1000 cells/mm^3
    - Platelet count is ≥ 100,000 cells/mm^3 for first dose and ≥ 50,000 cells/mm^3 for all subsequent doses

- Clinical Considerations
  - Premedication
    - Folic acid: Take folic acid 1.0 -1.25 mg orally once daily beginning 10 days before the first dose continue throughout therapy and for 30 days after the last dose
    - Vitamin B12: Administer vitamin B12 1 mg intramuscularly within 10 weeks prior to the first dose of pralatrexate and every 8-10 weeks thereafter

Pyrimidine Antagonists





5-Fluorouracil (5-FU)

- Indication
  - Breast, colorectal, gastric, pancreatic cancer, and head and neck cancer
- Administration
  - IV push or continuous infusion, topical
- Toxicity
  - Myelosuppression
  - Hand-foot syndrome: Dermatologic rash
  - Skin (Photosensitivity): Radiosensitizer
  - Cardiac: Coronary spasm
  - GI epithelial ulceration: Mucositis and diarrhea
  - Ocular toxicity
- Administration
  - 5-FU IV Push: Increased myelosuppression; Decreased mucositis and diarrhea, skin toxicity
  - 5-FU Continuous Infusion: Decreased myelosuppression; increased mucositis and diarrhea, skin toxicity
- Dose Adjustments
  - Renal or hepatic dysfunction
    - Consider discontinuation of therapy
      - Total bilirubin > 5

- Monitoring parameters
  - Consider discontinuation of therapy
    - Mucositis
    - Severe neutropenia, thrombocytopenia
    - Severe nausea/vomiting

- 5-Fluorouracil (5-FU) Clinical Considerations
  - Leucovorin
    - Used to enhance the effect of 5-FU
    - Leucovorin (reduced folate) increase levels cofactors required for ternary complex with 5-FdUMP and TS

Capecitabine (Xeloda)

- Oral produg of 5-FU
- Indication
  - Breast
  - Colorectal cancer
- Administration
  - Oral (PO) 1250mg/m2 BID orally for 2 weeks followed by 1 week rest period (3 weeks); supplied: 150 and 500mg tablets
- Toxicity
  - Myelosuppression
  - Hand-foot syndrome: Dermatologic rash
  - Cardiac: Coronary spasm
  - GI: Mucositis and diarrhea
  - Ocular toxicity

- Renal Dysfunction
  - CrCl ≥ 50 mL/min = Full dose
  - CrCl 30–50 mL/min = 25% dose reduction
  - CrCl < 30 mL/min = Avoid use
- Counseling Points:
  - Oral agent: Patients need to be counseled to call the clinic with any changes in general health
  - Development of diarrhea, N/V, painful or red palms or feet, sore mouth
  - Monitor INR when given with warfarin: Increased INR
  - Taken within 30 minutes of a meal

Floxuridine (FUDR)

- Indication:
  - Gastric or colorectal cancer with hepatic metastases
- Administration: Continuous arterial infusion (hepatic artery infusion
- Toxicity:
  - Myelosuppression

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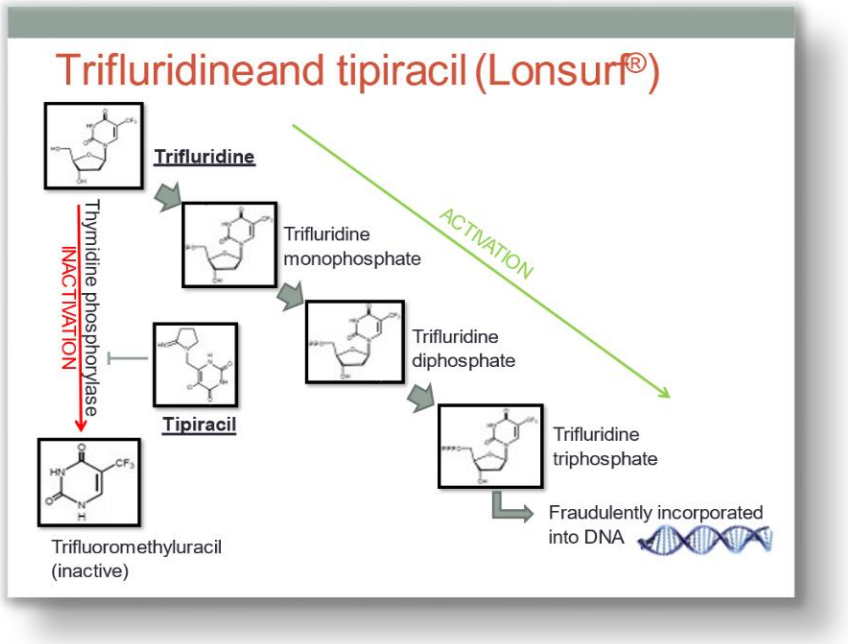
    - Hand-foot syndrome (dermatologic rash)
    - Cardiac (coronary spasm)
    - GI epithelial ulceration (mucositis/diarrhea)
    - Hyperbilirubinemia
    - Catheter-related complications:
    - Thrombosis, hemorrhage or infection, slippage of the catheter
- Monitoring:
    - Because of the possibility of severe toxic reactions, all patients should be hospitalized for initiation of the first course of therapy
    - Dose reductions or breaks may be needed depending on toxicity
    - Keep line open with heparinized saline when not in use

Uridine Triacetate (Vistogard)

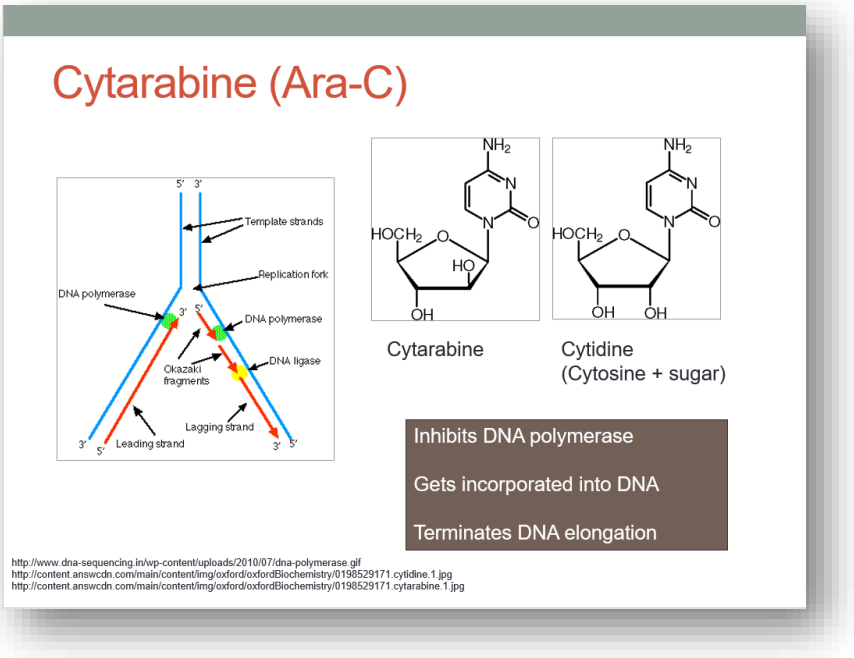
- A pyrimidine analog indicated for the emergency treatment of adult and pediatric patients
    - Following a fluorouracil or capecitabine overdose, regardless of the presence of symptoms
    - Early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g. gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration
- Mechanism of Action
    - Uridine reduces incorporation of fluorouridine triphosphate into RNA of hematopoietic progenitor cells and gastrointestinal mucosal cells to reduce fluorouracil toxicity in these tissues
    - Start within 96 hours
- Administration
    - How supplied: single-dose 10 gm packet of orange-flavored, oral granules
    - Adult dose: 10 grams (1 packet) PO every 6 hours x 20 doses, without regard to meals
    - Pediatric dose: refer to prescribing information for details
    - Administration:
        - Mix each dose with 3-4 oz of soft foods such as applesauce, pudding , or yogurt and ingest within 30 minutes of mixing. Do not chew the uridine triacetate granules. Drink at least 4 ounces of water



Trifluridine and tipiracil (Lonsurf®)

- Indications:
  - Metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (RAS wild-type).
  - Metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of therapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.
- Administration:
  - 35 mg/m2/dose (based on trifluridine component, rounded to nearest 5 mg, cap at 80 mg) PO BID on days 1-5 and days 8-12 of each 28-day cycle
- Toxicity:
  - Myelosuppression
  - Diarrhea
  - Nausea
  - Fatigue
- Renal Dysfunction:
  - CrCl < 30 mL/min and ESRD: has not been studied
- Hematologic Toxicity:
  - ANC < 500 or neutropenic fever or platelets < 50,000 interrupt therapy; Upon recovery may resume with dose reduced by 5 mg/m2/dose

- Counseling Points
  - Oral agent: Patients need to be counseled to call the clinic with any changes in general health
  - Development of diarrhea, N/V
  - Taken within one hour of completion of morning and evening meals



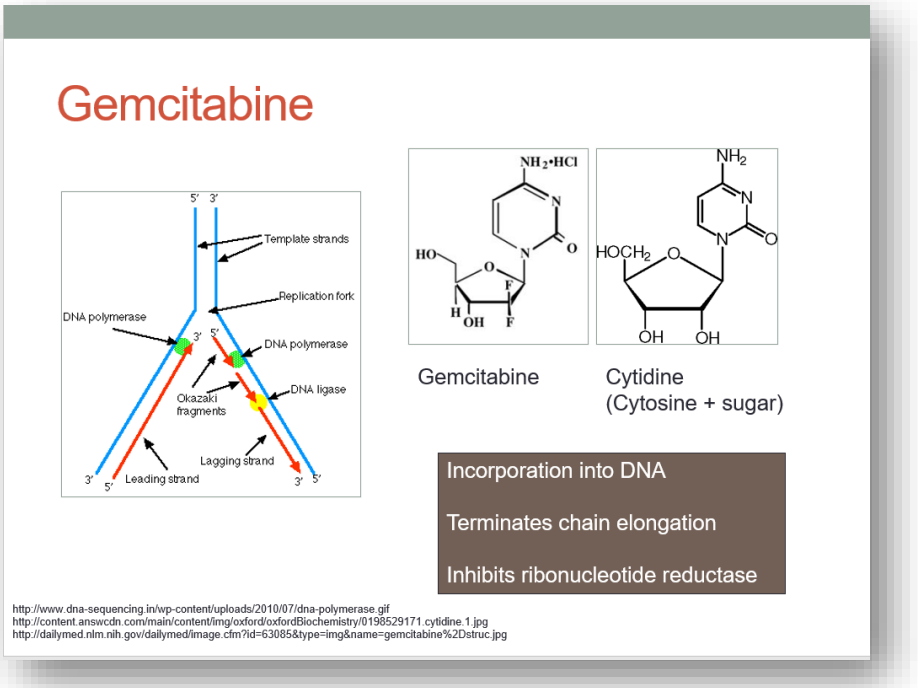
Cytarabine (Ara-C)

- Indication
  - Acute myeloid leukemia (AML) or acute lymphoid leukemia (ALL)
  - Burkitt's lymphoma (high-grade lymphomas)
  - Mantle cell lymphoma
- Administration
  - IV continuous infusion (low dose = 100mg/m2 CIVI q 24h x 7 days) or IV infusion (high dose = 3gm/m2 IV q 12h x 6 doses)
  - IT (intrathecal) cytarabine
- Toxicity
  - Myelosuppression
  - N/V/D
  - Mucositis
  - Cerebellar toxicity (high dose): Neuro-checks each shift
- Conjunctivitis (high dose): Give with dexamethasone eye drops
- Hepatic dysfunction
- Pulmonary edema

- Rash
- Cerebellar toxicity
    - Prevention and early detection is paramount
    - Treatment is supportive
    - Toxicity may be irreversible
    - Dose reduction in elderly or kidney disease
    - Immediately discontinue cytarabine in patients with cerebellar toxicity
- Renal dysfunction
    - No formal recommendations but dose reductions may be required in renal dysfunction
    - For patients receiving high dose cytarabine (does not apply to continuous infusion 100mg/m2)
- Hepatic dysfunction
    - No formal recommendations but dose reductions may be required in hepatic dysfunction

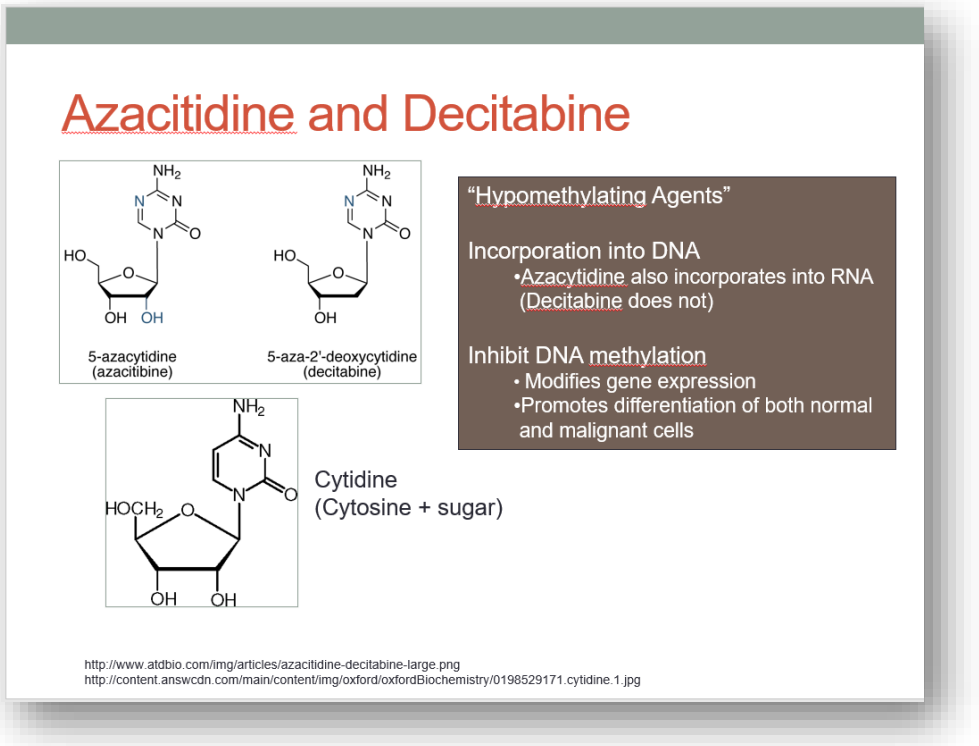
Question: A 69-year-old patient is receiving high dose cytarabine 2 gm/m2 IV every 12 hours x 4 doses for treatment of Mantle Cell Lymphoma. Which type of neurotoxicity is most likely to occur?

A. Encephalopathy
B. Cerebellar ataxia
C. Aseptic meningitis
D. Seizure



Gemcitabine (Gemzar®)

- Indications:
  - Ovarian, breast, non-small cell lung, pancreatic, and bladder cancer
  - Cholangiocarcinoma
- Administration:
  - IV infusion: 1000 -1250mg/m^2 IV over 30 min
- Toxicity:
  - Myelosuppression
  - Thrombocytopenia: Decreased production (common), TTP (rare)
  - N/V/D: Low emetogenicity
  - Fever
  - Hepatic dysfunction



Azacytidine

- Indications: MDS, AML
- Administration:
  - IV infusion (Vidaza®); 75 mg/m^2 daily x 7 days q 4 weeks
    - Dilute in normal saline (not D5W): D5W causes increased degradation of 5-azacytidine
  - Subcutaneous (Vidaza®): 75 mg/m^2 daily x 7 days q 4 weeks
    - Divide doses > 4mL into 2 syringes and inject into separate sites
  - Oral (Onureg®): 300 mg daily x 14 days q 4 weeks
    - Anti-emetic premedication should be provided for at least first two cycles; Do not interchange with SQ/IV forms
- Toxicity:
  - Myelosuppression
  - Nausea/vomiting
  - Renal dysfunction: Rare
  - Hepatic dysfunction: High dose
  - Muscle tenderness, weakness: High dose
  - Lethargy, confusion, coma: High dose

Decitabine (Dacogen)

- Indication:
  - Myelodysplastic syndrome
  - Off label: Acute myeloid leukemia
- Administration:
  - IV infusion
    - 15 mg/m^2 over 3 hours repeated every 8 hours for 3 days q 6 weeks
    - 20 mg/m^2 over 1 hour repeated daily for 5 days q 4 weeks
  - Needs to be mixed in a COLD bag, allows for longer stability
- Toxicity:
  - Myelosuppression
  - Nausea/vomiting
  - Renal dysfunction (rare)
  - Hepatic dysfunction (high dose)
  - Hyperglycemia
  - Fever
  - Peripheral edema

Decitabine/Cedazuridine (Inqovi®)

- Indication
  - Myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS
- Administration:
  - Oral (35 mg decitabine/100mg cedazuridine)
  - Give on empty stomach: At least 2 hours before or after meals
  - Give daily for Days 1-5 of a 28-day cycle.
- Toxicity: Like IV formulation
- Role of cedazuridine:
  - Oral absorption of decitabine is low due to activity of cytidine deaminase in the gut
  - Cedazuridine developed to serve as a cytidine deaminase inhibitor
  - Combination allows for mimicking of IV decitabine pharmacokinetics with oral formulation
  - Should not be used as substitute for decitabine IV midcycle or in combination with other agents

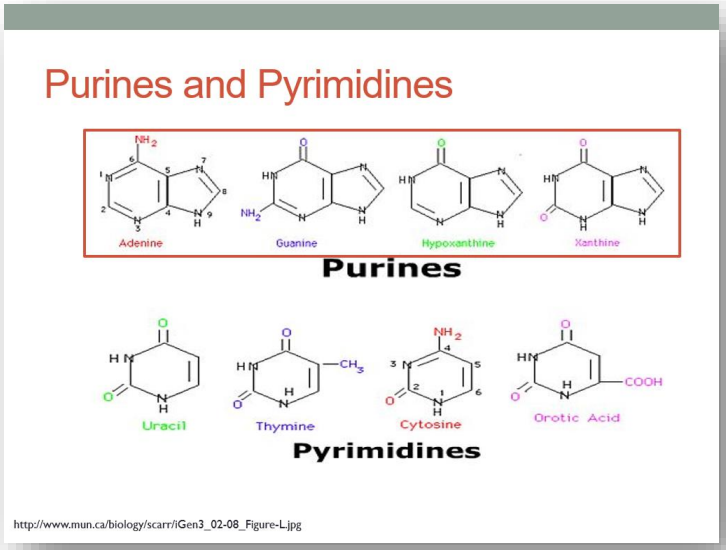
Azacytidine and Decitabine Clinical Considerations

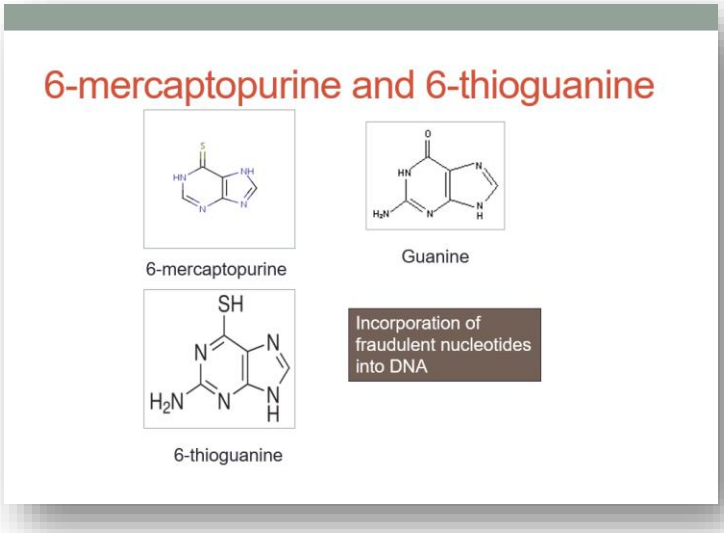
- Patients should be treated for a minimum of 4-6 cycles
  - May take multiple cycles to see an effect
- Dose adjustments may be needed depending on hematologic response
  - Some clinicians opt to treat through cytopenia
- Renal and hepatic dysfunction
  - Hepatic dysfunction

- No formal recommendations, but may need to hold dose until hepatic dysfunction resolves (T Bili or SGPT < 2 x ULN – decitabine specific)

- Renal dysfunction
  - No formal recommendations, but may need to hold dose until renal dysfunction resolves (Scr < 2mg/dL – decitabine specific)

Purine Antagonists





6-mercaptopurine (6-MP)

- Indication:
  - Acute lymphoid leukemia (ALL)
  - Administration:
  - Oral (PO)
    - 50mg tablet (scored) and 20 mg/mL suspension
    - 2.5 mg/kg/day (100-200 mg) PO; may increase after 4 weeks to 5 mg/kg daily or 1.5-2.5 mg/kg/day PO as single dose (usually with methotrexate)
- Toxicity
  - Myelosuppression
  - Gastrointestinal
  - Hepatoxicity including veno-occlusive disease
  - Immunosuppression
- Clinical Considerations
  - Drug Elimination
    - Necessary enzymes : Xanthine oxidase, thiopurine methyltransferase (TPMT)
  - Drug Interactions:
    - Interacts with allopurinol and febuxostat: Inhibit xanthine oxidase
      - Allopurinol and febuxostat inhibit mercaptopurine elimination
      - Concurrent use requires a 75% decrease in the 6-mercaptopurine dose
      - Genetic screening
    - Can test patients for TPMT deficiency
      - Patients deficient in TPMT will experience greater toxicity and require dose reduction
  - Genetic screening:
    - Can test patietns for TPMT deficiency
    - Patients deficient in TPMT will experience greater toxicity and require dose reduction

6-thioguanine (6-TG)

- Indication
  - Acute myeloid leukemia (AML): induction and consolidation therapy
- Administration:
  - Oral (PO)
    - Available as a 40mg tablet (scored)
    - 2 mg/kg/day PO; after 4 weeks may increase to 3 mg/kg/day if no improvement or myelosuppression
- Toxicity:
  - Myelosuppression
  - Gastrointestinal
  - Hepatoxicity
- 6-thioguanine: Clinical considerations

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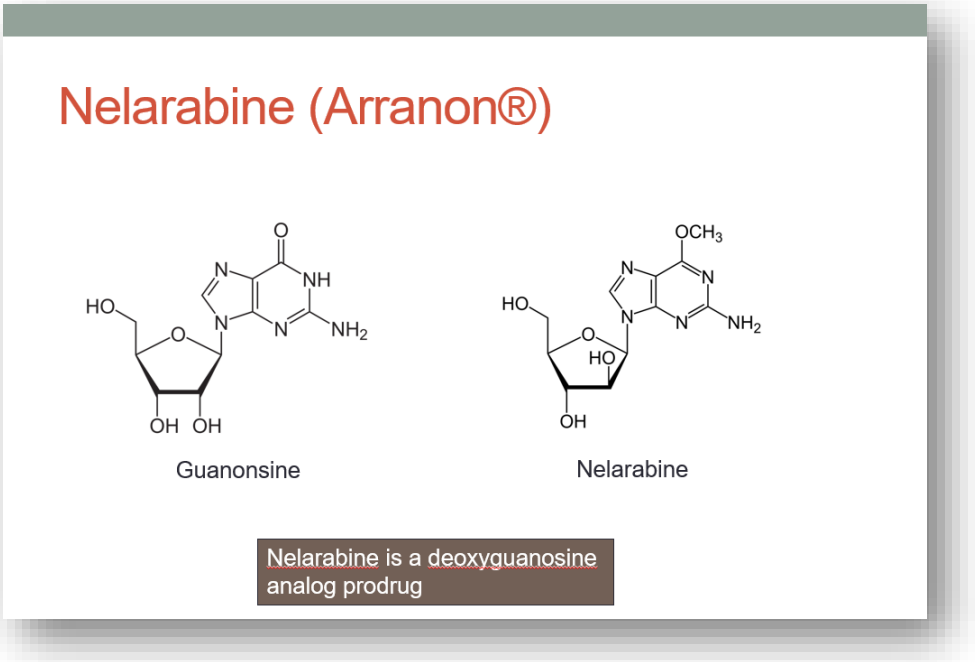
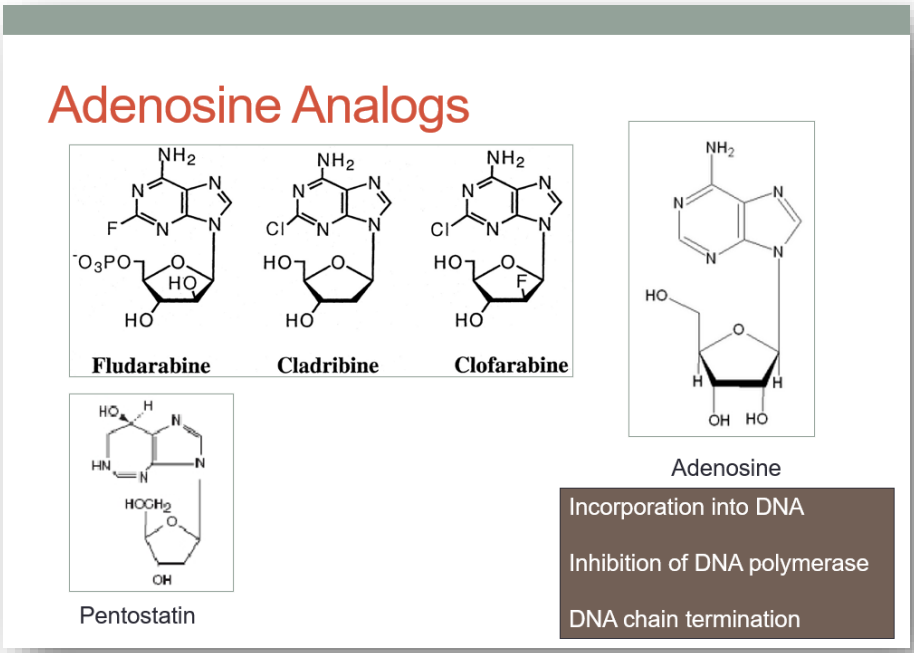
- Drug Elimination:
  - Necessary enzymes: Thiopurine methyltransferase (TPMT)
- Drug Interactions:
  - Does NOT interact with allopurinol and febuxostat (not a substrate for xanthine oxidase)
- Genetic Screening
  - Can test patients for _____
    - Patients deficient in TPMT will experience greater toxicity



Nelarabine (Arranon®)

- Indication:
  - T-cell acute leukemia
  - T-cell lymphoblastic lymphoma: Used in relapsed or treatment refractory disease
- Administration:
  - IV: Adult - 1500 mg/m^2 IV over 2 hours on days 1, 3 and 5 q 3 weeks; *Administered undiluted
- Toxicity:
  - Neurotoxicity (somnolence, neuropathy, encephalopathy)
  - Myelosuppression
  - Fatigue
  - Nausea and vomiting (minimal)
- Dose Adjustments:
  - Discontinued for neurologic events grade ≥ 2
  - May delay treatment for hematologic toxicity



Fludarabine (Fludara)

- Indication
  - B-cell CLL
  - Acute myeloid leukemia
  - NHL (follicular)
  - Lymphodepletion
- Administration
  - IV: 25mg/m2 IV daily x 5 days – 28-day cycle
  - Oral: 40 mg/m^2 PO daily x 5 days – 28-day cycle
- Toxicity:
  - Myelosuppression
  - Immunosuppression with resulting infections
    - PJP prophylaxis
  - Neurotoxicity (at high doses)
  - Interstitial pneumonitis
    - Seen when combined with pentostatin
- Clinical considerations
  - Renal:
    - CrCl ≥ 70 mL/min = Full dose; CrCl 30-70 mL/min = 20% dose reduction; CrCl < 30 mL/min = Avoid use

- Counseling points:
    - CD4 and CD8 counts may ↓ to 150 to 200/mm^3 after 3 courses of therapy
    - Lymphopenia may persist for 1 year
        - = ↑ infection risk
        - Monitor for fever and symptoms of infection

Question: Which of the following antibiotics is NOT an effective form of PCP prophylaxis for patients receiving purine analogs (including fludarabine):

A. Bactrim (sulfamethoxazole/trimethoprim)
B. Pentamidine
C. Ciprofloxacin
D. Dapsone
E. Atovaquone

Pentostatin (Nipent)

- Indication: Hairy-cell leukemia, CLL, GVHD
- Other uses: B-cell CLL
- Administration:
    - IV: 4 mg/m^2 IV every other week
- Toxicity:
    - Nausea
    - Immunosuppression
    - Nephrotoxicity
    - CNS disturbances
    - Interstitial pneumonitis: Seen when combined with fludarabine

Pentostatin (Nipent) Clinical Considerations

- Renal:
    - Dose reduction recommended in renal dysfunction:
        - CrCl ≥ 60 mL/min = Full dose (4 mg/m2 q 14 days); CrCl 41-60 mL/min = 3 mg/m^2 q 14 days; CrCl 20-40 mL/min = 2 mg/m^2 q 14 days
- Counseling Points
    - Hydration
        - Give at least 1-2 liters of D5NS to ensure a sufficient urine output (administer before and after dose)

Cladribine

- Indication: Hairy-cell leukemia, AML
- Administration
    - IV: 0.09 mg/kg/day CIVI daily x 7 days
        - Dilute in normal saline (not D5W)
            - D5W causes increased degradation of cladribine

- Toxicity
  - Myelosuppression
  - Fever (up to 40% of patients)
  - Immunosuppression with resulting infection complications
  - Rash
  - Neurotoxicity (high dose)

- Dose Reductions
  - Can consider dose reductions with renal impairment or neurotoxicity

Clofarabine (Clolar)

- Indication
  - Acute lymphoid leukemia (pediatric ages 1-21) or adult acute myeloid leukemia
- Administration:
  - IV
    - Pediatric: 52mg/m^2 IV daily x 5 days
    - Adult: 30-40 mg/m^2 IV daily x 5 days
- Toxicity
    - Myelosuppression or infections
    - Elevated liver function tests
    - Rash
    - Capillary leak syndrome
    - Can be administered with steroids to help prevent capillary leak syndrome
- Clinical Considerations
  - Renal
    - CrCl ≥ 60 mL/min = Full dose; CrCl 30 – 60 mL/min = 50% dose reduction; CrCl ≤ 30 mL/min = Not recommended
  - Other considerations:
    - Discontinue with signs of capillary leak syndrome or grade 3 toxicites
      - Can consider 25% dose reduction when organ function returns to baseline; Requires close monitoring

Miscellaneous

Hydroxurea (Hydrea)

- Indication:
  - Resistant chronic myeloid leukemia
  - Head/neck cancer (squamous cell)
- Other uses:
  - Acute myeloid leukemia
  - Polycythemia vera
  - Essential thrombocytosis
  - Sickle cell anemia
- Administration: Oral (500 mg capsule)

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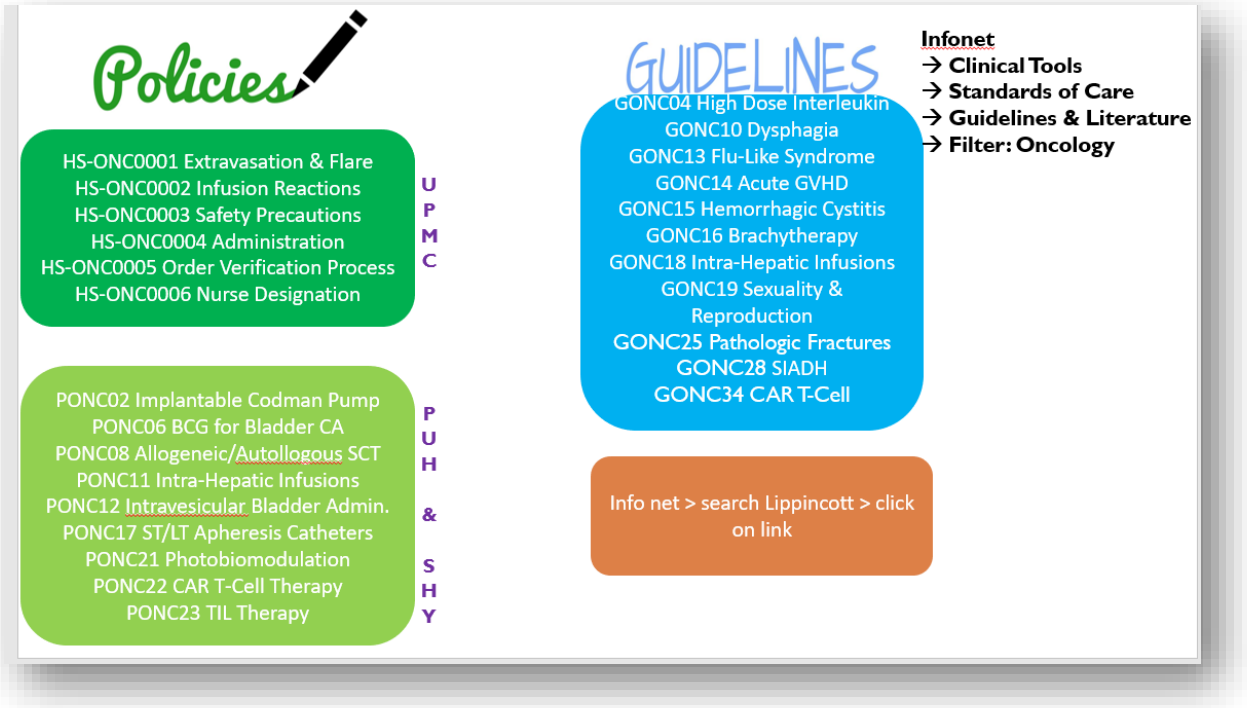
- Dosing:
  - 15 mg/kg/day
  - Highly individualized and titrated
  - Renally cleared (patients with CrCl < 60ml/min may need dose reduction)

- Clinical Considerations
  - Toxicity:
    - Myelosuppression
    - Secondary malignancy
    - Cutaneous vasculitis/Rash
    - Macrocytosis
    - GI
    - Hypersensitivity
  - Other considerations:
    - Lack of macrocytosis may indicate noncompliance in chronic users

Antineoplastic Therapy Administration

Standards and Guidelines

- Oncology Nursing Society (ONS)
  - Oncology certification
- National Comprehensive Cancer Network (NCCN)
- State Board of Nursing
  - Adequate knowledge and skills required for areas of highly specialized practice; Graduate nurses can administer chemotherapy in Pennsylvania (PA)
- Occupational Safety and Health Administration (OSHA)
  - Safe handling and disposal practices National Institute for Occupational Safety and Health (NIOSH) Guidelines
- Centers for Disease Control (CDC)
- American Society of Health System Pharmacists (ASHP)
- Institutional policies: The ultimate guide to practice
  - UPMC Infonet: PUH/SHY and UPMC Hillman Cancer Center Policies



Preparing Patient for Chemo

- Informed consent
- Pre-Treatment evaluation
- Patient education

Informed Consent

- Required for standard and investigational therapy in PA
- Check institutional policy: Who may obtain consent
- Check institutional policy: Time limit on consent is one year at UPMC
- Reconsent for additional therapy, change in regimen, change in route
    - Not if something is held or dose is reduced

Who can obtain consent? POLICY HS-0NC0005

- Medical oncologist or hematology attending physician who oversees the patient's care is responsible for and must obtain informed consent
- The physician may delegate the responsibility to
    - Qualified fellow: Those who have completed the 3-month fellowship training
    - Chemotherapy credentialed APP

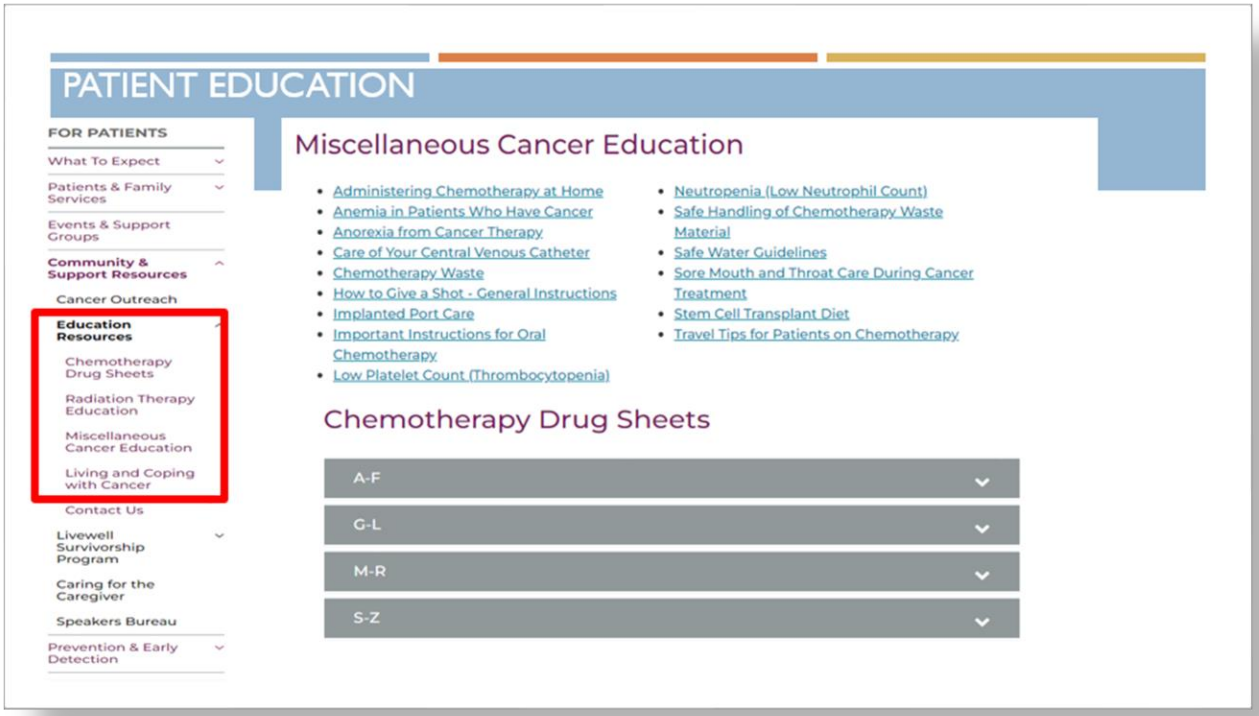
The consent process should include

- Discussion of the patient's diagnosis
- Treatment plan
- Goals of therapy
- Known risks and benefits
- Alternative care options

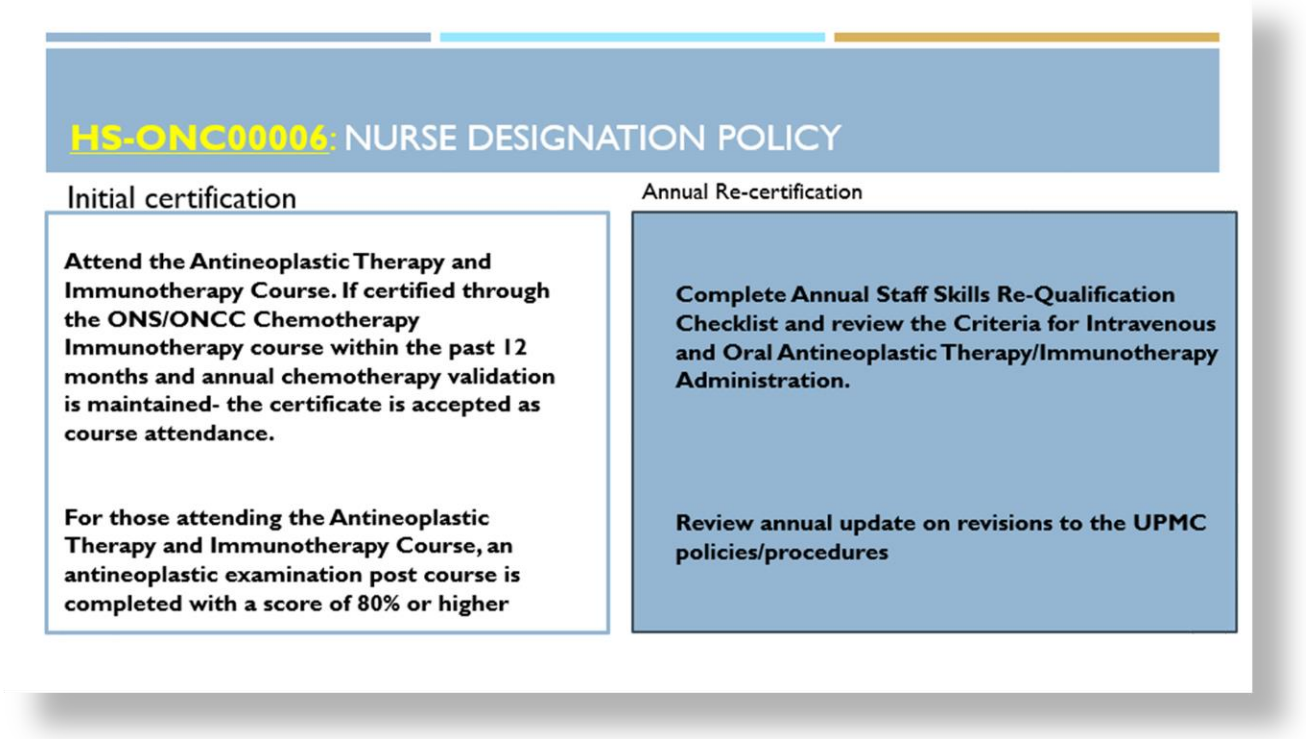
The attending/qualified fellow/chemotherapy credentialed APP shall sign the consent form after the consent discussion occurs

Pretreatment Evaluation

- Medical/surgical history
- Tumor type, stage/grade
- Recent treatment
- Psychosocial status: ECOG vs. Karnofsky
- Nutritional status
- Performance status
- Insurance/financial issues


PATIENT EDUCATION
FOR PATIENTS
What To Expect
Patients & Family Services
Events & Support Groups
Community & Support Resources
Cancer Outreach
Education Resources
Chemotherapy Drug Sheets
Radiation Therapy Education
Miscellaneous Cancer Education
Living and Coping with Cancer
Contact Us
Livewell Survivorship Program
Caring for the Caregiver
Speakers Bureau
Prevention & Early Detection
Miscellaneous Cancer Education
Administering Chemotherapy at Home
Anemia in Patients Who Have Cancer
Anorexia from Cancer Therapy
Care of Your Central Venous Catheter
Chemotherapy Waste
How to Give a Shot - General Instructions
Implanted Port Care
Important Instructions for Oral Chemotherapy
Low Platelet Count (Thrombocytopenia)
Neutropenia (Low Neutrophil Count)
Safe Handling of Chemotherapy Waste Material
Safe Water Guidelines
Sore Mouth and Throat Care During Cancer Treatment
Stem Cell Transplant Diet
Travel Tips for Patients on Chemotherapy
Chemotherapy Drug Sheets
A-F
G-L
M-R
S-Z

Nurse Designation Policy: HS-ONC0006



Chemotherapy Administration Process

- Pre-pharmacy
  - Consent
  - Orders
  - First RN check
  - Second RN check
  - Orders sent to pharmacy
- Pharmacy
  - Pharmacist checks orders
  - Orders entered into EMAR
  - Drug is mixed and sent to treating RN
- Pre-administration
  - Chemo nurse redlines order
  - Administer premeds, check _____ access
- Administration
  - 2 RNs check chemo against paper orders
  - 2 RNs check chemo against EMAR
  - 2 patient identifiers by 2 RNs
  - Administration and rate verification
  - Documentation and Patient monitoring

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Order and Verification Process for the Administration of Antineoplastic and Immunotherapy BRM Drugs:HS-ONC0005

Pre-Pharmacy

- Consent
- MD approves orders
- RN #1 checks orders
    - Correct patient first and last name and second identifier
    - Informed consent for treatment
    - Allergy
    - Height and weight
    - Labs
    - Regimen
    - Verify correct pathway is ordered for the patient and patient diagnosis match
    - Premeds/Fluids
    - BSA/Dose
    - Verify appropriate insurance verification has been completed
    - Additional order section(s) are reviewed
    - Both antineoplastic drug qualified nurses initial the appropriate section on the paper chemotherapy order form
- RN #2 checks orders
- Sent to pharmacy

Chemotherapy Order Verification

- Performed independently by two chemotherapy-qualified nurses
- Performed by pharmacists mixing drug
- Order is checked for potential errors or omissions
- Critical step in eliminating errors
- Review required lab studies and compare to specified treatment parameters
    - Pregnancy test
    - Complete blood count
    - Liver function tests
    - Renal function
- Compare drug dosage and schedule to the protocol, known regimen, past orders, and/or physician documentation
- Verify dosage calculations
    - Ordered dose within ___ of nurse calculations
- Review completeness of order
    - Necessary hydration and anti-emetics
    - Protectants and rescue agents
    - Hypersensitivity pre-medication
    - Monitoring: Neurological checks, urine pH, vital signs
- Ensure emergency drugs are available

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- Verify physician's signature
    - UPMC: Fellow cannot write orders independently in first three months
- Verbal orders, (not used in outpatient settings) emergency situations, order clarification, and faxed orders
    - Check your hospital policy

Chemotherapy Administration: Drug Verification

- Once medication received from pharmacy two nurses check the drug against the chemotherapy order
    - Patient: Name, FIN, MRN, date of birth
    - Drug
    - Dose
    - Route of administration
    - Time/date
- Second RN must document that information has been checked
    - Follow institutional guidelines
- Administering RN then proceeds to patient to administer chemotherapy
- NIOSH guidelines
    - Dictate hazard level of drug
    - Recommend protective equipment to wear for each hazard level

Chemotherapy Dosing

- Usually based on body surface area (m^2) or weight
- Accurate height and weight are essential
- Dosing weight may be based on ideal weight or adjusted weight rather than actual weight
    - Ideal body weight (IBW): Used to ensure safe dosage in the case of obesity or fluid overload purposes
    - Stem cell transplant (SCT) regimens
    - Adjusted body weight (ABW): Used if the ideal body weight and actual body weight differ by > 30%
        - Also ensures safe dosage
- Dosing weight i.e., actual, ideal, or adjusted is a physician decision

Height and Weight

- Coats, hats, and shoes must be removed
- Do not rely on information provided by the patient: Need accurate measurements
- Must be verified by two RNs for a new patient this must be documented in electronic medical record (EMR)
- Metric: Kilograms and centimeters is the correct method of measurement
- English: Pounds and inches is the correct method of measurement

All calculations and formulas can be found in appendix A: Antineoplastic Therapy Formulas

Conversion Equations

Metric/English Conversions

1 kg = 2.2 lbs.

kg = lbs. ÷ 2.2

lbs. = kg x 2.2

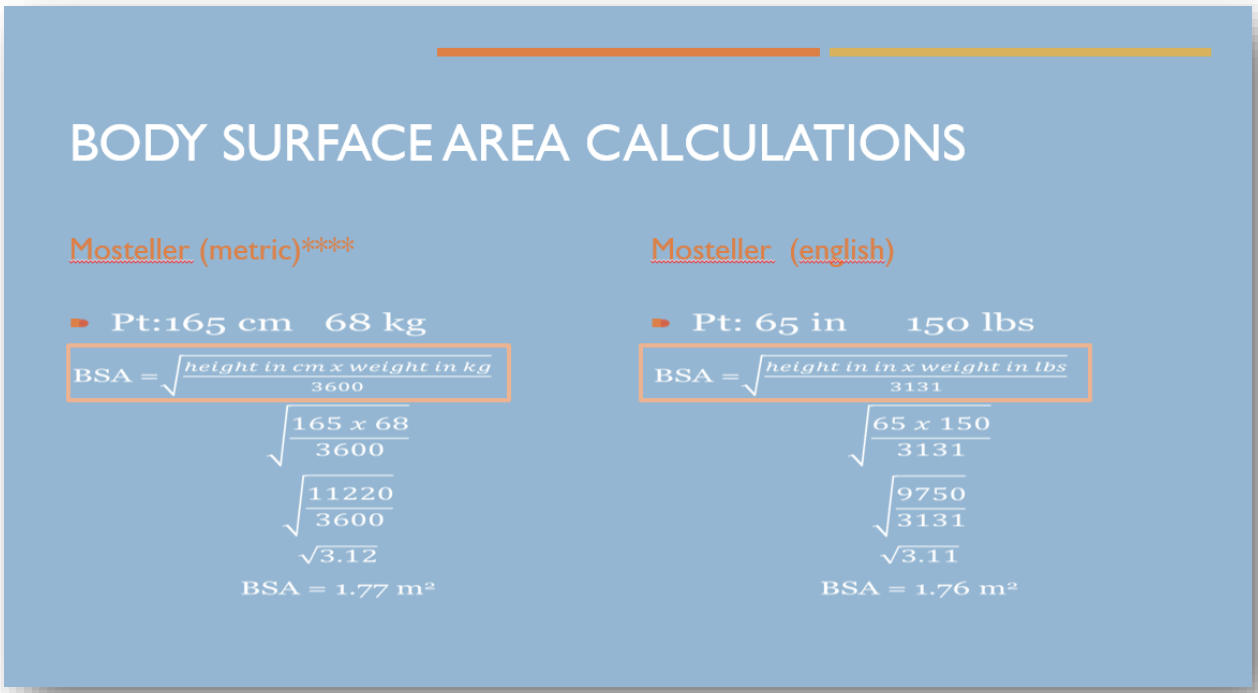
2.54 cm = 1 in

cm = in x 2.54

in = cm ÷ 2.54

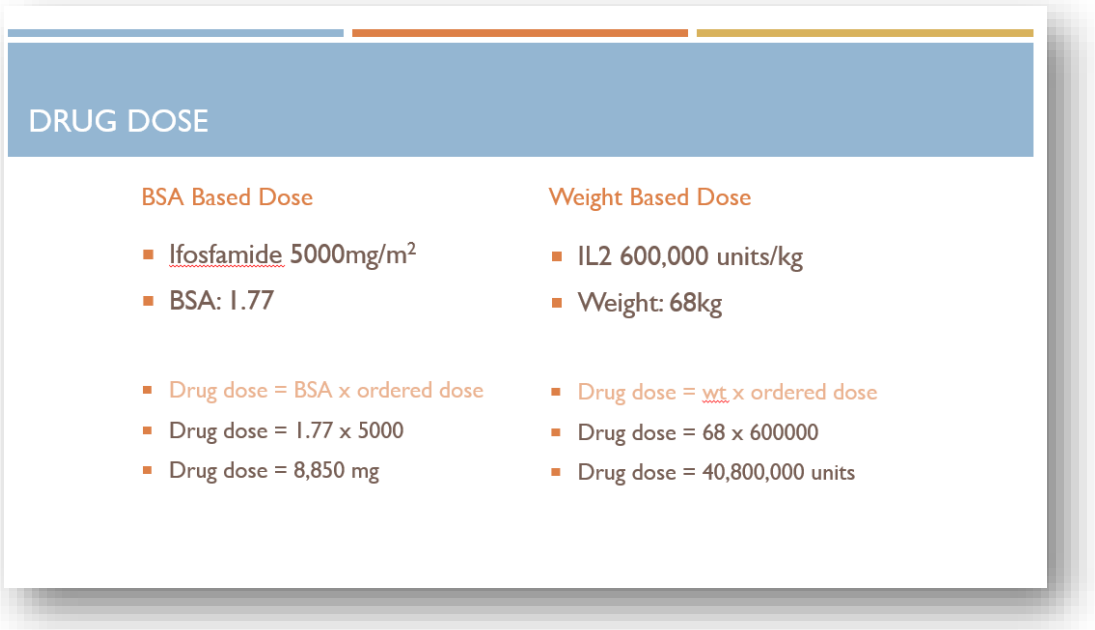
Ideal Body Weight Calculation Formula

Male	Female
50 kg for 5 feet	45.5 kg for 5 feet
add 2.3 kg for every inch over 5 feet	add 2.3 kg for every inch over 5 feet
IBW = 50kg + 2.3 (in > 5 ft)	IBW = 45.5 kg + 2.3 (in > 5ft)
Example: 5’2”	Example: 5’2”
IBW = 50 kg + 2.3(2)	IBW = 45.5 kg + 2.3 (2)
IBW = 50 + 4.6	IBW = 45.5 + 4.6
IBW = 54.6 kg	IBW = 50.1 kg



Drug Dose

- After patient's weight has been determined we need to determine the drug dose
- Drugs can be dosed based on weight or BSA
- Determine if actual, ideal, or adjusted body weight is to be used
    - Weight, actual, ideal or adjusted is determined by physician



Practice Equations

Pt is 65 inches and weighs 150 pounds

1. Body Surface Area (BSA) Calculations
   Drug Dose: BSA Based Dose
   Ifosfamide 5000mg/m^2
   BSA: _____

   Drug dose = BSA x ordered dose
   Drug dose = _____ x 5000
   Drug dose = _____

2. Weight Based Dose
   Weight: 68kg
   IL2 600,000 units/kg

   Drug dose = weight x ordered dose
   Drug dose = _____ x 600000
   Drug dose = _____ units

Carboplatin Dosing

- Calvert Formula is used to calculate the dose of carboplatin
  - Dose in mg = AUC x (GFR + 25)
- Step 1: Calculate the creatinine clearance (CrCl) from the serum creatinine
  - CrCl = glomerular filtration rate (GFR) in Calvert Formula

_____
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CARBOPLATIN DOSING

- Calvert Formula is used to calculate the dose of Carboplatin
  - Dose in mg = AUC x (GFR + 25)

- **Step 1**: calculate the creatinine clearance (CrCl) from the serum creatinine
  - CrCl = glomerular filtration rate (GFR) in Calvert Formula
- Cockcroft-Gault Equation:
  - $\text{CrCl (male)} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum creatinine}}$
  - $\text{CrCl (female)} = \left(\frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum creatinine}}\right) \times 0.85$

- Step 2: Calvert formula
  - Dose in mg = AUC x (GFR + 25)
  - Area under the curve (AUC)
- Glomerular filtration rate (GFR): Estimated from serum creatinine clearance
  - If estimating GFR, recommends that clinicians consider capping estimated GFR at a maximum of 125 mL/min
- Physician provides numerical value for the AUC in the chemotherapy order
- AUC = measure of drug exposure
  - Used to determine how long a patient should have active drug in the body
  - Higher AUC = more toxicity

Male

Step 1: Creatinine clearance
- Age: 65, Weight: 70 kg
  Serum creatinine 1.2
  - CrCl = _____

Step 2: Calvert formula
- AUC 4
- Carboplatin dose = _____

Female

Step 1: Creatinine Clearance
- Age: 65, Weight: 70 kg
  Serum creatinine: 1.2
  - CrCl = _____

Step 2: Calvert formula
- AUC 4
- Carboplatin dose = _____

General Principles for Chemo Dosing
- Always write out full name of drug
- Decimal points
  - Zero always before the decimal
    - Correct: 0.5 Incorrect: .5
  - Zero never after the decimal (trailing zeros)
    - Correct: 5 Incorrect: 5.0
- Physician or Pharmacist responsible for calculation of BSA and dose
  - No “blank” spaces
- Rounding of final dose may be done by physician or pharmacist

Drug Dose Summary
- Physician determines which weight to use
  - Actual weight
  - Ideal body weight
  - Adjusted body weight
- Determine if drug is weight based vs. BSA based
- Calculate drug dose
  - Dose = drug x BSA
  - Dose = drug x weight
  - Carboplatin = use Calvert formula

True or False A patient's chemotherapy has been dose reduced due to nephrotoxicity. The patient needs a new consent.

Which of the following are used to calculate antineoplastic therapy
A. Actual body weight
B. Adjusted body weight
C. BSA
D. All of the above

_____
_____
_____
_____
_____

Which of the following is not associated with carboplatin dosing?

A. AUC
B. Bilirubin level
C. Calvert formula
D. Creatinine clearance

Adjusted Body Weight Formula

- If actual body weight and ideal body weight differ by > 30%
- Used with dose intensification
- Limited data available
- Adjusted body weight = 0.25(actual body weight - IBW) + IBW
- Example
    - Actual weight: 100 kg Ideal weight: 50 kg
        - 50% difference in weight
        - Adjusted body weight = 0.25(100 – 50) + 50
        - Adjusted body weight = 0.25(50) + 50
        - Adjusted body weight = 12.5 + 50
        - Adjusted body weight = 62.5 kg

Chemotherapy Order Verification

- Compare drug dosage and schedule to the protocol, known regimen, past orders, and/or physician documentation
- Verify dosage calculations
    - Ordered dose within 10% of nurse calculations
- Review completeness of order
    - Necessary hydration and anti-emetics
    - Protectants and rescue agents
    - Hypersensitivity pre-medications
    - Monitoring: Neurological checks, urine pH, vital signs
- Ensure emergency drugs are available
- Verify physician's signature
    - UPMC: Fellow cannot write orders independently in first _____ months
- Verbal orders, (not used in outpatient settings) emergency situations, order clarification, and faxed orders
    - Check your hospital policy

10% Rule

- Complete your calculation
- Determine if the physician dose is within 10% of your calculation
- Safe dose administration range:
    - Upper limit = your dose calculation x 1.1
    - Lower limit = your dose calculation x 0.90

_____
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_____
_____
_____

OR

- Find 10% of your dose = 0.1 x your dose
  - Upper limit = your dose calculation + 10%
  - Lower limit = your dose – 10%

10% Rule Example

Your calculated dose: 75 mg Physician calculated dose: 100mg

Method 1:

Upper limit = 75 x 1.1
Upper limit = 82.5
Lower limit = 75 x 0.90
Lower limit = 67.5

Method 2:

10% of your dose = 75 x 0.1
10% of your dose = 7.5
Upper limit = 75 + 7.5 Lower limit = 75-7.5
Upper limit = 82.5 Lower limit = 67.5

Safe dose administration range is 67.5- 82.5 mg

Is this dose safe to administer? Yes/No

EMR Order Check

- You must check the MAR/EMR against the
  - _____ chemotherapy order sheet
  - _____ order sheet
- Ensures that there were no errors when _____ drug, doses, or administration time into the computer
- Done _____ chemotherapy administration
  - UPMC: First nurse to hang the chemo is responsible
- Documentation
  - Written orders: Redline (inpatient)
  - Electronic orders: Document that the EMR verified

_____
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_____

Dosing considerations for the transgender patient

Dosing considerations for the transgender patient

3. Calculated CrCl in Transgender Patients

It is recommended to obtain a 12 or 24 hour urine collection for accurate GFR calculation. If 12 or 24 hour urine collection is not possible, the below chart is to be used to calculate CrCL based on Cockcroft-Gault equation.

Duration of Hormonal Gender-Affirming Therapy	***Recommendation for IBW Dosing***	***Recommendation for Estimation of Renal Function***
Patient not taking gender-affirming hormonal therapy or started therapy < 1 month prior to admission.	Calculate IBW based on sex at birth.	Calculate renal function based on sex at birth.
Initiation of therapy < 6 months prior to admission.	Consider calculating IBW based on sex at birth.	Consider calculating estimated renal function based on sex at birth.
Initiation of therapy ≥ 6 months prior to admission.	Consider calculating IBW based on gender identity.	Consider calculating estimated renal function based on gender identity.

Webb, AJ; McManus D; Rouse GE, et al. Implications for medication dosing for transgender patients: A review of the literature and recommendations for pharmacists. Am J Health-Syst Pharm. 2020: 77: 427-33.

When determining BSA in a transgender patient, BSA should be calculated as done for any other patient. When BSA is calculated using ABW or IBW, as clinically indicated or per the MD request, the ABW or IBW should be calculated using the chart below with UPMC standard ABW and IBW equations. The calculated weight will then be used to calculate BSA.

Duration of Hormonal Gender-Affirming Therapy	***Recommendation for IBW Dosing***	***Recommendation for Estimation of Renal Function***
Patient not taking gender-affirming hormonal therapy or started therapy < 1 month prior to admission.	Calculate IBW based on sex at birth.	Calculate renal function based on sex at birth.
Initiation of therapy < 6 months prior to admission.	Consider calculating IBW based on sex at birth.	Consider calculating estimated renal function based on sex at birth.
Initiation of therapy ≥ 6 months prior to admission.	Consider calculating IBW based on gender identity.	Consider calculating estimated renal function based on gender identity.

Webb, AJ; McManus D; Rouse GE, et al. Implications for medication dosing for transgender patients: A review of the literature and recommendations for pharmacists. Am J Health-Syst Pharm. 2020: 77: 427-33.

True or False The physician orders 100mg of drug X. When you calculate the patient's dose you calculate that the patient should receive 85mg of the drug. The ordered medication is ok to give to patient.

During the order verification process what information must be verified:

A. Antiemetic regimen
B. Chemotherapy dosing
C. Hydration
D. Schedule of drugs
E. All of the above

Preparation of Chemotherapy in Pharmacy

- Print a copy of orders
- Send copy to Pharmacy
- Place original orders in patient's chart
- Pharmacy enters orders and mixes drug

Pre-Administration and Red Lining

- Nurse must check the written order against the electronic order. This is called red lining

- Review administration procedure with patient and family
- Administer premedication to patient
- Verify medication for vesicant properties of drug and allergy potential
- Verify compatibility with other IV medications/IVF
- Check for patent venous access
- PPE and safety equipment in the room

Chemotherapy Administration Process: Drug Verification

- One chemo nurse needs to verify with a second chemo or non-chemo nurse in the presence of the patient
- Two patient identifiers
- Date to be administered
- Day of treatment (for multiple day therapy)
- Correct drug(s)
- Correct dosage(s)
- Order/sequence of administration
- Expiration dates/and times
- Appearance and physical integrity of drug
- Route and rate of administration
- The infusion device is checked to ensure that drug/tubing is connected, device is turned on, and the infusion device/rate is programmed correctly

Intravenous Access

- New intravenous sites are recommended for vesicant agents, smallest gauge and shortest length catheter
- Must verify patency and blood return
    - Lowering bag
    - Gentle aspiration
    - Site must be free of edema and leakage

Peripheral IV Sites to Avoid

- Sites of limited/obstructed flow
- Sites with impaired vascular supply
- Previous radiation therapy sites
- Bruised, edematous, or areas of phlebitis
- Sites distal to veins that have experienced venipuncture in the past 24 hours
- The use of the antecubital and hand veins

Central Line Patency

- Central line patency may be verified by gentle aspiration of blood, dye study
    - Chest x-ray shows tip placement but not flow through catheter
    - Dye study may be needed to view flow of fluid from catheter

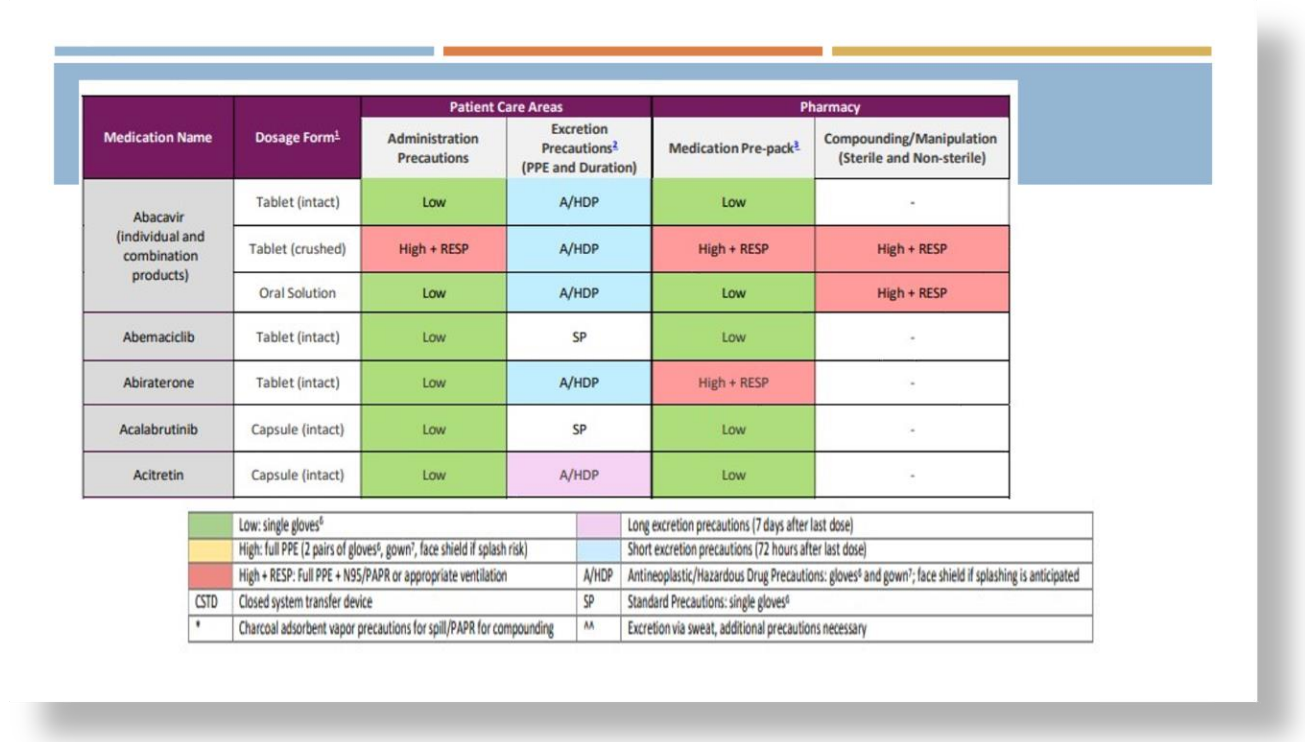
_____
_____
_____
_____
_____

- Use of declotting agent
    - If absence of blood return, notify physician
    - Anticipate order for chest x-ray to verify placement
    - If placement verified, ask for an order for a declotting agent

Nursing administration of injectable and oral antineoplastics and immunotherapy: HS-ONC0004

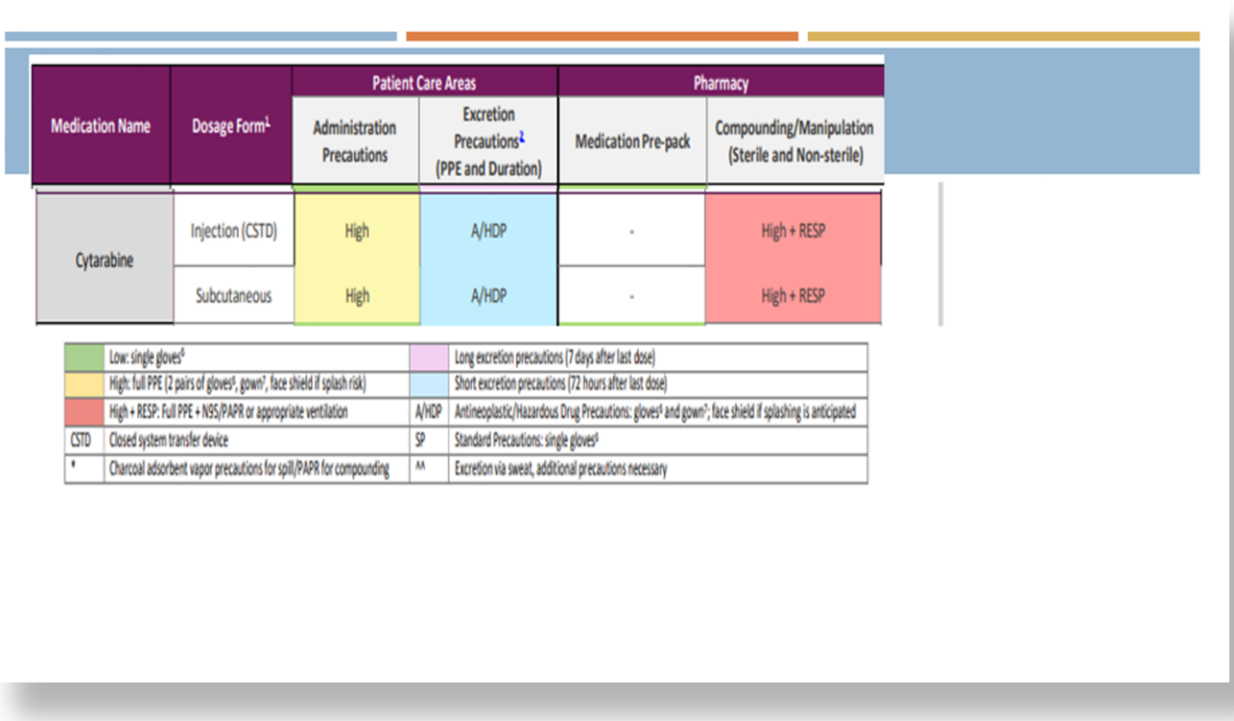
Chemotherapy Administration Protective Attire and Equipment

- Approved chemotherapy gown made of polyethylene-coated polypropylene with closed front, long sleeves with elastic or knit cuffs
- Two pairs of disposable powder-free approved chemotherapy gloves (one glove under cuff of gown and one over)
- Use syringes and intravenous sets with closed system device for all hazardous IV infusions
- Use disposable, absorbent, plastic-backed pad underneath intravenous push work area to absorb droplets of the drug that may inadvertently be spilled on work surface
- Signage for hazardous excretion managed and chemotherapy IV infusion as indicated
- Individuals who are pregnant, lactating, or trying to conceive should avoid contact with traditional cytotoxic chemotherapy agents



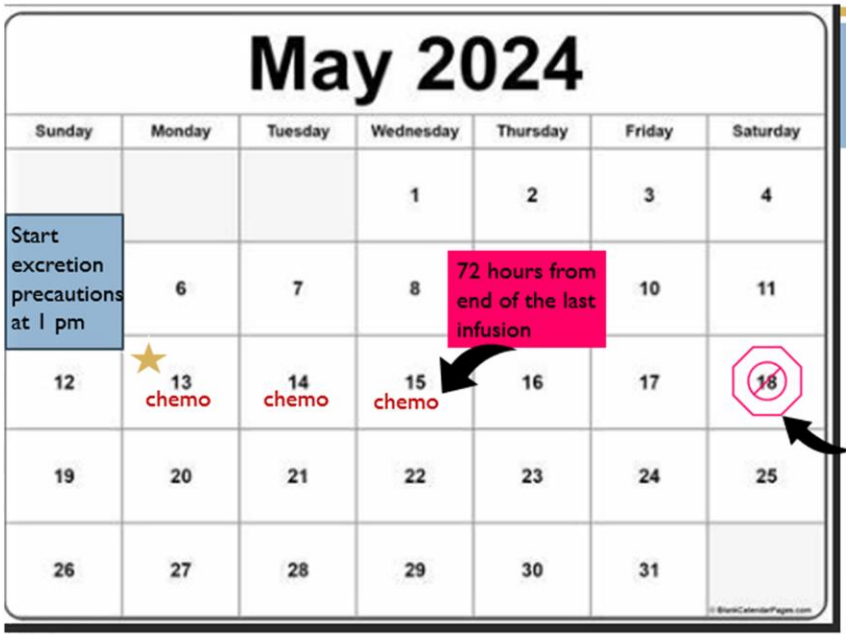
Medication Name	Dosage Form[1]	Patient Care Areas		Pharmacy	
		Administration Precautions	Excretion Precautions[2] (PPE and Duration)	Medication Pre-pack[3]	Compounding/Manipulation (Sterile and Non-sterile)
Abacavir (individual and combination products)	Tablet (intact)	Low	A/HDP	Low	-
	Tablet (crushed)	High + RESP	A/HDP	High + RESP	High + RESP
	Oral Solution	Low	A/HDP	Low	High + RESP
Abemaciclib	Tablet (intact)	Low	SP	Low	-
Abiraterone	Tablet (intact)	Low	A/HDP	High + RESP	-
Acalabrutinib	Capsule (intact)	Low	SP	Low	-
Acitretin	Capsule (intact)	Low	A/HDP	Low	-

	Low: single gloves[5]		Long excretion precautions (7 days after last dose)
	High: full PPE (2 pairs of gloves[5], gown[7], face shield if splash risk)		Short excretion precautions (72 hours after last dose)
	High + RESP: Full PPE + N95/PAPR or appropriate ventilation	A/HDP	Antineoplastic/Hazardous Drug Precautions: gloves[5] and gown[7]; face shield if splashing is anticipated
CSTD	Closed system transfer device	SP	Standard Precautions: single gloves[5]
*	Charcoal adsorbent vapor precautions for spill/PAPR for compounding	^^	Excretion via sweat, additional precautions necessary



Medication Name	Dosage Form[1]	Patient Care Areas		Pharmacy	
		Administration Precautions	Excretion Precautions[2] (PPE and Duration)	Medication Pre-pack	Compounding/Manipulation (Sterile and Non-sterile)
Cytarabine	Injection (CSTD)	High	A/HDP	-	High + RESP
	Subcutaneous	High	A/HDP	-	High + RESP

	Low: single gloves[5]		Long excretion precautions (7 days after last dose)
	High: full PPE (2 pairs of gloves[5], gown[7], face shield if splash risk)		Short excretion precautions (72 hours after last dose)
	High + RESP: Full PPE + N95/PAPR or appropriate ventilation	A/HDP	Antineoplastic/Hazardous Drug Precautions: gloves[4] and gown[7]; face shield if splashing is anticipated
CSTD	Closed system transfer device	SP	Standard Precautions: single gloves[5]
*	Charcoal adsorbent vapor precautions for spill/PAPR for compounding	^^	Excretion via sweat, additional precautions necessary



EXAMPLE

cytarabine

Q 24 hrs for 3 days infuse over 1 hour

Start at 1 pm on 5-13-24

Start May 13th at 1 pm

End May 18th at 2 pm.

Start excretion precautions at the start of the first infusion. And end precautions 3 or 7 days from the END of the last infusion

What

is a Closed-System Drug Transfer Device?

- **Closed system**[1]: a device that does not exchange unfiltered air or contaminants with the adjacent environment.
- **Closed-system drug transfer device (CSTD)**[1]: a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system.

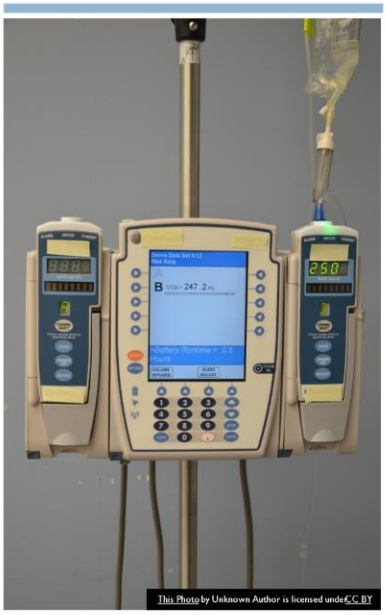
OnGuard® meets the NIOSH definition of a closed-system drug transfer device in testing using actual antineoplastic agents.

Why

use a Closed-System Drug Transfer Device?

- **Hospital and OPM pharmacists** are at risk from the effects of exposure to hazardous drugs.
- **Pharmacy Techs and Nurses** are at risk from the effects of exposure to hazardous drugs.
- **Exposure to Cytotoxic agents** may have a toxic effect.
- **Exposure** to chemotherapy agents may leave a healthcare worker at risk for all the negative effects of the agent.

CDC and NIOSH have stated that certain drugs, such as chemotherapy agents, can be associated with a variety of both short-term and long-term health effects.[1,2]



USE IV PUMP SAFEGUARDS WHEN GIVING ANTINEOPLASTIC THERAPY

- The Alaris pumps have Guardrails feature for medications used (chemo and others)
- Guardrails is a safety feature to protect from giving an incorrect dose of medication
- Guardrails provides dosing rate and amount infusion double/triple check for safety
- May need to plug in patients weight or BSA

IV Chemotherapy Administration

- At bedside, RN checks patient using two identifiers
- Wash hands
- Don protective attire
- Use pump IV pump with safeguards when giving antineoplastic therapy
- Administer chemotherapy
- Shorter infusions first

Intravenous Push

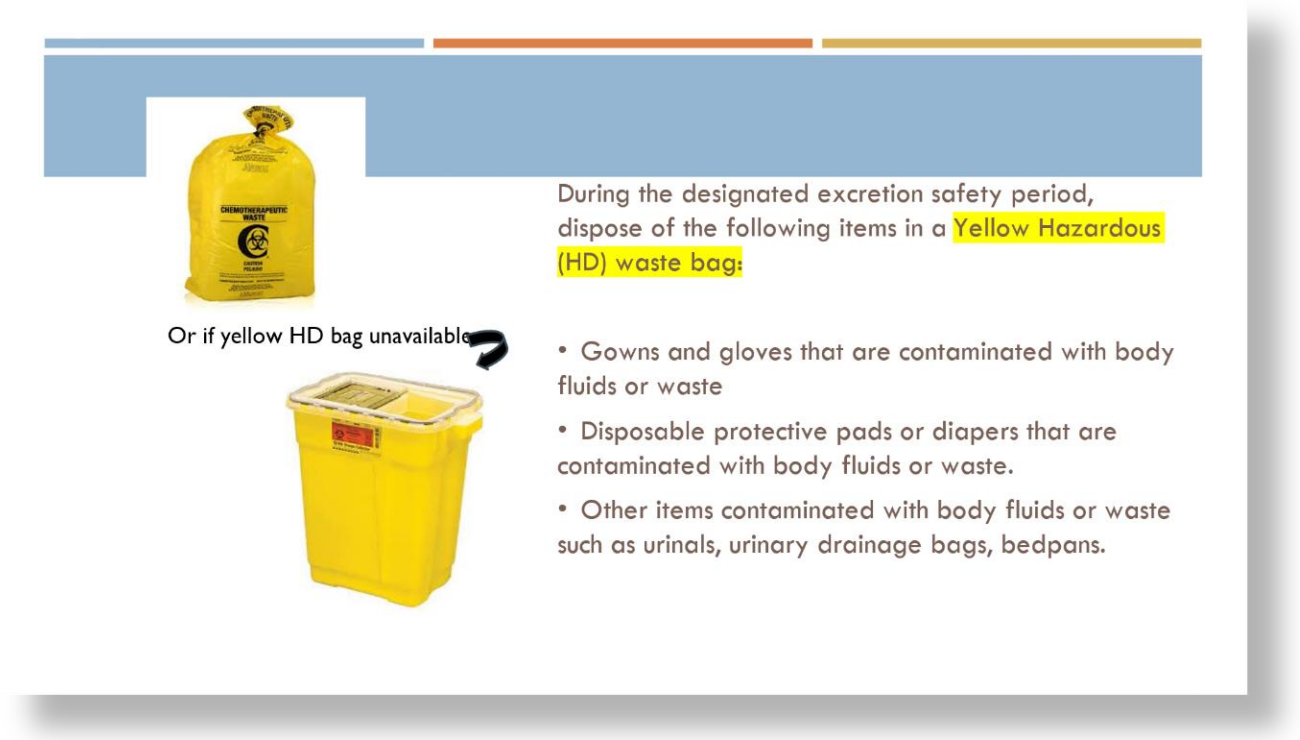
- Do not administer directly through hub of intravenous catheter, use gravity IVF
- Push slowly enough to permit some IV solution to flow along with drug
- Cannula inserted at y-site closest to patient
- Do not inject faster than _____ml/min
- Check blood return every 2-3 cc of the drug and stop for signs of extravasation
- Flush line when complete
- Dispose of all material in the appropriate container

Intravenous Infusion

- Two RN check: Verification of correct patient and dose at the bedside
- Connect infusion directly to intravenous catheter or to y site (closest to patient) through a maintenance solution

_____
_____
_____
_____
_____

- Second nurse must verify pump settings and tubing connections
- Continuous infusion of vesicants must be through a _____ _____
- Monitor Intravenous site throughout infusion as per policy
    - Vesicant infusions require more frequent monitoring



Leaving Chemotherapy Area

- Hang “High Alert Medication” sign on IV pump
    - If something happens to patient while they are not on the floor, this sign alerts untrained staff to the hazardous nature of chemotherapy
- Avoid with vesicant infusions
- Alert receiving area of chemo infusion
- Consider need to interrupt chemotherapy if patient going for procedure or surgery

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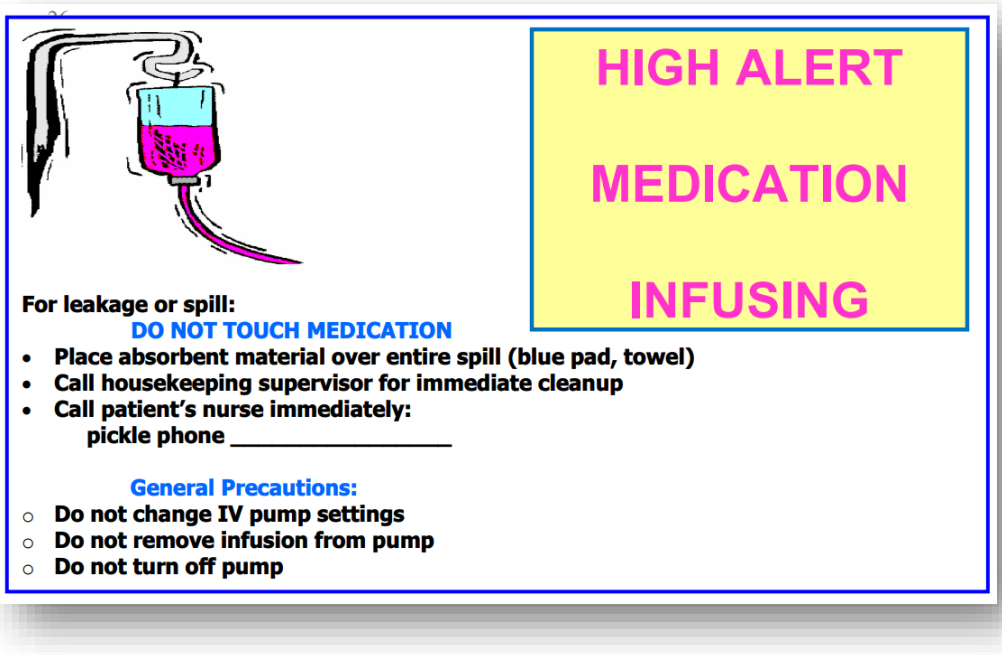


Oral Chemotherapy Administration

- Chemotherapy drug should be placed in separate medicine cup than any other medications
- Watch the patient take the drug
- Give patient emesis basin: If patient does vomit, you must check emesis to see if drug has been vomited
    - If drug has been vomited, notify physician for further instruction

Documentation

- Time
- Drug
- Dosage
- Route
- Assessment/location/patency of venous access
- Duration and sequence of administration
- Patient education
- Double check process

Safety Precautions Related to Chemotherapy and Biologics: HS-ONC0003

Disposal and Excretion Safety

- Appropriate yellow container/bag: Seal when ¾ full
- Excretion safety precautions for 3 or 7 days
- Posted sign in inpatient room

_____
_____
_____
_____
_____

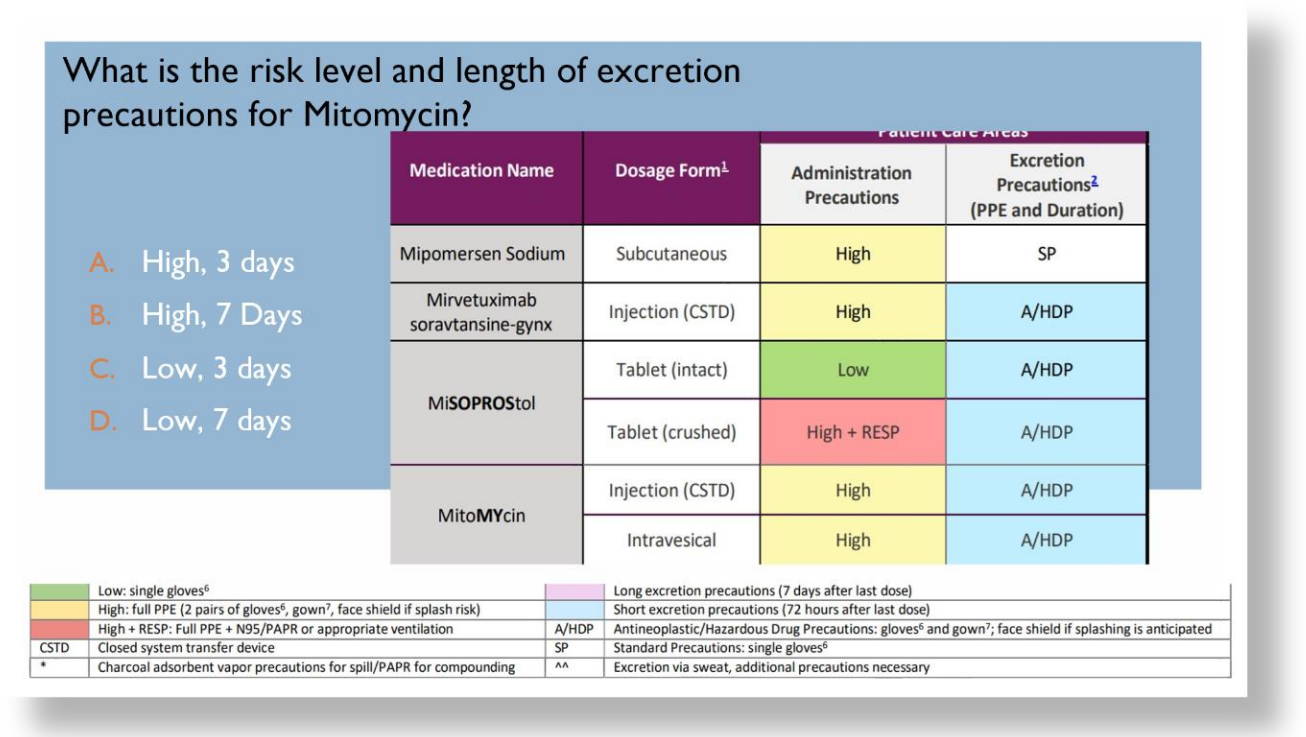
- Chemotherapy gloves for handling body fluid
- Gown, goggles/face shield may also be needed to protect from splashing
- Flush toilet immediately, no double flush in hospital setting
- Limit unnecessary specimen collection
- Teach patient, family, friends about excretion safety

True or False Vesicant antineoplastic agents should be administered first.

A. True
B. False

During chemotherapy administration, the second nurse is used to verify all of the following information except:

A. Administration time/rate
B. Antineoplastic drug
C. Correct patient
D. Presence of blood return

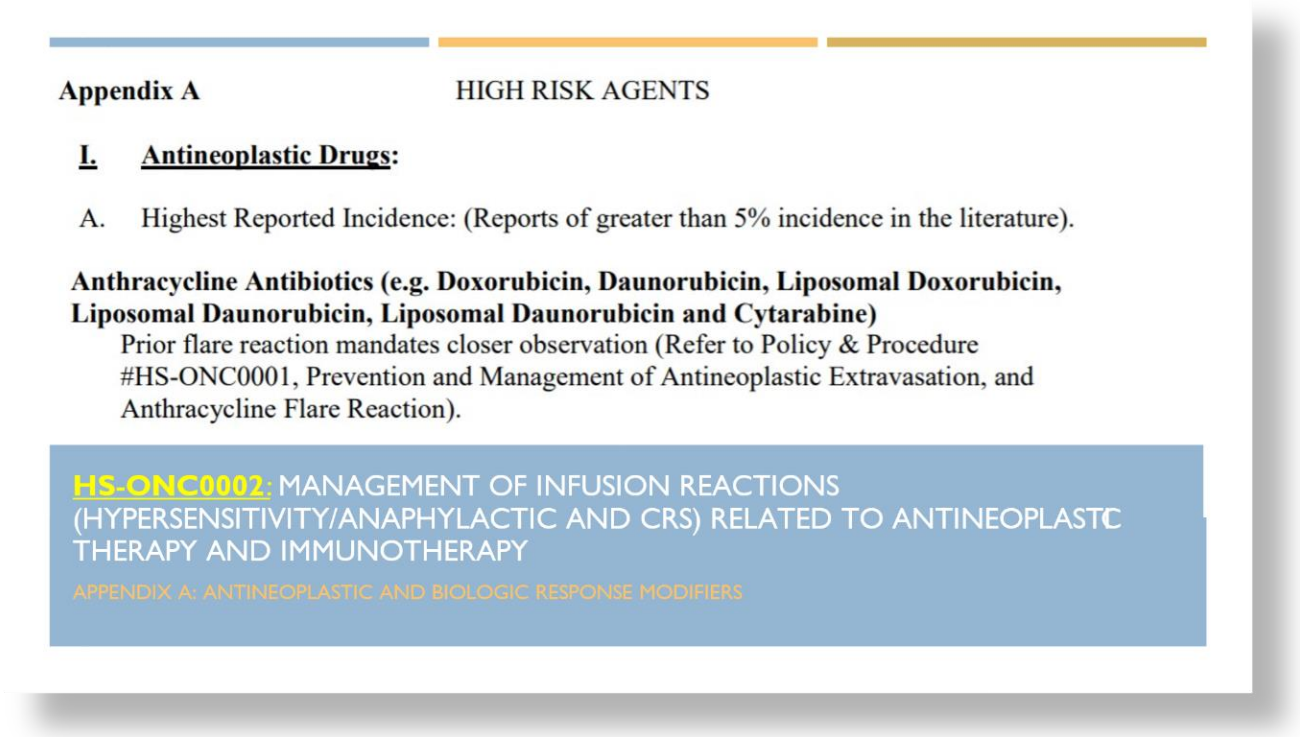


What is the risk level and length of excretion precautions for Mitomycin?

A. High, 3 days
B. High, 7 Days
C. Low, 3 days
D. Low, 7 days

Medication Name	Dosage Form[1]	Patient Care Areas: Administration Precautions	Patient Care Areas: Excretion Precautions[2] (PPE and Duration)
Mipomersen Sodium	Subcutaneous	High	SP
Mirvetuximab soravtansine-gynx	Injection (CSTD)	High	A/HDP
MiSOPROStol	Tablet (intact)	Low	A/HDP
	Tablet (crushed)	High + RESP	A/HDP
MitoMYcin	Injection (CSTD)	High	A/HDP
	Intravesical	High	A/HDP

	Low: single gloves[6]		Long excretion precautions (7 days after last dose)
	High: full PPE (2 pairs of gloves[6], gown[7], face shield if splash risk)		Short excretion precautions (72 hours after last dose)
	High + RESP: Full PPE + N95/PAPR or appropriate ventilation	A/HDP	Antineoplastic/Hazardous Drug Precautions: gloves[6] and gown[7]; face shield if splashing is anticipated
CSTD	Closed system transfer device	SP	Standard Precautions: single gloves[6]
*	Charcoal adsorbent vapor precautions for spill/PAPR for compounding	^^	Excretion via sweat, additional precautions necessary



Appendix A HIGH RISK AGENTS

I. Antineoplastic Drugs:

A. Highest Reported Incidence: (Reports of greater than 5% incidence in the literature).

Anthracycline Antibiotics (e.g. Doxorubicin, Daunorubicin, Liposomal Doxorubicin, Liposomal Daunorubicin, Liposomal Daunorubicin and Cytarabine)
Prior flare reaction mandates closer observation (Refer to Policy & Procedure #HS-ONC0001, Prevention and Management of Antineoplastic Extravasation, and Anthracycline Flare Reaction).

HS-ONC0002: MANAGEMENT OF INFUSION REACTIONS (HYPERSENSITIVITY/ANAPHYLACTIC AND CRS) RELATED TO ANTINEOPLASTIC THERAPY AND IMMUNOTHERAPY

APPENDIX A: ANTINEOPLASTIC AND BIOLOGIC RESPONSE MODIFIERS

Management of Infusion Reactions (Hypersensitivity/anaphylactic and CRS) Related to Antineoplastic Therapy and Immunotherapy: HS-ONC0002

Antineoplastic drugs

- Highest reported incidence: Anthracycline antibiotics
  - Doxorubicin
  - Daunorubicin
  - Liposomal Doxorubicin
  - Cytarabine

Risk of Exposure

- Direct contact, aerosolization, ingestion
- Patient body fluids
- Chemo spills, break in line or chemotherapy container
- Malfunctioning equipment
- Reduce risk by
  - Hand hygiene and proper PPE
  - Preparation of drugs in designated area, preferably pharmacy hood
  - Keep food away from mixing and administration areas
  - Food and drugs in separate refrigerators
  - Avoid hand to mouth contact
  - Utilize closed system transfer device
  - Ensure secure connections of IV tubing setup

Management of Spills

- Stop further drug leakage if possible
- Ensure patient safety
- Cover spill
- Obtain Spill Kit
- Put on protective attire: Gloves, gown, mask, eye shield, booties, respiratory protection (fit-tested N-95 or PAPR)
- Use items/absorbent material in spill kit to clean spill
- Detergent wipe down x3 following product protocol
- Dispose of all contaminated materials in appropriate container
- Soap and water to clean skin
- Eye wash station for splashing in eyes

Contaminated Linens because of a drug spill or contact with body fluids that may contain residual hazardous drug residue because of incontinence, vomiting, or diaphoresis require special handling.

- Separate contaminated linen. Roll or fold contaminated areas into the center of the linen bundle so the driest areas are on the outside.
- Place linen into Yellow infectious linen bag and then into a second Yellow infectious linen bag.
- Place the double bagged Yellow infectious linen bag in the usual location for linen pick-up.

CHEMOTHERAPY OR HAZARDOUS DRUG CONTAMINATED LINEN

Antitumor Antibiotics

Two Classifications

- Anthracyclines
  - Doxorubicin
  - Daunorubicin
  - Epirubicin
  - Idarubicin
  - Mitoxantrone
    - Anthracenedione
- Miscellaneous Agents
  - Actinomycin D or Dactinomycin
  - Bleomycin
  - Mitomycin C

Anthracyclines

- Natural products
  - Actinobacteria *Streptomyces peucetius*
- Share a common, four-membered anthracene ring complex with attached sugar portion
  - Ring complex: Chromophore
  - Intense colors: Red, orange, yellow
- Widest range of clinical use in oncology
- Frequently used in combination with other chemotherapeutic agents

Pharmacokinetics

- Extensive tissue binding
  - Distribute rapidly to all body tissues, except in the central nervous system (CNS)
  - 75% protein bound in plasma
- Half-life: 20-30 hours
- Metabolized in liver and excreted in bile
- Urine: < 10% eliminated
  - Enough to color urine

Mechanism of Action

- DNA intercalation
  - Flat, planar molecules insert into double-helix of DNA lead to structure changes
- Oxygen free radicals formed
  - Quinone structure enhances reduction-oxidation reactions, promoting free radicals
- Target topoisomerase II
  - Accumulate double and single-DNA strand breaks

Toxicity

- Myelosuppression: Acute, dose limiting
  - Leukopenia, thrombocytopenia, and anemia
- Moderate to severe nausea/vomiting
  - Premedication is vital

- Alopecia: Total
- Mucositis
- Infertility
- Cardiac toxicity: Acute and chronic

Monitoring for Cardiotoxicity

- MUGA
    - LVEF > 50%
    - 15% decrease from baseline = Caution
- Signs and symptoms of congestive heart failure (CHF)
    - Shortness of breath (SOB)
    - Decrease in activity (DOE)
    - Peripheral edema
    - Enlarged heart

Cardiac Toxicity

- Acute cardiotoxicity
    - First 24 hours after drug administration
    - Not appear to be dose related
    - Self-limited
    - Rhythm disturbances
        - ST-T wave changes
        - Sinus tachycardia
        - Ventricular premature beats
    - No increase risks of future events

- Chronic Cardiotoxicity
    - Dose-limiting toxicity
    - Attributed to free radical formation within heart muscle
        - Disrupts excitation and contraction

- Chronic Cardiotoxicity Risk Factors
    - Total dose
    - Schedule
    - Previous chest irradiation
    - Elderly and very young
    - Females
    - History of cardiac disease/hypertension
    - Concurrent cytotoxic drugs with cardiac toxicity
        - Trastuzumab (Herceptin®), paclitaxel, cyclophosphamide

Cardiotoxicity prevention

- Scheduling
    - Bolus vs continuous IV infusion

_____
_____
_____
_____
_____

- Zinecard, ICRF-187 (dexrazoxane)
  - Only FDA approved agent
  - Disrupts iron-anthracycline complex and prevents reactive free radical formation

Treatment Options for Anthracycline Cardiotoxicity

- Stopping and/or changing therapy
- Standard of care for CHF
  - ACE inhibitors
  - Angiotensin receptor blockers (ARB)
  - Diuretics
  - Beta-blockers
  - Digoxin
  - Nitrates
  - Hydralazine

Extravasation

- Deep ulceration with necrosis
  - Raised red edges and necrotic centers
  - Heal slowly, if at all
- Management
  - Standard of Care: COLD compress
  - Application of cold pack to site
    - 30-60 minutes: Alternate off/on for 15 minutes X 24 hours
    - Elevate/rest extremity X 24-48 hours
  - Anecdotally useful is topical dimethylsulfoxide (DMSO)
- Totect (dexrazoxane)
  - Anthracycline extravasation
  - 1000 mg/m^2 IV day 1, and day 2, 500 mg/m^2 IV day 3
    - Maximum dose 2000 mg day 1 and 2, 1000 mg day 3
    - Administer over 1-2 hours
  - Treatment on days two and three should start same time as on the first day
  - Administered within six hours of the extravasation
  - Cold compresses should be discontinued at least 15 minutes prior to initiation

Drug Resistance

- Drug efflux pumps
- Topoisomerase II point mutations
- Topoisomerase II down regulation
- Enhanced expression of different forms of topoisomerase II
  - Alpha
  - Beta

Which of the following side effects must be monitored prior to starting therapy and during therapy with anthracyclines?

A. Hand-Foot syndrome
B. Cystitis
C. Cardiotoxicity
D. Pulmonary toxicity

Which of the following is the major route of metabolism with anthracyclines?

A. Kidney
B. Liver
C. Lungs
D. Intracellular

Doxorubicin (Adriamycin)

Indications

- Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), multiple myeloma
- Lung, ovarian, breast, gastric, thyroid, sarcoma, and pediatric cancers

Route of Administration

- IV push IV infusion, IV continuous infusion, hepatic arterial infusion

Dosing in Organ Dysfunction

- Dose reduce in hepatic dysfunction
- Based upon bilirubin
    - Bilirubin 1.2-3 mg/dl: Reduce dose 50%
    - Bilirubin 3.1-5 mg/dl: Reduce 75%
    - Bilirubin > 5 mg/dl: Omit dose

Cardiac Toxicity

- Most thoroughly characterized in class
- Cumulative dose: 400-550 mg/m^2

Additional Adverse Effects

- Red urine
- Hyperpigmentation of nail beds
- Tissue vesicant
- Facial flushing: Infusion too fast

Incompatibilities

- Heparin, dexamethasone, 5-FU, sodium bicarbonate, hydrocortisone, furosemide

Skin Reactions

- Dermatologic "flare"
    - During or immediately after injections

    - Redness and urticaria up the vein
    - Self-limiting: Approximately 30 minutes

Radiation Recall
- Reactivation of skin damage in sites of previous radiation therapy

Daunorubicin (Cerubine)

Indications
- Induction therapy for AML
- ALL

Route of Administration
- IV push, IV infusion
- Dosing in organ dysfunction

Dose Reduce in Hepatic Dysfunction
- Based upon bilirubin
- Severe renal dysfunction
- Creatinine > 3 mg/dL: Administer 50% of dose

Dosing Adjustment
- Bilirubin 1.2-3 mg/dl or AST 60-180 IU: Reduce dose 25%
- Bilirubin 3.1-5 mg/dl or AST > 180 IU: Reduce dose 50%
- Bilirubin > 5 mg/dl: Omit dose

Similar Potential for Cardiac Toxicity
- Total dose: 400-550 mg/m^2
    - Limited use (leukemia)
        - Clinically important cardiomyopathy is uncommonly seen

Incompatibilities
- Dexamethasone
- Heparin
- Sodium bicarbonate
- 5-FU

Idarubicin (Idamycin)

Indications
- Developed for treatment of AML
- Induction therapy for AML in adults

Route of Administration
- IV push over 10-15 minutes
- Dose: 12 mg/m^2/day for 3 days

Dosing in Organ Dysfunction
- No specific dose adjustments are recommended
- Less cardiotoxic toxicity than doxorubicin or daunorubicin in equivalent doses
    - Cumulative dose up to 150 mg/m^2

Other Adverse Effects
- Reddish urine
- Elevations in bilirubin and transaminases

Incompatibilities
- Dexamethasone
- Heparin
- Hydrocortisone
- Etoposide
- Methotrexate
- Vincristine
- 5-FU

Epirubicin (Ellence)

Indications
- Breast cancer

Route of administration
- IV push over 3-5 minutes

Dosage in organ dysfunction
- Dose reduce in hepatic dysfunction
- Based upon bilirubin or liver enzymes

Dosing Adjustments
- Bilirubin 1.2-3 mg/dl or AST 2-4 times ULN: Reduce dose 50%
- Bilirubin > 3 mg/dl or AST > 4 times ULN: Reduce dose 75%

Less cardiotoxic than doxorubicin
- Increase risk: Cumulative doses > 900 mg/m^2

Incompatibilities
- Heparin
- Alkaline pH solutions
- 5-FU

Liposomal Doxorubicin (Doxil) and Liposomal Daunorubicin (DaunoXome)

- Drug within liposome is protected from systemic degradation
    - Liposomes: Microscopic vesicles composed of a phospholipid bilayer that encapsulate active drugs
- Delivered in higher amounts to target tissues
- Cardiac toxicity is substantially less
- Extravasation injuries are less

Indication

- AIDS related Kaposi's Sarcoma, ovarian cancer, and breast cancer
- Newest indication: Multiple myeloma

Route of Administration

- IV infusion
- Initial rate: 1 mg/minute to minimize infusion reactions
    - Flushing, dyspnea, edema, fever, chills, rash, bronchospasm, and hypotension
    - Treatment: Slow infusion rate

Other Adverse Effects

- Palmer-plantar erythrodysesthesia
    - Dose adjustments
- Stomatitis
    - Dose adjustments
- Dosing in organ dysfunction
    - Based on bilirubin or liver enzymes

Doxil Dosing Adjustments

- Bilirubin 1.2-3 mg/dl: Reduce dose 50%
- Bilirubin > 3 mg/dl: Reduce dose 75%

Liposomal Daunorubicin (DaunoXome)

Indications

- First-line treatment for advanced HIV-associated Kaposi's Sarcoma

Route of Administration

- IV infusion

Dosing in Organ Dysfunction

- Adjust for impaired renal function
    - Creatinine > 3 mg/dL: 50% of dose
- Hepatic impairment based on bilirubin

Dosing Adjustments

- Bilirubin 1.2-3 mg/dl: Reduce dose 50%
- Bilirubin > 3 mg/dl: Reduce dose 75%

_____
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_____

Liposomal Daunorubicin and Cytarabine (Vyxeos)

- Acute myeloid leukemia: Newly diagnosed for therapy-related AML [t-AML] or AML with myelodysplasia-related changes [AML-MRC]
- Induction first cycle: Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 (liposomal) on days 1, 3, and 5
- Induction second cycle in patients who do not achieve remission with first cycle*:* Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 (liposomal) on days 1 and 3; the second induction cycle may be administered 2 to 5 weeks after the first induction cycle
    - If no unacceptable toxicity with previous cycle
- Consolidation: Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 (liposomal) on days 1 and 3; administer the first consolidation cycle 5 to 8 weeks after the start of the last induction; administer the second consolidation cycle 5 to 8 weeks after the start of the first consolidation cycle
- IV administration over 90 minutes (for induction and consolidation cycles) via an infusion pump through a central venous or peripherally inserted central catheter
    - Do not use an in-line filter
    - Flush the line with NS or D5W after infusion

Mitoxantrone (anthracenedione)

- Three-membered anthracene ring complex
    - No sugar group attached
- Intense blue color

Mitoxantrone (Novantrone)

- Anthracenedione
    - Synthesized for comparable antitumor activity to doxorubicin and improved safety profile
- Intercalating topoisomerase II inhibitor
    - Potential for free radical formation is less than with anthracyclines

Indications

- AML, NHL, breast cancer, prostate cancer
- Multiple sclerosis

Route of Administration

- IV push and infusion

Dosing in Organ Dysfunction

- No specific dose adjustments
- Moderate hepatic dysfunction
    - May dose reduce based on bilirubin

Cardiac Toxicity

- Reduced secondary to less free radicals

- Total cumulative dose: 160 mg/m^2

Ulceration with Extravasation
- Reduced because less free radicals
- Classified as vesicant

Other Toxicities
- Less than anthracyclines
- Blue-green discoloration of urine
- Blue tint to eyes and skin
- Alopecia: Selective for gray hair
- Jaundice, transient LFT increase

Incompatibilities
- Heparin, hydrocortisone

Valrubicin (Valstar)
- Carcinoma in situ of bladder, BCG-refractory disease, in patients not candidates for immediate cystectomy
- 800 mg intravesically once weekly for 6 weeks; solution should be retained for 2 hours (when possible) prior to voiding; delay therapy for at least 2 weeks after transurethral resection and/or fulguration

Precautions
- Bladder perforation or compromised bladder mucosa integrity
    - Delay therapy until bladder integrity is restored
- Cystectomy delay could lead to the development of metastatic bladder cancer; consider cystectomy if no complete response after 3 months of therapy
- Irritable bowel symptoms, severe; bladder spasm and spontaneous discharge of valrubicin instillate may occur
- Transurethral resection and/or fulguration; do not administer intravesical valrubicin within two weeks of transurethral resection and/or fulguration

Administration
- Use non-DEHP containing administration sets
- Insert urethral catheter and drain bladder; instill diluted solution slowly via gravity flow over several minutes
- Withdraw catheter; patient should void bladder after two hours

Adverse Effects
- Bladder pain, cystitis
- Dysuria, hematuria
- Incontinence, increased frequency of urination, nocturia
- Pain in urethra, spasm of bladder, urgent desire to urinate, urinary retention
- Urinary tract infectious disease

Anthracycline Review

- PRE-treatment
  - MUGA
  - Total dose
  - Total bilirubin
  - N/V
  - Infertility
  - Line access
  - Extravasation
    - Treatment: COLD compress
- Post-treatment
  - N/V
  - Bone marrow function
  - Cardiac toxicity
  - Alopecia
  - Mouth care

Cyclophosphamide, mitoxantrone, vincristine, prednisone (CNOP) could be used instead of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) for which of the following organ dysfunctions?

A. Liver
B. Heart
C. Kidney
D. Lungs

Miscellaneous Antitumor Antibiotics

Actinomycin D or Dactinomycin (Cosmegen)

- First actinomycin antibiotic isolated from *Streptomyces* species in the 1940s

Mechanism of Action

- Inhibits DNA and especially RNA synthesis
- Intercalates into DNA
- Generation of DNA strand breaks via interaction with topoisomerase II

Resistance

- Decreased drug accumulation within cells
- Overexpression of the multi-drug resistant (MDR) gene

Indications

- Pediatric tumors
- Sarcomas, testicular cancer, Wilm's tumor
- Potent radiation sensitizer

Pharmacokinetics
- Half-life 36 hours
- 20% excreted in urine and 13% in feces

Route of Administration
- IV push: 10-15 minutes

Toxicity
- Myelosuppression
  - Dose-limiting
  - Severe neutropenia and thrombocytopenia
  - Prolonged nadir: Delayed as long as 3 weeks
- Nausea/vomiting
  - Highly emetogenic
  - Can get worse each day
- Liver toxicity
- Diarrhea
- Alopecia
- Skin
  - Acne, rash, hyperpigmentation
- Fatigue
  - Extravasation: COLD compress
- Stomatitis
- Gastrointestinal pains

Doses
- Almost always in *micrograms*
- Dosing in organ dysfunction
  - No renal adjustment
  - Minimal hepatic metabolism: No adjustment

Bleomycin (Blenoxane)
- Mixture of cytotoxic glycopeptide antineoplastic antibiotics
  - Bleomycin A_2 (70%) and bleomycin B_2
  - Isolated from the fungus Streptomyces verticillus
- Strength is expressed in units of drug activity
  - Bleomycin 1 mg = 1 unit
- DNA-binding region and iron-binding are at opposite ends of the molecule

Mechanism of Action
- Requires binding of an iron-bleomycin complex to DNA
- Complex reduces O_2 to free oxygen radicals
- Oxygen free radicals: Lead to single and double strand DNA breaks
- Greatest effect on G2 phase of cell cycle

Mechanism corresponds to toxicities

- Lung toxicity

Lung Toxicity

- Dose limiting: > 400 units or single dose > 30 units
- Acute or chronic interstitial pneumonitis with interstitial pulmonary infiltrates
- Lung cell damage to vasculature from induction of cytokines and oxygen free radicals
    - Cannot move air from lung damage
- Lung damage
    - MOA of bleomycin + high oxygen in lungs = TOXICITY
- Symptoms
    - Cough/SOB
    - Crackles
    - Infiltrates on CXR
- Risk factors
    - Dose
    - Age > 70
    - Underlying lung disease
    - Prior irradiation to chest
    - Exposure to high concentration of oxygen
    - Renal impairment
- Prevention
    - Pulmonary function tests at baseline and with *each cycle*
    - Decrease bleomycin if decrease > 15% in either diffusion capacity of CO_2 or vital capacity

Indications

- Hodgkin's lymphoma, NHL, germ cell tumors, squamous cell of head and neck cancer, squamous cell of skin, cervix, vulva, and penis
- Sclerosing agent for malignant pleural effusions and ascites

Pharmacokinetics

- Eliminated renally: 45-70% in urine at 24 hours
- Half-life 2-4 hours
    - Renal failure: 20 hours
- Low protein binding

Toxicity

- Myelosuppression/immunosuppression
    - Mild
- Fever and chills
    - Schedule acetaminophen for 24 hours
- Mucocutaneous toxicity
    - Dose dependent
    - Mucositis, erythema, hyperpigmentation, alopecia, thickening of nail beds
    - Skin peeling leading to ulceration: 2nd to 3rd week

_____
_____
_____
_____
_____

- Mild nausea/vomiting
- Severe idiosyncratic reaction: Up to 30%
    - Increased in lymphoma patients
    - Similar to anaphylaxis
    - Hypotension, confusion, fever, chills, wheezing
    - Immediate or delayed for several hours

Treatment
- Volume expansion, vasopressors, antihistamines, steroids
- Give test dose
    - Give $\leq$ 2 units of bleomycin for the first two doses
    - Monitor vital signs every 15 min
    - Wait one hour before giving remainder of dose

Route of Administration
- Oral bioavailability is poor
- IV infusion, IV push, SC, or IM routes
- Intracavitary route for malignant pleural effusions and/or ascites
    - 45-55% absorbed systemically

Dosing in Organ Dysfunction
- Renal impairment

Incompatibilities
- Amino acid solutions, cefazolin, cisplatin, cytarabine, hydrocortisone, methotrexate, mitomycin, PCN, nafcillin, diazepam, furosemide

Dose Adjustments
- Creatinine Clearance: Reduce dose 25%
- Creatinine Clearance: Reduce dose 75%

Resistance
- Drug inactivation by increased expression of catabolic enzyme called bleomycin hydrolase
    - Low amounts in skin and lung: Toxicities
- Increased expression of DNA repair enzymes
- Decreased drug accumulation via decrease drug uptake in cell

Mitomycin C (Mutamycin)
- Extracted from *Streptomyces* species
- Aziridine agent related to nitrogen mustards

Mechanism of Action
- Acts like an alkylating agent
- Produces DNA cross linking

- Cell cycle non-specific
- Inhibits DNA and RNA synthesis

Pharmacokinetics
- Hepatic metabolism
- Half-life 23-78 minutes
- High concentrations found in kidney, tongue, muscle, heart, and lung tissue

Route of Administration
- IV infusion, IV push
- Flush with 5-10 mL of IV solution before and after drug administration

Indications
- Breast cancer, colorectal cancer, esophageal cancer, gastric carcinoma, pancreatic cancer

Dosing in Organ Dysfunction
- Renal adjustments may be indicated
- Consult individual protocols

Toxicity
- Myelosuppression
  - Prolonged nadir for 4- 6 weeks
  - Cumulative effects
- Cardiotoxicity: CHF in 3% -15%
  - Doses > 30 mg/m^2
- Fever
- Alopecia
- Interstitial pneumonitis
- Nail discoloration
- Nausea/vomiting
- Hemolytic uremic syndrome (HUS)
  - Renal failure
- Extravasation
  - Potent vesicant can lead to ulceration
- Neurotoxicity
  - Paresthesias

Extravasation Management
- Observe closely
- Few agents effective as antidotes
  - Dimethylsulfoxide (DMSO) may help
- Delayed dermal reactions are possible

Miscellaneous Antitumor Antibiotics: Review

Actinomycin D/ Dactinomycin

- Pre-treatment
  - N/V Worse each day
  - Extravasation: *Cold compresses*
  - Dose in micrograms
- Post-treatment
  - Nausea/vomiting
  - Bone marrow function
    - Prolonged nadir
  - Diarrhea/ GI
  - Alopecia
  - Rash

Bleomycin

- Pre-treatment
  - PFTs
- Severe idiosyncratic reactions
  - TEST DOSE
    - Renal function
    - Fevers/chills
- Post-treatment
  - Lung toxicity
  - Skin
  - Alopecia
  - Mucocutaneous toxicity

Mitomycin C

- Pre-treatment
  - Renal function
  - Extravasation
- Post-treatment
  - Bone marrow function
  - Prolonged nadir
  - Hemolytic uremic syndrome (HUS)
  - Cardiac toxicity
  - Alopecia

A patient on bleomycin must be monitored for which of the following?

A. Liver toxicity
B. Cardiac toxicity
C. CNS toxicity
D. Pulmonary toxicity

_____
_____
_____
_____
_____

A patient getting IV doxorubicin has line access issues and unfortunately, an extravasation event has occurred. Which of the following is best to manage the event?

A. Apply cold packs and have patient move/bend arm frequently
B. Apply cold packs and have patient rest extremity
C. Apply cold packs and SQ dexrazoxane
D. Apply hot packs and IV dexrazoxane

Chemotherapy Protectants

Chemotherapy Protectants

- Agents that are used to provide protection from the toxic effects of chemotherapy or radiation therapy

Protectant Drugs

- Leucovorin
- Dexrazoxane
- Amifostine
- Palifermin
- Mesna

Leucovorin

- Protectant for methotrexate (MTX)
    - MTX
        - Mechanism of action: Works in the S phase of cellular division and blocks the transformation of folic acid in the _____ division of the cell
        - Uses in oncology
            - Acute lymphocytic leukemia (ALL)
            - Meningeal leukemia
            - Head and neck cancer
            - Osteosarcoma in high doses with leucovorin rescue
        - _____ _____
        - Non-oncology uses
            - Rheumatoid arthritis
            - Psoriasis
            - Crohn's disease
- Use for rescue
    - Rescues bone marrow and mucosa from high dose MTX
    - Counteracts the mechanism of action for MTX
    - Actively competes with methotrexate for binding site
    - Caution: Leucovorin _____ the effects of 5FU
    -
- How Does Leucovorin Rescue Work?
    - Stops the action of MTX by blocking the transport pathways which allows folic acid to enter the cells
    - Can only rescue normal cells that have not already had lethal damage from the effects of MTX
    - Treatment with leucovorin must be initiated within _____ hours of starting high dose MTX to be effective

_____
_____
_____
_____
_____

- Administration and Drawing MTX Levels
    - Administration: Give an IV dose 24 hours after the start of MTX followed by oral doses every 6 hours until MTX levels are 0.05
        - Dose adjustments can be made for delayed clearance
        - BUN, creatinine, potassium, and urine output should be monitored together to assess for kidney function
    - Times to draw MTX levels
        - 4-hour IV bolus infusion: 24 hours after the start of the infusion followed by daily morning labs
        - 24-hour infusion: 24 hours after the completion of the bag, followed by daily morning labs
- When used with 5FU, increases the effects of MTX

Zinecard (dexrazoxane)

- Protectant for cardiomyopathy with _____
- Reduces incidence and severity of cardiomyopathy associated with doxorubicin when cumulative dose is ≥ 300 mg/m2
- Handle with chemo precautions
- May increase bone marrow depression and decrease tumor response rates if additional anthracyclines are administered
- Administration
    - Rapid IV infusion
        - Dexrazoxane must be IV infusion
    - Generic formulation IV infusion
        - Administer dexrazoxane first, then doxorubicin; Administer doxorubicin over 15 minutes within 30 minutes after beginning the infusion of dexrazoxane
    - Potential toxicities and side effects
        - Increases the bone marrow suppression caused by doxorubicin
        - May cause elevation in liver and renal function studies or pain at injection site

Ethyol (amifostine)

- Chemoprotectant
    - Protects from effects of cisplatin
    - Decreases cumulative nephrotoxicity and detoxifies active metabolites from cisplatin
    - May be considered for the reduction of grade 3 and 4 neutropenia associated with chemotherapy and/or in place of dose reduction or use of growth factor
- Radioprotectant
    - Protects parotid glands and anus/rectum if in the field
    - Prevents xerostomia and _____

_____
_____
_____
_____
_____

- Administration
    - Chemo protectant**:** Administer over 15 minutes: Give 30 minutes prior to cisplatin
    - Radio protectant:
        - Xerostomia: Administer over 3 minutes, give 15–30 minutes prior to the radiation treatment
        - Prostatitis: IV once daily prior to radiation therapy

- Side effects
    - Hypotension: Most common side effect, more common at chemoprotectant dose
    - Stop anti-hypertensives 24 hours prior to dose
    - Treat symptoms with IV fluids and Trendelenburg's position
    - Refer to dosing guidelines for patients experiencing hypotension
- Nausea: Pre-medicate with serotonin antagonist and decadron

Mesna

- Protectant from Ifex (ifosfamide)
    - Bladder protectant given with ifosfamide and cyclophosphamide to prevent hemorrhagic cystitis; used with high dose cyclophosphamide in stem cell transplant
    - Hemorrhagic cystitis
        - Sterile cystitis characterized by _____ _____
        - Clinical presentation:
            - Mild, moderate, or gross hematuria
            - Bladder irritation
            - Blood clots in the bladder leading to potential hemorrhage
    - Acrolein: Hepatic metabolite of both drugs that causes acute bladder irritation leading to hemorrhagic cystitis causing cell death
    - During hepatic metabolism of both cyclophosphamide and ifosfamide, acrolein is generated, filtered by the kidneys, and concentrated in the bladder
    - Excess acrolein causes damage to the integrity of the urothelium including swelling, bleeding, and ulceration of the bladder mucosa leading to hemorrhagic cystitis
- Administration: Can be given IV or PO
    - Can be given as IV bolus or continuous infusion as indicated by dose of ifosfamide given
- Common Side Effects
    - Can cause false positive result on urinalysis for ketones
    - May cause mild nausea, vomiting, and diarrhea

_____
_____
_____
_____
_____

Palifermin

- Protectant for mucositis following chemotherapy
- Prophylaxis for patients requiring autologous hematopoietic stem cell transplant
- Administration: Total of 6 doses is given
    - 60 mcg/kg/day IV bolus
    - Three consecutive days before myelotoxic therapy
        - Third dose should be given 24 to 48 hours prior to starting myelotoxic therapy
    - Three consecutive days after myelotoxic therapy
        - First doses should be administered after, but on the same day of, hematopoietic stem cell infusion and at least seven days after most recent dose of palifermin

- Common Side Effects
    - Edema
    - Erythema
    - Pruritus
    - Arthralgia
    - Dysesthesia
    - Fever
    - Pain
- Adverse events
    - Gastrointestinal: High lipase level in serum
- Special considerations
    - Potential for tumor growth in nonhematologic malignancies
    - Nursing mothers should either discontinue nursing or discontinue drug
- Nursing implications
    - Teach patient to report any changes in skin, signs and symptoms of infection, or changes in tongue or taste
    - Teach patient systematic oral cleansing after meals and at bedtime
    - Assess patient baseline pain

Cytokines, L-asparaginase, and Vaccine

Interferons (IFNs)

- Earliest biotherapy agents: Discovered 1957
- Family of glycoproteins
- Production stimulated by various infections
- Immunoregulatory functions
- Designated α, β, γ, and ω on the basis of association with certain producer cells and functions
- All animal cells can produce interferons
- Used as antineoplastics and biological response modifiers

Biological Activity

- Inhibition of oncogenes
- Inhibition of viral replication
- Promotion of dendritic-cell development
- Increase function of immune effector cells
- Antiangiogenic effects
- Direct antiproliferative effects

Types and indications

- IFN – β (beta): 1a and 1b
  - 1a: Avonex®, Rebif®, CinnoVex®
  - 1b: Betaferon®, Betaseron ® Extavia®, Ziferon®
- IFN- γ(gamma)/(Actimmune®)
  - Chronic granulomatous disease
- IFN- α (alpha): 2a and 2b
  - *2a* (Roferon®): Hairy cell leukemia, AIDS related Kaposi's sarcoma, CML, chronic hepatitis C, adjuvant in malignant melanoma
  - *2b* (Intron® A): Condyloma acuminatum (epidermal manifestation related to HPV cause increased cancer risk in men and women), hepatitis B and C, hairy cell leukemia, high risk malignant melanoma, AIDS related Kaposi's sarcoma
  - *2b* (Sylatron®): Melanoma

Pharmacokinetics

- Metabolized and excreted primarily by the kidneys
- Well-absorbed following SC/IM injection
- Peaks at 6-8 hours

Adverse Effects

- Flu-like symptoms
  - Fever, chills
  - Malaise
  - Arthralgias
  - Fatigue
- Hypotension
- Nausea
- Anorexia/weight loss
- Taste changes
- Xerostomia
- Myelosuppression
- Hypothyroidism
- CNS Effects
  - Impaired memory
  - Poor concentration
  - Seizures
  - Paranoia
  - Hallucinations
  - Psychoses
  - Somnolence
  - Irritability
  - Headache

Management of Adverse Events (AEs)

- Fatigue
  - Intermittent schedule better tolerated
  - Taking drug at bedtime may help
- Flu-like syndrome
  - Symptoms diminish with repeated injections
  - Best managed with acetaminophen

Dosing

- Single doses can range from 2 million international units (MIU) to at least 35 MIU/m^2
- Check specific protocol/regimen
  - Melanoma: 3 MIU once a day for 48 weeks
  - CML: 9 MIU QD x 18 months
  - Kaposi's sarcoma = 3 million IU's once a day for 12 weeks
- Verify brand of IFN ordered
- Dosing is not interchangeable
- Drug is given SC, IM, IV

Dose Modifications

Symptom	Evaluation	Hold dose/resume	Dose modifications
Anorexia	Calorie counts	Missing three meals for seven days in one week	33-50% with nutrition consult
Weight loss	> 10% weight loss	> 10% weight loss in one week	33-50% with nutrition consult
Fatigue	Thyroid function	≥ 2 level decline in ECOG PS in 1-2 weeks	33-50% after dose delay of 1-2 weeks
Depression	Beck's evaluation	Moderate depression for 1-2 weeks	33-50% with psychiatric eval
AST	Liver function tests (LFTs)	> 10 times normal limit: Return to 3 times normal limit	33-50% when LFTs are < 3 times normal limit
WBC	Absolute neutrophil count (ANC)	< 250/mm^2 for one week	33-50% when ANC > 250/mm^2

Nursing Care Issues

- Chemotherapy safety: Low risk
- Patient education
  - Self-injection
  - Signs/symptoms of infection, bleeding, nutrition
  - Symptom management
  - Skin care
  - Contraception
- Assess for depression on each contact
- Manufacturer tools for patient education and support

Which of the following toxicities associated with use of IFN improves with continued use?

A. Fatigue
B. Neutropenia
C. Flu-like symptoms
D. Depression
E. Anemia

Interleukin 2 (IL2)

- Biological response modifier
- Modifies the relationship between the immune system and the tumor

Biological Activity

- Promotes proliferation, differentiation, and recruitment of T and B cells, natural killer (NK) cells and thymocytes
- Causes cytolytic activity in lymphocytes that leads to interaction between immune system and malignant T-cells

- Can stimulate lymphokine-activated killer (LAK) cells and tumor-infiltrating lymphocyte (TIL) cells

Indications
- Labeled Indications
  - Metastatic renal cell carcinoma
  - Metastatic melanoma
- Additional use
  - Tumor infiltrating lymphocyte protocols

Pharmacokinetics
- Metabolized and excreted by the kidneys
- Half-life distribution: 13 minutes
- Elimination half-life: 85 minutes

Adverse Effects
- Cytokine-induced capillary leak syndrome (CLS)
  - Hypotension
  - Visceral edema
  - Dyspnea
  - Tachycardia
  - Arrhythmia
  - Atrial fibrillation
- Increased liver function tests
- Pruritis
- Flu-like symptoms
  - Fever, chills, rigors
  - Malaise
  - Arthralgias/myalgias
- Neurotoxicity
- Infection
- Oliguria, increase creatinine
- Myelosuppression
- Nausea/vomiting/diarrhea (N/V/D)
- Earliest manifestations of CLS: Hypotension, tachycardia, fever, chills
  - Approximately 2 hours after first dose
- Oliguria frequently manifests in first 24 hours
- Nausea/vomiting/diarrhea become more prominent toward end of therapy
- Edema, weight gain, and pulmonary congestion are progressive with treatment
- Majority of side effects reverse with termination of IL-2, most patients ready for discharge 1-3 days after last dose

Dosing
- Metastatic renal cell carcinoma and metastatic melanoma
  - 600,000 IU/kg every 8 hours for a maximum of 14 doses

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- Repeat after 9 days for a total of 28 doses/course
- Decision to continue treatment usually made after 2 courses (4 cycles)
- Continue if response observed

Monitoring

- Daily
  - CBC with diff
  - CMP
  - Weight
  - Strict I/Os
- Routinely
  - Vitals
  - I/Os

Dosing Issues

- No dose reductions: Only omissions
- Doses are held according to symptomatic recovery from the previous dose
- A delay longer than 3 doses (24 hours) should result in discontinuation of cycle
- Guidelines for delay or discontinuation of IL-2 therapy are based on relative and absolute criteria
- Action taken based on various criteria
  - With appropriate corrective therapy and time delay to allow for recovery, patients with relative criteria may receive another IL2 dose
  - Presence of any absolute criteria that is not easily reversible is generally an indication to stop therapy

Monitoring and Interventions

- Fever/chills/myalgias
  - Prophylactic APAP and indomethacin
  - Breakthrough
    - Increase frequency of indomethacin
    - Consider infectious disease workup if fever within first 24 hours
- Blood pressure
  - Goal SBP 80-90
  - Aggressive fluid resuscitation: Crystalloid > colloid
  - Vasopressor support PRN: Phenylephrine 40mg/100mL
    - 0.1 to 2mcg/kg/min
      - Titrate to response
- Renal function/urine output
  - Oliguria
    - IVF
    - Low-dose dopamine at 2 mcg/kg/min
  - Goal: Urine output 10 to 20 mL/hour
- Arrhythmias
  - Stop IL2 therapy
  - Correct electrolytes, anemia, hypoxia

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- Administer supportive care medications PRN
- Pulmonary
  - Goal: O_2 saturation ≥ 95%
  - If not maintained with supplemental O_2, discontinue
  - Do not use inhaled corticosteroids
- Edema/weight gain
  - Result of IVF for BP and oliguria
  - Do NOT use diuretics during therapy
    - Ineffective and dangerous
  - Patients will likely auto-diurese after completion of therapy
- Gastritis, nausea, vomiting, diarrhea
  - Prophylactic prochlorperazine 10 mg every 6 hours
  - PRN N/V
    - Haloperidol 0.5 mg every 6 hours IV
    - Prochlorperazine 10 mg every 6 hours IV
    - Ondansetron 4 mg every 6 hours IV
    - Lorazepam 0.5-1 mg every 6 hours PO/IV
- PRN diarrhea
  - Loperamide 2 mg every 3 hours PO
  - Diphenoxylate: 2.5 mg/atropine 25 mcg every 3 hours PO
- Electrolyte disturbances
  - Hypocalcemia
    - Goal: Maintain above lowest normal value
    - Calcium gluconate, 10% 1 gram over 1 hour IV
  - Hypokalemia
    - Goal: Maintain above 3.6 mmol/L
    - Potassium chloride 10 mEq over 1 hour IV
  - Hypomagnesemia
    - Goal: Maintain above lowest normal value
    - Magnesium sulfate 1 gram over 1 hour IV
  - Hypophosphatemia
    - Goal: Maintain above lowest normal value
    - Potassium phosphate 10-15 mmol over 6 hours IV
  - Hypoalbuminemia
    - Observe
- Hematologic
  - Anemia: Transfuse packed red blood cells (PRBCs) PRN
  - Thrombocytopenia: Transfuse PRN
- Acidosis
  - Infuse sodium bicarbonate IV PRN
- Dermatologic
  - Oatmeal baths and non-steroidal lotions
  - Hydroxyzine 10-20 mg PO every 6 hours
  - Diphenhydramine 25–50 mg IV/PO every 6 hours

- Neurologic
    - Agitation and/or combativeness
        - Haloperidol 1- 5 mg IV/IM PRN
    - Anxiety
        - Lorazepam 0.5 -1 mg PO/IV every 6 hours PRN
    - Insomnia
        - Temazepam 15 -30 mg qhs PO
        - Zolpidem 5 -10 mg qhs PO
- Infections
    - Prevention of line sepsis
        - Cephalexin 250 mg PO BID
        - Ciprofloxacin 500 mg PO BID
    - If infection is suspected, discontinue IL2 and treat

Nursing Care Issues

- Consider stopping antihypertensives before admission (24 hours)
- No steroids
- Chemotherapy safety: Low risk
- Drug incompatible with NSS: Only D5W
- Do not filter
- Incompatible with other drugs
- Use plastic IV bags
- Administer IV over 15 minutes

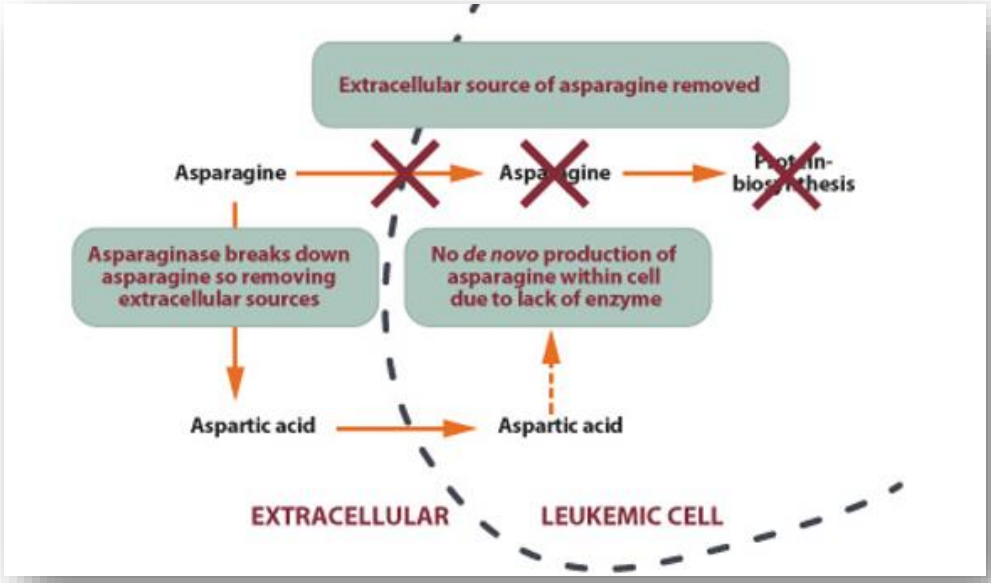
Which of the following symptoms is NOT related to capillary leak syndrome?

A. Hypotension
B. Fever
C. Tachycardia
D. Oliguria
E. Edema

L-asparaginase

- Enzyme that capitalizes on the inability of lymphoid cancer cells to synthesize L-asparagine: Amino acid
- Lymphoid cells need L-asparagine but can't make it
- Lymphoid cells depend on a circulating supply to proliferate
- L-asparaginase breaks down L-asparagine in the circulating supply (to NH3 and aspartic acid)
- Leukemia cells die due to the inability to acquire the amino acid: L-asparagine
- FDA-approved use: ALL

L-asparaginase Mechanism of Action



Two Types

- Erwinaze: Erwinia asparaginase
  - Derived from Erwinia chrysanthemi: A gram negative bacillus
- Oncaspar: Pegylated asparaginase
  - Pegylated: Attachment of a polyethylene glycol (PEG) polymer chain to another molecule
  - For patients with hypersensitivity to other formulations
  - Extended duration of action and possibly less immunogenicity
  - Most commonly used in pediatrics

Dosing and Administration

- Protocol/regimen/product specific dosing
- IM route
  - Not more than 2 ml in one site
  - Check site for erythema after dose
- IV route
  - Can cause phlebitis: Y-site through running IV
  - PEG formulation: Give in 100ml NSS/D5W over 1-2 hours

Pharmacokinetics

- Drug remains primarily in plasma and lymphatic fluid
- Cleared by phagocytes
- No renal or hepatic involvement
- Does not effectively cross the blood/brain barrier

Adverse Effects

- Pancreatitis
- Hepatitis
- Anaphylaxis
- DIC
- Fever

Hypersensitivity

- Occurred in ≥ 30% of patients receiving E. coli formulation
  - Reactions range from mild: Skin rash and urticaria, to life threatening, bronchospasm, anaphylaxis
- Seen in 14% of patients receiving Erwinia asparaginase
- Reactions less common with PEG-asparaginase
  - Attachment of a PEG to a drug or therapeutic protein can mask the agent from the host's immune system
  - Decreases immunogenicity and subsequent reactions

Pancreatitis

- Develops during induction
- Incidence ~ 9-10%
- Monitor amylase and lipase once/twice weekly and symptoms
- Anorexia, nausea and vomiting, fever, jaundice, increased urination, abdominal pain, + GI bleeding
- Manage with fluids, antibiotics, analgesics, TPN
- May require dose interruption or discontinuation

Liver Toxicity/Coagulation

- Two thirds of patients have elevated LFT's starting within the first two weeks of treatment
  - Leading to the depression of hepatically-derived clotting factors resulting in excessive bleeding or clotting
- Fibrinogen level used as a marker of abnormal coagulation
  - Check before each dose
  - Maintain > 100 mg/dl with cryoprecipitate/FFP

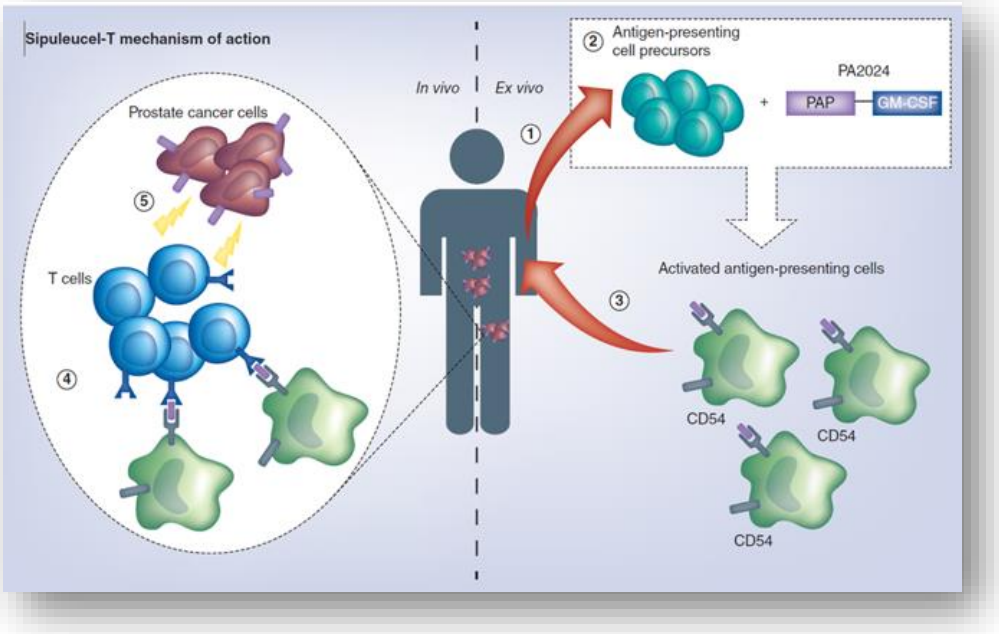
True or False: PEG asparaginase is known to have a higher risk of hypersensitivity reaction than Erwinia asparaginase due to the polyethylene glycol (PEG) polymer chain that is attached to the enzyme

A. True
B. False

Provenge (sipuleucel-T)

- FDA indication: For asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer
- Autologous cellular immunotherapy
- Complicated manufacturing and logistics

Mechanism of Action



Dosing

- Each dose contains ≥ 50 million autologous CD54+ cells obtained through leukapheresis activated with PAP-GM-CSF
- Administer doses at two-week intervals for a total of three doses
- If unable to receive a scheduled infusion, an additional leukapheresis procedure will be necessary prior to continuing a course of treatment

Administration

- Identity of the patient must be matched to the patient identifiers on the infusion bag and on the final product disposition notification
- Do not infuse until confirmation of product release is received from the company
- Keep the sealed infusion bag in the insulated polyurethane container inside the shipping box until ready for administration
- Prior to infusion, inspect bag for signs of leaks or damage
- Gently mix to re-suspend contents
- Infusion must begin prior to the expiration date and time: Do NOT infuse if expired
- Infuse over 60 minutes: Infuse the entire contents of the bag
- Do NOT use a cell filter for infusion
- For acute infusion reaction, interrupt or slow infusion rate
- If infusion is interrupted, keep infusion bag at room temperature; do not resume if bag is retained at room temperature for > 3 hours
- Observe patient for at least 30 minutes after infusion

Adverse Effects: Initial Infusion-Related Events Usually Present Within the First 24 Hours

- Flu-like symptoms
- Headache
- Dizziness
- Pain
- Nausea/vomiting
- Constipation
- Anemia
- Severe infusion related reaction
- Citrate toxicity

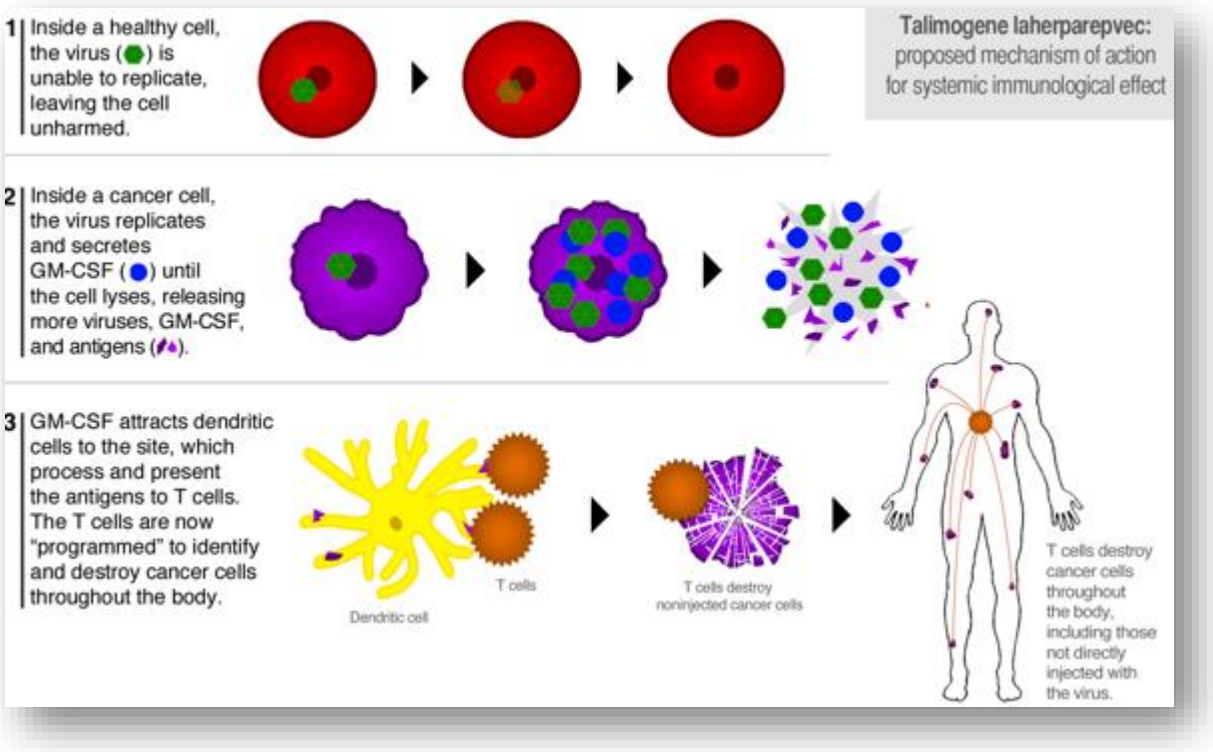
Which cells are activated with PAP-GM-CSF to create the autologous vaccine for each patient?

A. CD20+
B. CD30+
C. CD54+
D. CD33+
E. CD52+

Imlygic (Talimogene laherparepvec, TVEC)

- Live, attenuated, genetically modified herpes simplex virus type 1 (HSV-1) oncolytic virus
- Vaccine
- Treatment (local) of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
- FDA indication: Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
    - Intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound

TVEC Mechanism of Action



Dosing

- The volume of TVEC to be injected is based on lesion size
  - > 5 cm: Inject up to 4 mL
  - > 2.5 cm to 5 cm Inject up to 2 mL
  - > 1.5 cm to 2.5 cm: Inject up to 1 mL
  - > 0.5 cm to 1.5 cm: Inject up to 0.5 mL
  - ≤ 0.5 cm: Inject up to 0.1 mL

Administration

- Clean the lesion and surrounding areas with alcohol and allow to dry
- Using a single insertion point, inject TVEC along multiple tracks as far as the needle allows within the lesion to achieve dispersion; multiple lesion points may be used if a lesion is larger than the radial reach of the needle
- Inject TVEC evenly and completely within the lesion by pulling the needle back without removing it from the lesion
- Redirect the needle as necessary while injecting the remainder of the dose; continue until the full dose is evenly and completely dispersed
- Remove the needle from the lesion slowly to avoid leakage
- Repeat steps for other lesions to be treated
- Use a new needle if the needle is completely removed from a lesion and each time a different lesion is injected

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- Apply pressure with sterile gauze for at least 30 seconds after the injection is completed; swab the injection site(s) and surrounding areas with alcohol
- Change gloves, then cover lesion(s) with an absorbent pad and dry occlusive dressing, and wipe the exterior of the dressing with alcohol
- The injection site should be covered for at least the first week after each treatment or longer if the injection site is weeping or oozing and replace dressing if it falls off
- Initial visit: Inject up to 4 mL at a concentration of 10^6 (1 million) PFU/mL. Inject largest lesion(s) first; inject remaining lesion(s) based on lesion size until maximum injection volume is reached or all lesions have been treated
- Second visit (3 weeks after initial treatment): Inject up to 4 mL at a concentration of 10^8 (100 million) PFU/mL
    - Inject any new lesion(s) that have developed since initial treatment first; inject remaining lesion(s) based on lesion size until maximum injection volume is reached or all lesions have been treated
- Subsequent visits, including reinitiation (2 weeks after previous treatment): Inject up to 4 mL at a concentration of 10^8 (100 million) PFU/mL
    - Inject any new lesion(s) that have developed since previous treatment first; inject remaining lesion(s) based on lesion size until maximum injection volume is reached or all lesions have been treated

Adverse Effects

- Flu-like symptoms
- Headache
- Dizziness
- Nausea/vomiting
- Diarrhea/constipation
- Pain at injection site
- Pain in extremity

Miscellaneous

- Immunocompromised or pregnant should not prepare or administer TVEC and should not come into direct contact with injection sites, dressings, or body fluids of treated patients
- Wear personal protective equipment
- Herpetic infections have been reported disseminated herpetic infection may occur in
- If herpes-like lesions develop, follow standard practice to prevent viral transmission
    - Contact a health care provider for evaluation
- TVEC is sensitive to antiviral therapy, consider the risks and benefits of treatment prior to administering antiviral agents

True or False: There is a lifetime maximum amount of TVEC that a patient can receive

A. True
B. False

_____
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_____

Error Prevention

Definition

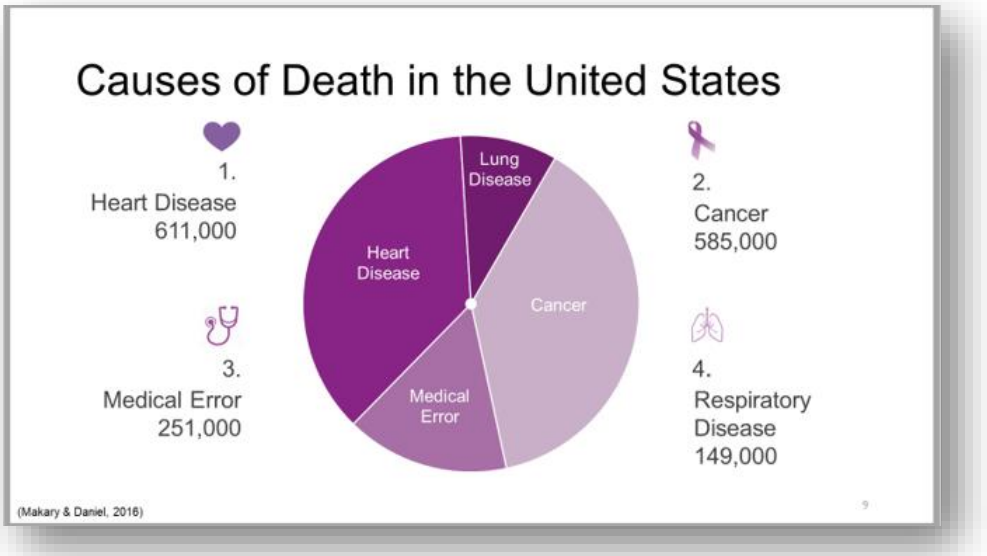
- Unintended act or act that does not achieve intended outcomes
- Failure of a planned action to be completed as intended
- Use of the wrong plan to achieve an aim
- Deviation from the planned process
- May or may not cause patient_____

Types

- Error of _____
- Error of _____

Terminology Surrounding Medical Errors

- Patient safety event
- Active error
- Adverse event
- Latent error
- Negligence
- Near miss
- Never event
- Sentinel event



Error Statistics

- Sepsis: Affects an estimated 31 million people worldwide, causing over five million deaths per year
- Healthcare-associated infections (HAIs) occur in 7-10 out of every 100 hospitalized patients in high-income counties and low and middle-income counties respectively
- Radiation errors involve overexposure to radiation and cases of wrong-patient and wrong-site identification, the estimates overall incidence of errors is around 15 per 10,000 treatment courses
- Venous thromboembolism (blood clots) one of the most common and preventable cause of patient harm, contributes to 1/3 of the complications attributed to hospitalization

Joint Commission Patient Safety Measures

- Identification of patient dangers, risks, and use of two correct identifiers
- Prompt communication methods
- Focus on infection prevention, alarm fatigue, and high-risk medications
- Attention to identification in medication administration and surgical procedures

Examples of Medical Error

- A pharmacist entered chemotherapy for a future appointment and noted that there was a 5 cm discrepancy of height from previous doses. All previous chemotherapy doses were calculated based on a height of 145 cm and the upcoming dose was calculated based on a height of 150 cm. This resulted in an increase of dose. The pharmacist confirmed with ordering office that the patient's height was 150 cm, and that the previous height was incorrect. All previous doses were given at the lower dose.
    - What could have been done differently to prevent this error?

      _____
      _____

- An order was sent to an infusion center from the physician's office was written as Herceptin [trastuzumab] 2 mg/kg (184 mg) in 250 mL NS IV over 30 minutes cycle 1 day 8 and day 15 Q 21 days. The order was interpreted as "Administer Q 21 days" when intended dosing was day 1, day 8, and day 15, causing the patient to miss doses day 8 and day 15. The oncologist was notified, the patient informed, and the dosing schedule was adjusted for remaining doses.
    - What could have been done differently to prevent this error?

      _____
      _____

Importance of Error Reporting

- Reduction of occurrence
- Facilitates learning
- _____ to reporting

_____
_____
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Debriefing After an Error

- Recovery process
- _____
- A nurse's experience
    - https://www.youtube.com/watch?v=2ZVO4gqpiH4

How to Report Error at UPMC

- RiskMaster
- UPMC Risk Management at 412-647-3050
- UPMC Patient Safety Officer for your facility
- Initial Investigation Event Report (IIER) form
- UPMC Policies
    - HS-PT1200 and HS-RI1305

What to report at UPMC

- Missed or incorrect diagnoses
- Wrong patient, incorrect site, or procedure
- Patient-related medical events involving treatments or procedures
- Infections
- Inappropriate medication administration
- Falls
- Patient/family complaints
- Laboratory or radiology errors
- Equipment malfunctions
- Skin breakdown (stage II or higher)
- Stolen, missing, or damaged property (including vehicles)
- Lack of appropriate follow-up care

Who Should Report Events and When?

- Any _____ gains knowledge of a reportable event
- Pennsylvania Medical Care Availability and Reduction of Error (Mcare) Act requires within 24 hours
- Protection exists within Whistleblower Law

A Just Culture

- At UPMC, A Just Culture is used to respond to and analyze error
    - Empowers staff
    - Provides consistent guidelines
    - Ensures _____
    - Assures leaders act in a fair and consistent manner
    - Creates system accountability
    - Fosters a culture of learning and safety

Errors and the Multidisciplinary Team

- Instance of error

_____
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- Importance of multidisciplinary team
- Key components for effectiveness
- Location of team members

The At-Risk Oncology Patient

- Cancer care is complex and hazardous for patients and providers
- Patients with cancer cannot tolerate mistakes
- _____warrants extra risk

Outpatient Oncology Risk

- Distribution of care
- Lack of education
- Time limitations
- Treatment location
- _____

Educational Efforts

- Knowledge of prescribed regimen
- Knowledge of patient history and status
- Patient and caregiver involvement
- Error detection or prevention

UPMC Systemwide Policy HS-ONC0005

- Two antineoplastic drug qualified nurses must verify:
    - Informed consent
    - Allergies
    - Height and weight
    - Labs
    - Regimen
    - Premeds/fluids
    - _____
- An antineoplastic drug qualified RN and one other RN must verify:
    - Comparison to order
    - Patient identifiers
    - Date to be administered
    - Day of treatment
    - _____
    - Expiration date and time
    - Appearance and physical integrity of the drug

Factors Impacting Education

- Disease state
- Receptiveness

_____
_____
_____
_____
_____

- Limited language proficiency
- Lower levels of education
- Misperceptions of illness severity
- Intellectual disability or mental illness

Considerations in Patient Education

- Assessment of readiness or willingness to learn
- Caregiver support
- Communication with multidisciplinary team
- Documentation
- Effectiveness
- Follow-up of instruction

Examples for Education Inclusion

- “Your infusion pump will be set to 200 ml per hour, meaning that this infusion will take one hour to complete.”
- “You will receive this blue tablet before each infusion as a premedication.”
- “The IV medication you will be receiving is red.”
- “Now that we have confirmed your name and date of birth, let’s read your chemotherapy label together.”

Extravasation of Vesicant and Irritant Chemotherapeutic Agents

Anecdotal and Controversial Subject

- Based on animal data and case reports
- Toxic local tissue reactions account for 0.1-6% of all adverse effects of antineoplastic agents despite careful technique

Defining Terms

Extravasation	Inadvertent escape of a medication/fluid from a vein into surrounding tissue
Infiltration	Agents that are capable of producing venous pain at the site and along the vein with or without an inflammatory reaction
Vesicant	Inadvertent escape of a vesicant from a vein into surrounding tissue
Irritant	Agents that do not cause tissue necrosis or irritation when infiltration occurs
Nonirritant/Nonvesicant	Agents that are capable of forming a blister or tissue necrosis when extravasated

Vesicants

- Ado-trastuzumab emtanasine
- Bendamustine Hcl
- Platinol
- Dactinomycin
- Daunomycin
- Docetaxel
- Doxorubicin
- Enfortumab vendotin-ejfv
- Epirubicin
- Etoposide
- Ibritumomab tiuxetan
- Idarubicin
- Liposomal daunorubicin and cytarabine
- Mechlorethamine Hcl
- Melphalan
- Oxaliplatin
- Paclitaxel
- Paclitaxel protein-bound
- Teniposide
- Trabectedin
- Mitomycin
- Vinblastine
- Vincristine
- Vinorelbine
- Mitoxantrone
- Loncastuximab tesirine-lpyl

The process of tissue destruction caused by leakage of vesicants into the tissue is by nature indolent and progressive

Irritants

• Bleomycin • Busulfan • Carboplatin • Carmustine • Cisplatin • Cladribine • Cyclophosphamide • Cytarabine • Dacarbazine • Etoposide	• 5-fluorouracil • Gemcitabine • Daunorubicin liposomal • Doxorubicin liposomal • Streptozocin • Irinotecan • Ifosfamide • Temsirolimus • Topotecan

The process of tissue destruction caused by leakage of vesicants into the tissue is by nature indolent and progressive

Categories of Extravasation of Chemotherapeutic Agents

- Those that _____ not bind to tissue nucleic acids: Cause immediate tissue damage but are quickly metabolized or inactivated
- Those that _____bind to tissue nucleic acids: Cause immediate injury, lodge in the tissue, and bind to DNA

Degree of Injury

- _____
- Amount
- _____ of exposure
- Affected tissues

Risk Factors

- Debilitation
- Previous treatment: Multiple _____
- Elderly: Friable veins, history of circulatory disease
- Small peripheral veins
- Venous spasm due to changes in body temperature, hypertension, and psychological factors
- Previously _____ site: Radiation recall
- Extremity edema: Due to axillary surgery
- Peripheral neuropathy due to disease or treatment: May blunt pain perception
- Vesicant potential of the drug
- _____ of the drug
- Amount of drug infiltrated
- Duration of tissue exposure
- Inability to communicate discomfort such as very young or pre-medicated patients

_____
_____
_____
_____
_____

Signs and Symptoms of a Peripheral Extravasation

- _____ of blood return, however, may be present
- Swelling
- Erythema, inflammation
- Leaking at catheter entrance site
- _____, burning, or stinging
- Alteration in IV flow rate that slows or stops

Chemical Phlebitis

- Heralded by burning sensation along the course of the involved vein, followed by a streak of erythema along the course of the vein
- Commonly associated with anthracyclines, nitrogen mustard, nitrosureas
- Treat with warm, moist compress and avoid repeated venipuncture

Vessel Irritation

- Aching and _____ along the vein
- Reddish or dark discoloration along the length of the vein

Flare Reaction

- Adriamycin, daunomycin, nitrogen mustard
- Occurs in _____% of cases
- Transient: 30 minutes
- Erythematous streak along the course of the vein
- Pruritis, urticaria

Signs and Symptoms of Extravasation in a Venous Access Device (VAD)

- Assess chest wall for swelling
- Assess chest wall for _____, leaking at catheter exit site: If external catheter
- May have referred pain/burning to shoulder, neck, or arm
- May have edema/erythema to port pocket
- Note fluttering or flopping in chest

Causes of Drug Extravasation in Implanted Ports

- Needle _____
- Thrombosis within catheter tip within subclavian vein: Back-tracking of drug around catheter and into skin pocket
- Separation of catheter from port, or catheter fracture, and embolization onto the heart

_____
_____
_____
_____
_____

Risk Factors for VAD Extravasation

- High-risk location of port: Groin, abdomen
- Improperly secured port within pocket: “Floats”
- Damaged catheter
- Improper needle _____ for septum depth
- Improper _____ of needle in septum
- Obesity
- Vigorous patient activity: Heavy lifting, sports
- Twiddlers’ syndrome
- Vigorous coughing
- Inability to communicate discomfort: Very young or pre-medicated patients

Extravasation Management

- Requires immediate recognition and emergency treatment
    - Peripheral extravasation
        - Immediately _____ infusion
        - Leave IV catheter in place
        - Remove IV tubing
        - Aspirate residual drug/blood
        - _____ area in cm/in and mark area
        - Estimate volume extravasated
        - Photograph the site
        - Remove IV
        - Cover with light dressing
        - Inject _____ antidote (if any) by standing/MD order
            - Make as few punctures as possible and reposition needle under skin to infiltrate the entire area of infiltration
        - Apply warm or cold compresses as indicated
            - Heat
                - Vincristine, vinblastine, vincristine liposomal, vinorelbine and etoposide
                - Rationale: Vasodilation facilitates absorption
                - Use immediately for 30-60 minutes at a minimum, then on for 15-20 minutes QID for 48-72 hours
            - Cold
                - Oxaliplatin, cisplatin, adriamycin, epirubicin, dactinomycin, daunorubicin, idarubicin, and mechlorethamine
                - Rationale: Vasoconstriction localizes extent of absorption
                - Use immediately for 30-60 minutes at a minimum, then on for 15-20 minutes QID for 48-72 hours
        - Elevate extremity

_____
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_____
_____

- VAD Extravasation
  - Follow steps of peripheral extravasation
  - Treat subcutaneous tissue if indicated
  - Radiographic study: Chest x-ray to rule out mechanical obstruction and check placement catheter dye study/venogram diagnoses clot formation or defect

Antidotes

- Animal models such as pig, mouse, rat, or dog
  - Extrapolation from animals to humans is difficult
- Unproven therapies
  - Corticosteroids
  - Sodium bicarbonate
  - Dimethyl sulfoxide (DMSO)
  - Propranolol and isoproterenol
- Sodium thiosulfate
  - Used subcutaneous with cold compresses for mechlorethamine, Platinol (cisplatin), and Eloxatin (oxaliplatin)
- Hyaluronidase
  - Used subcutaneous with warm compresses for etoposide for a large volume (> 20 mg/mL) or high concentration infiltrate > 0.5 mg/mL and vinca alkaloids: Vincristine, vinblastine and vinorelbine

Antitumor Antibiotics

- Most common extravasation is _____, but daunorubicin, epirubicin, and idarubicin also common
  - Cold compresses
- No antidote until the FDA approved Totect in September 2007

Totect (dexrazoxane)

- A new agent for _____ extravasation only
  - Doxorubicin, daunorubicin, epirubicin, and idarubicin
- Administration
  - Given IV daily for three days
  - First infusion within six hours of event
  - BSA is used to calculate the dose
    - Maximum dose is 2000 mg
  - _____ drug: Safe handling with gloves and gown
  - Day one: 1000 mg/m^2
  - Day two: 1000 mg/m^2
  - Day three: 500 mg/m^2

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- Side effects
    - _____
    - _____
    - Fever
    - Infusion site reactions: Pain, phlebitis
    - Nausea/vomiting: Use premeds
    - Reversible increase in liver function tests (LFTs)

Taxanes
- Controversial
- Oncology Nursing Society (ONS) recommends cold compresses and UPMC policy recommends cold compresses if patient complains of pain

Charting
- _____ and _____
- Number of insertions attempts and location
- Needle size and type or type of VAD
- Anatomic vein
- Name of _____, total dose ordered, and dilution in mg/mL
- Approximate amount of agent extravasated and solution
- Sequence of administration
- Nursing management of extravasation
- Photo documentation
- Subjective patient description of discomfort and/or sensation
- Appearance of site
    - Note size in cm/in
- Physician notification
- Follow-up measures
- Incident report: Per institutional policy

Plastic Surgery Consult
- Critical time for plastic surgery referral: Severe pain, early necrosis, blistering
- Debridement and/or skin graft

Prevention
- Develop institutional guidelines
- Credentialing program for staff
- Consider _____ early in treatment
- Select preferred site
- Avoid vein where there was a recent venipuncture
- Start IV catheterization attempts distally
- Secure needle but allow visibility of site: Assess _____ _____ per policy
- Monitor patient after ambulation
- Avoid extremity with impaired _____

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- Evaluating a VAD for use
    - 100 cc fluid bolus if suspicious
    - Read surgical/radiology reports
    - Ensure dressing over implanted port is secure

- Teach patient about risk
    - Report to nurse any discomfort or unusual sensations during administration
    - Observe and report any chest wall swelling or exit site leak if VAD
    - If extravasation does occur, explain what happened, what will be done, and the importance of follow up
- Insure consistent patient follow-up

Cost Considerations in Extravasation-Related Injuries

- Increased length of stay
- Consultations with specialists: Plastics, neurologist
- Debridement or grafting
- Higher drug costs: Antidotes, analgesics, antibiotics
- Follow-up care
- Physical therapy
- Additional medical supplies
- Lost wages

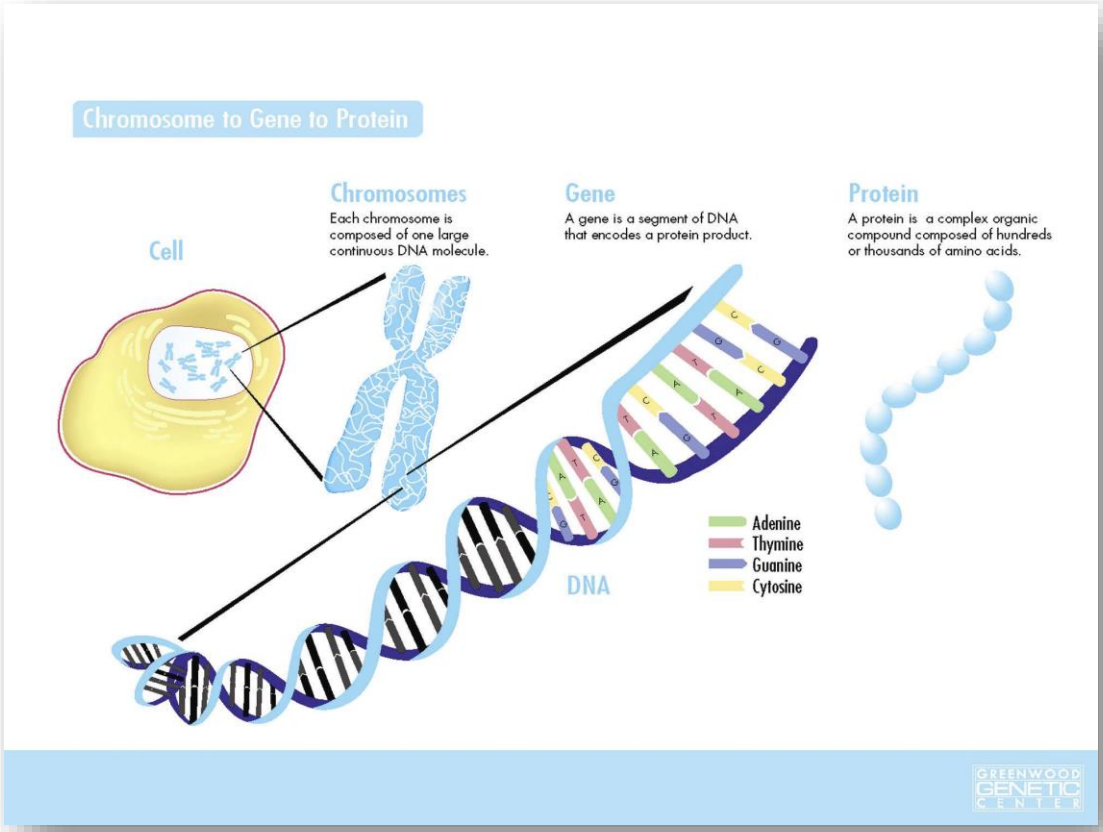
Litigation Involving Extravasation Considerations

- When a malpractice suit is brought against a nurse after the extravasation of a vesicant agent, the following questions are raised
    - Formal policy/guidelines followed
    - Drug administered in accordance with MD orders
    - Stopped infusion immediately if complaint of pain or burning
    - Appropriate action taken to manage extravasation
    - Physician informed promptly
    - Accurate description in medical record

Fallacy: The Less You Document the Less You Implicate Yourself

- Use FACT to chart
    - F = Factual
    - A = Accurate
    - C = Complete
    - T = Timely

Genomics and Genetics: Partners in Personalized Cancer Care



Genomics: The study of all of a person's genes (the genome), including interactions of those genes with each other and with the person's environment.

Genetics: The study of heredity and the variation of inherited characteristics.

Cancer Genomics: The study of the DNA sequence and gene expression differences between tumor cells and healthy cells

Cancer Genomics and Precision Medicine

- Gives information about the specific genetic characteristics of the tumor and allows for targeted therapies

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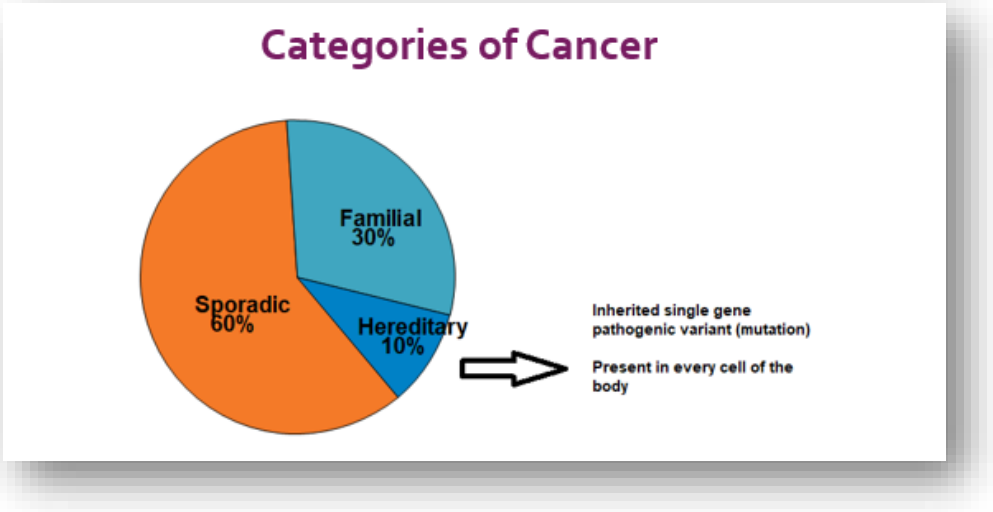
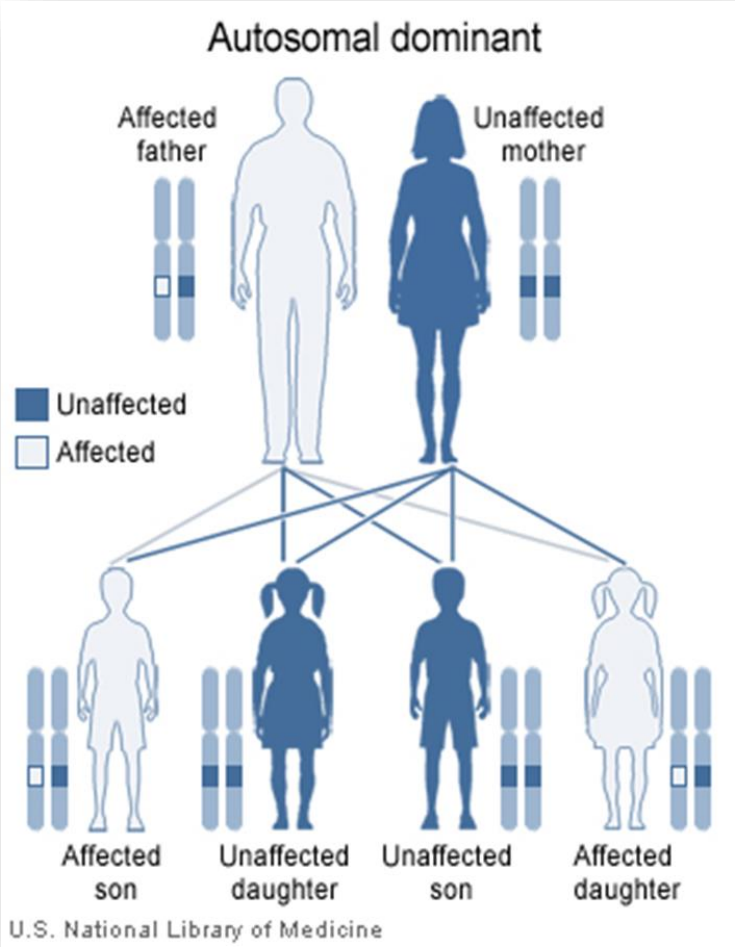
- Testing can include whole genes or hot spots: BRAF V600E
- Identification of a pathogenic variant (PV) can inform treatment
- Examples
    - BRAF* PV thyroid - BRAF inhibitor and a MEK inhibitor (dabrafenib + trametinib)
    - EGFR PV lung cancer – EGFR TK inhibitor (afatinib)
    - FLT3-ITD* PV in AML- FLT3-ITD inhibitors (daunorubicin + idarubicin

Cancer Genetics: The study of heredity and inherited risks for cancer

- Hereditary cancer predisposition syndromes
    - Ex: BRCA1/2, Lynch syndrome

Categories of Cancer





- Incomplete penetrance
- Transmission through males and females
- Both maternal and paternal history is relevant

Features of Hereditary Cancer

- Multiple family members with the same or related types of cancer
- Several generations of cancer
- Young age of diagnosis (≤ 45)
- Individuals with _____ primary cancers
- Rare types of cancer (male breast cancer, ovarian, pancreatic)
- Suggestive tumor studies (high-grade prostate, triple negative breast, MMR protein loss)
- Ethnicity (Ashkenazi Jewish)

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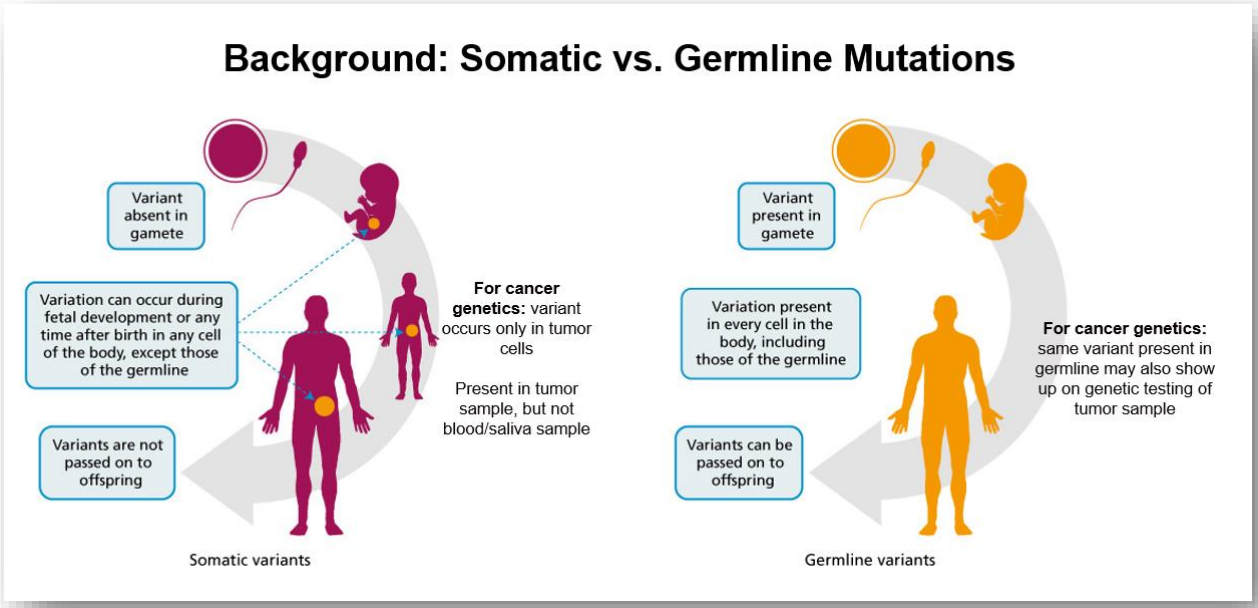
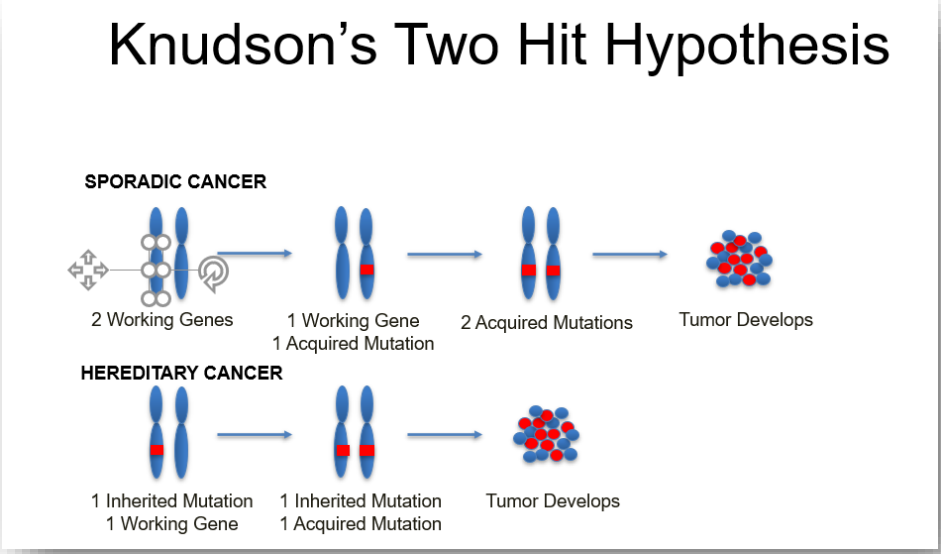
BRCA – Associated Cancer Risks

Cancer Type	General Population Risk	Mutation Risk BRCA 1	Mutation Risk BRCA 2
Breast	12%	65-79%	61-77%
Second primary breast	2% within 5 yrs Up to 11% lifetime	13% within 5 yrs 53% within 20-45 yrs	8% within 5 yrs 65% within 20-45 yrs
Ovarian	1-2%	36-53%	11-25%
Male breast	0.1%	1.2%	Up to 9%
Prostate	~11%	Increased	15% by age 65 20% lifetime
Pancreatic	1.5%	1-3%	2-7%
Melanoma	~2%	~2%	Elevated risk

Cancer Risks in Lynch Syndrome (MLH_1, MSH_2, MSH6, PMS_2)

Cancer	General population	Lynch syndrome
Colorectal	5%	Up to 70%
Endometrial	3%	40-60%
Ovarian	1.4%	7%
Gastric	<1%	5-8%
Renal pelvis/ureter	<1%	6%
Pancreatic	1.4%	4%
Small bowel	<1%	4%
Brain	<1%	2%


Background: Somatic vs. Germline Mutations
Variant absent in gamete
Variation can occur during fetal development or any time after birth in any cell of the body, except those of the germline
Variants are not passed on to offspring
Somatic variants
For cancer genetics: variant occurs only in tumor cells
Present in tumor sample, but not blood/saliva sample
Variant present in gamete
Variation present in every cell in the body, including those of the germline
Variants can be passed on to offspring
Germline variants
For cancer genetics: same variant present in germline may also show up on genetic testing of tumor sample


Knudson's Two Hit Hypothesis
SPORADIC CANCER
2 Working Genes
1 Working Gene
1 Acquired Mutation
2 Acquired Mutations
Tumor Develops
HEREDITARY CANCER
1 Inherited Mutation
1 Working Gene
1 Inherited Mutation
1 Acquired Mutation
Tumor Develops

Background: Germline vs. Tumor Testing

Germline

- Sample
  - Blood
  - Saliva/buccal
  - Cultured skin fibroblasts
- Types of testing
  - Analysis of germline DNA
  - Single gene, multigene panel, or single site analysis
- Purpose/information provided
  - Can identify germline PVs in genes associated with cancer predisposition syndromes
    - Guide options for prevention and risk-reduction
    - Allows for single-site testing of family

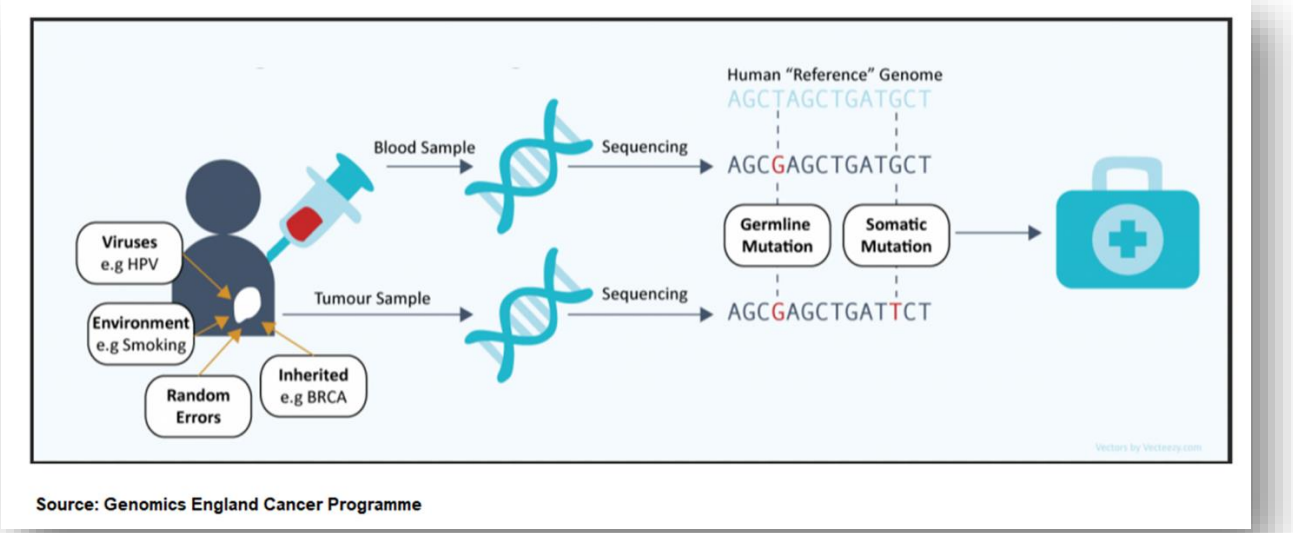
Genomic Tumor Studies

- Sample
  - Solid tumor sample
  - Liquid biopsy
- Types of testing
  - Targeted analysis of some tumor DNA hotspots
- Purpose/information provided
  - Can aid in determining treatment options or enable targeted therapy to specific gene
  - May identify somatic variant in tumor that could also be present in germline
    - If variant present in tumor sample ~30-50% allelic fraction there is an increased suspicion that variant may also be present in germline
    - Not equivalent to germline testing
      - Cannot diagnose hereditary cancer predisposition syndrome with tumor test alone

Referrals to Genetics

- Multiple family members with the same or related types of cancer
- Several generations of cancer
- Yound age of diagnosis
- Individuals with multiple primary cancers
- Rare types of cancer more likely associated with hereditary cause
  - Male breast cancer
  - Medullary thyroid cancer
  - Retinoblastoma
  - Pheochromocytoma

- Suggestive tumor studies
    - High grade prostate
    - Triple negative breast cancer
    - MMR protein loss
    - Tumor testing with a variant present at ~30-50% allelic fraction in gene associated with a hereditary cancer syndrome

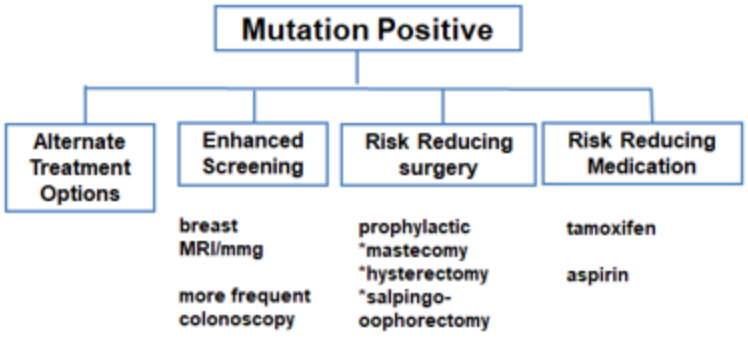


Source: Genomics England Cancer Programme

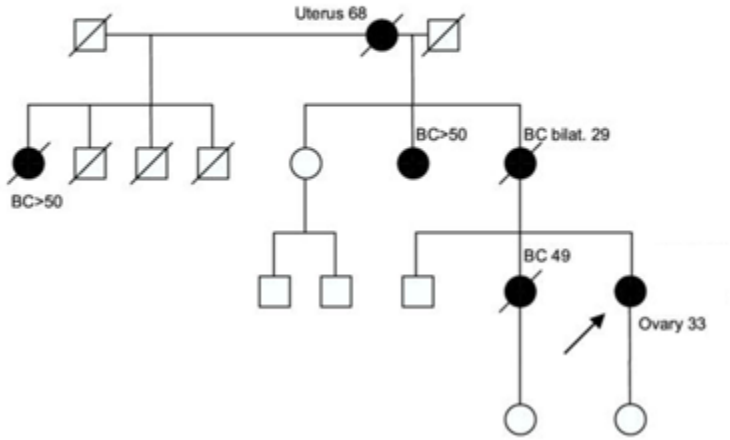
Why refer cancer patients to genetics?

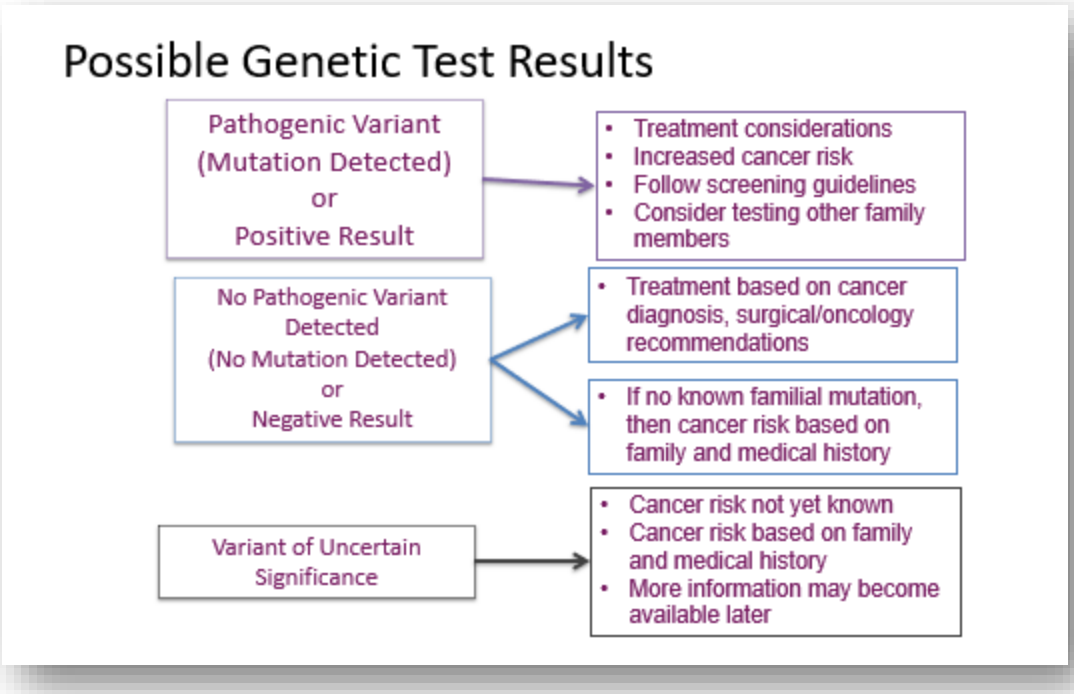
- Information for treatment
    - PARP inhibitors: BRCA 1/2
    - Anti-PD1 therapy: Lynch syndrome
- Help clarify risk for additional primary cancers
- Most informative person to test to clarify risk for family members

Clinical Management of Mutation-Positive Patient



Informative Family Member




Possible Genetic Test Results
Pathogenic Variant (Mutation Detected) or Positive Result
Treatment considerations
Increased cancer risk
Follow screening guidelines
Consider testing other family members
No Pathogenic Variant Detected (No Mutation Detected) or Negative Result
Treatment based on cancer diagnosis, surgical/oncology recommendations
If no known familial mutation, then cancer risk based on family and medical history
Variant of Uncertain Significance
Cancer risk not yet known
Cancer risk based on family and medical history
More information may become available later

Hematopoietic Growth Factors

What are Growth Factors?

- Glycoproteins naturally made in our body that play a role in proliferation, differentiation, and survival of primitive hematopoietic stem and progenitor cells as well as in functional activation of some mature cells
- We can administer them in larger doses than what is made in the body to help stimulate different blood lines

Types of Growth Factors

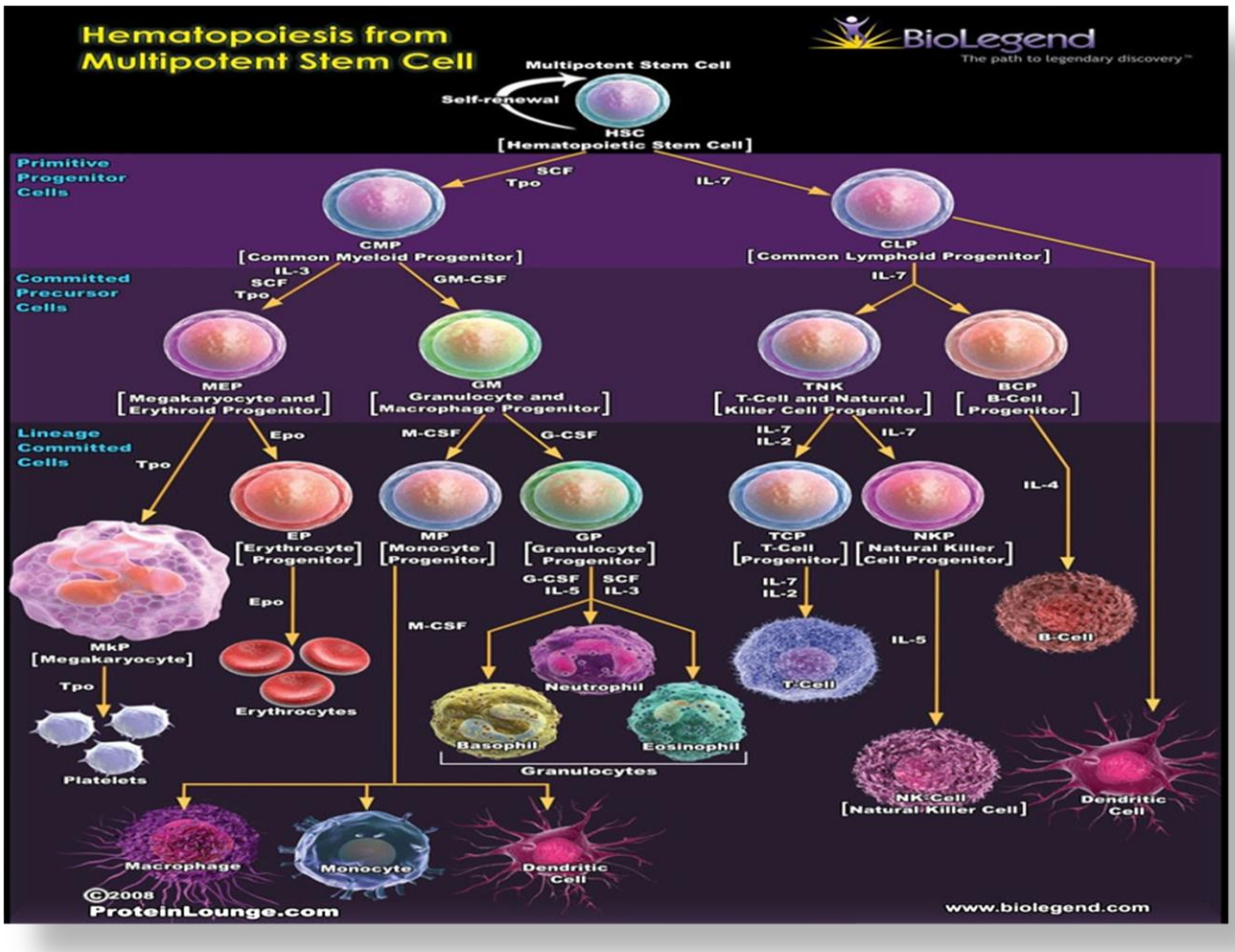
- G-CSF (↑ WBCs)
- Erythropoietin (↑ RBCs)
- Thrombopoietin & thrombopoietin mimetics (↑ platelets)
- ~~Stem cell factor & Flt3 ligand~~
- ~~IL-3~~
- ~~GM-CSF ie Sargramostim (Leukine®)~~
- ~~HIF inhibitors~~

Targeted Patient Population

- To support patients undergoing chemotherapy in between cycles to maintain treatment schedule
- Primary treatment
    - Ex: Hairy cell leukemia, T-LGL, low risk MDS, aplastic anemia, Fanconi anemia, sickle cell anemia
- Stem cell transplant
    - Ex: Mobilization, donors, inpatient until engraftment, graft failure
- HIV infection-associated neutropenia
- Chronic renal failure +/- dialysis
- Preop erythropoietin to reduce the need for transfusion in individuals who refuse blood transfusion ie Jehovah's witnesses

Benefits of Growth Factors:

- Cost-effective
    - Decrease admissions, transfusion needs
- Improve patient outcomes
    - Decrease neutropenia and risk of infection
    - Decrease anemia and fatigue/activity intolerance
    - Decrease thrombocytopenia and risk of bleeding
- Improved quality of life



Myelosuppression

- Suppression of bone marrow activity resulting in
  - Neutropenia
  - Anemia
  - Thrombocytopenia
- Can occur due to
  - Chemotherapy
  - Radiation
  - Biotherapy
- Most common dose-limiting toxicity of treatment

Neutropenia

- Neutrophils are in constant production due to short life span
- Decreased number of circulating neutrophils resulting in decreased absolute neutrophil count (ANC)

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    - Increased risk &/or severity of infection
    - Impaired immune response can quickly lead to sepsis
- Typical signs of inflammation & infection are absent ie fever, pus etc. as there are not enough neutrophils to create symptoms
- Infection is the most common cause of death in a patient with cancer

Neutropenia Risk Factors

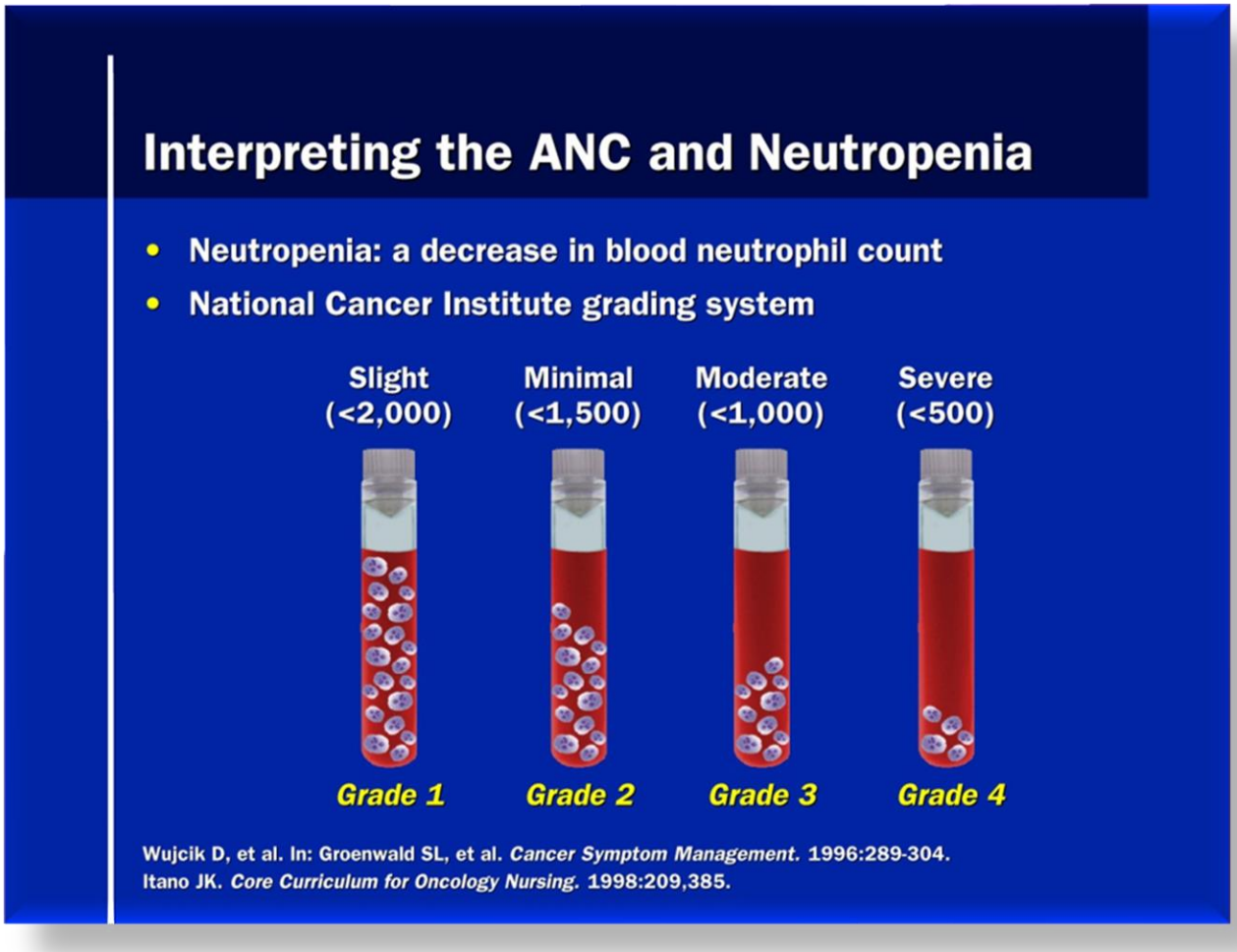
- Myelosuppressive chemotherapy regimen
    - Additional cycles of chemotherapy
- History of prolonged neutropenia &/or febrile neutropenia (defined as ANC<500 + fever≥38.3C)
    - In general, the risk of serious infection increases substantially when the ANC is <500 for ≥7 days
- Hematological malignancies and/or bone marrow involvement
- Age ≥65 years
- Comorbidities
- Malnutrition
- Low ANC prior to starting treatment
- Prior extensive radiation therapy

Calculating the ANC

- ANC = Absolute neutrophil count
- ANC=Total WBC x (segs + bands) / 100

Example

- Total WBC = 2,000
- Banded neutrophils = 1%
- Segmented neutrophils = 55%
- ANC = 2,000 x 56% = 112000 / 100
    - 1,120 cells/mm^3



G-CSF (↑ WBCs): Given to help decrease length and/or severity of neutropenia

Filgrastim (Neupogen)

- Short acting
- Dose: 5-10mcg/kg/day (typically SQ)
- Available as either 300 or 480 mcg
- Schedule depends on indication

Pegfilgrastim (Neulasta)

- Long acting
- Dose: 6 mg SQ once a cycle

Side Effects of G-CSFs:

- Allergic reaction or injection site reaction

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- Ostealgia (bone pain)
    - Solutions: Claritin +/- tramadol or oxy
- Fever
- Nausea (43%)
- Chest pain (13%)
- Thrombocytopenia (up to 38%)
- Splenic rupture (rare)

Additional considerations
- Monitor CBC each dose
- Neutropenic precautions

Anemia
- Mature RBCs are biconcave to change shape to fit through tiny capillaries
- Carry oxygen throughout the body
- 26 days to form a RBC
- Deficiency of healthy red blood cells (RBCs) as evidenced by a decreased Hgb and Hct
- Causes fatigue, weakness, dyspnea depending on severity, onset, and comorbidities

Grade (severity)	NCI Scale Hgb (g/dL)
0 (none)	Men: 14 - 18 Women 12 - 16
1 (mild)	10 to WNL
2 (moderate)	8-10
3 (serious/severe)	6.5 - 7.9
4 (life-threatening)	< 6.5

Erythropoietin (EPO)
- Naturally produced by kidneys
- Regulated by negative feedback loop

Erythropoietin Stimulating Agents (ESAs)

- Used to decrease need for blood transfusions and/or to decrease effects of anemia
- Originally intended for renal failure patients
    - Can be used with or without dialysis
- Controversial in heme malignancy patients
- Not indicated in patients receiving chemotherapy anticipating cure

Darbepoietin alfa (Aranesp)

Erythropoietin alfa (Epogen, Procrit)

- Check iron stores beforehand
- Typically, weight based
- Subcutaneous weekly
- Monitor CBC weekly and hold if Hgb > 10-10.5 g/dL depending on indication
- Aranesp® has longer ½ life
- Side effects (>10%): HTN, thrombotic events, headache, edema, N/V, dyspnea, abdominal pain, cough, itching/skin rash, injection site pain, arthralgia, fever

Thrombocytopenia

- Platelets are the smallest blood cells, fragments of megakaryocytes
- Stored in the spleen and then released to meet the body's needs
    - 80% in circulation, 20% stored in the spleen
- Play significant role in clot formation & tissue repair/regeneration
- Sticky and adhere to injured blood vessels/tissues to form a platelet plug to stop the flow of blood

Risk Factors for Thrombocytopenia

- Myelosuppressive chemotherapy
- Radiation
- Bone marrow involvement
- DIC
- Fever (causes increased destruction)
- Concomitant diseases ie cirrhosis, diabetes
- Infection
- Vitamin B12 or folate deficiencies

Platelet growth factors

- Thrombopoietin (TPO): Hormone thought to regulate platelet production
- Given to help increase platelet production to decrease effects of thrombocytopenia
- Platelet transfusions continue to be treatment of choice for therapy-related thrombocytopenia in oncology patients
    - Different thresholds depending on patient & medical site/platelet availability

Romiplostim (Nplate®)

- Used in treatment of idiopathic thrombocytopenia (ITP)
- Use the lowest dose to maintain platelets ≥50k
- Contraindicated in MDS, hemolytic anemia patients
- Subq weekly
    - 1 mcg/kg; adjust based on platelet count; max dose 10 mcg/kg/week; stop if platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the max dose
    - no dosage adjustments for kidney or liver impairment
- Side effects (>10%): Skin rash, GI, dizziness, headache, insomnia, MSK pain, oropharyngeal pain, URI, fever

Eltrombopag (Promacta®)

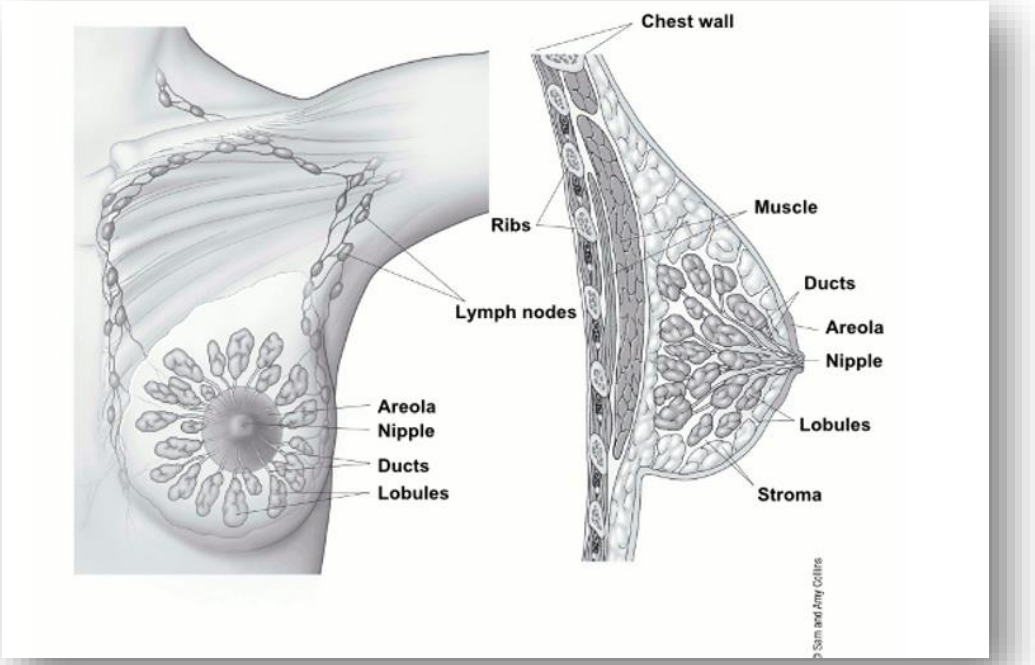
- Used in treatment of persistent/chronic idiopathic thrombocytopenia (ITP), chronic hep C–associated thrombocytopenia and aplastic anemia
    - Often used with standard immunosuppressive therapy (horse ATG and cyclosporine) x 6 months to treat aplastic anemia.
- Oral, once daily
- No side effects (>10%) in adults
- Stop if thromboembolic event

Hormonal Therapy: Breast Cancer

Breast Cancer

- Cells of the breast tissue start to grow out of control
- Once enough abnormal cells are present, these can be appreciated as a lump by the patient or seen on imaging such as mammogram
    - Can include malignant and non-cancerous tumors
- Ductal carcinomas: Cancers that begin in the ducts that bring milk to the nipple (most common)
- Lobular carcinomas: Cancers that begin in the glands that make milk
- Other cancers: Lymphomas, sarcomas
- DCIS/LCIS: Ductal and lobular carcinomas in situ that have not invaded the basement membrane

Normal Breast Tissue



Breast Cancer Burden

- Worldwide
  - Two million cases worldwide
  - Incidence greater in Western Europe vs Eastern Africa
  - Survival is greater than 80% in the US versus 40% in low income countries, mostly thought due to differences in screening and early detection
- United States
  - In 2024, an estimated 310,720 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S.
  - About 2,790 new cases of invasive breast cancer are expected to be diagnosed in men in 2024
  - A man's lifetime risk of breast cancer is about 1 in 883
  - About 43,780 women in the U.S. are expected to die in 2024 from breast cancer, though death rates have been decreasing since 2000
  - There are more than 4 million women living in the US with a history of breast cancer
  - Breast cancer is the second most commonly diagnosed cancer in women

Risk Factors for Development of Breast Cancer

- Age: Over 55 has greater prevalence
- Sex: Females greater than males
- Genetics
  - BRCA1/BRCA2: Approximately 70% risk of breast cancer by age 80
  - Many others of variable/unknown risk: ATM, BARD1, CHEK2, PALB2
  - PTEN, and TP53
- Family history
- Race
  - White > African American > Asian American
- Breast tissue density
  - Exposure to estrogen
  - Alcohol consumption
  - Obesity
  - Physical activity
  - Decreased risk with increased physical activity

Detection of Breast Cancer

- History and physical exam
- Painless, hard lump or mass
- Swelling of the breast
- Nipple changes, retractions, or discharge
- Nodules, erythema, dimpling on the skin

Imaging

- Mammogram: 3D with tomosynthesis
- Ultrasound
- MRI

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Biopsy
- Stereotactic
- _____ vs fine needle

Pathological Examination
- Hormone receptors: Estrogen receptors (ER), progesterone receptor (PR)
- HER2 receptor testing
- Tumor size
- Ki67
- Nuclear grade and Nottigham score
- Lymph node sampling
- Final pathological staging

Treatment of Breast Cancer
- Chemotherapy: Is it needed
    - Oncotype, patient preference, comorbidities
    - Can be given in neoadjuvant, adjuvant, or metastatic setting
- Surgery
    - Lumpectomy
    - Mastectomy, bilateral mastectomies
    - Axillary lymph node dissection versus sentinel node evaluation
- Radiation
    - Mammosite
    - Hypofractionated
    - Whole breast
    - Boost to tumor bed/axillae
- Hormonal therapy
    - Selective estrogen receptor modulators (SERMs)
    - Selective Estrogen Receptor Downregulators (SERDs)
    - Aromatase Inhibitors (AIs)
- HER2 directed therapy
    - Trastuzumab, pertuzumab, neratinib, lapatinib, TDM-1

How Do We Suppress Estrogen?
- Naturally through aging: Menopause
- Medications
    - Luteinizing hormone releasing hormone (LHRH) analogues
    - SERMs
    - SERDs
    - AIs
- Surgery
    - Bilateral salpingoophorectomy
- Radiation
    - Ovarian irradiation

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LHRH Antagonists

- Suppress ovarian function in pre- and peri-menopausal patients
- Initial increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH), after continuous administration results in ovarian suppression and decreased estrogen
- Used to lower testosterone in prostate cancer
- Given as an IM injection every 1-3 months depending on drug, indication, and dose
- Side effects
    - Hot flashes, weight gain, edema, mood alterations, acne
- Three main drugs
    - Lupron (leuprolide)
    - Zoladex (goserelin)
    - Trelstar (triptorelin)

SERMs

- Mechanism of Action
    - Blocks the _____ receptor in breast tissue
- Drugs in class
    - Nolvadex: Tamoxifen
    - Evista: Raloxifene
    - Fareston: Torimefene
- Indications
    - Cancer prevention in high-risk patients, pre-menopausal, post-menopausal, and men, only with ER positive disease
- Can be used in the neoadjuvant, adjuvant, locally recurrent, and metastatic setting
- Depending on the indication, may be taken for 1-2 years up to 10 years
- Side effects
    - Thrombotic events: Increased risk of DVT, PE, and stroke
    - Uterine malignancy: Adenocarcinomas and sarcomas
    - Menopausal symptoms: Hot flashes, night sweats, vasodilation, peripheral edema
    - Mood changes
    - Weight gain
    - Hyperlipidemia
    - Vaginal discharge

- Interactions with Selective serotonin reuptake inhibitor (SSRI)
    - Concomitant use with select SSRIs may result in decreased tamoxifen efficacy
    - Strong CYP2D6 inhibitors and moderate CYP2D6 inhibitors are reported to interfere with transformation to the active metabolite
    - Avoid grapefruit and grapefruit juice

Tamoxifen

- Pre- and Post-menopausal women for adjuvant therapy
    - 20mg daily for 5-10 years
- Treatment of DCIS and prevention of invasive malignancy
    - 20mg daily for 5 years

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- Breast cancer risk reduction in high-risk lesions or family history
    - 20mg daily for 5 years
- Treatment of metastatic disease
    - 20-40mg daily until toxicity or progressive disease

SERDs

- Mechanism of Action
    - Block the effects of estrogen in the breast tissue
    - May also reduce the number of estrogen receptors and change the shape of the receptor so that estrogen cannot bind
- Drugs in class
    - Faslodex (fulvestrant)
    - Elacestrant (Orserdu) – FDA approval 1/2023 but availability unknown
        - Indications: ER positive advanced or metastatic breast cancer in post-menopausal women
        - Dosing is the same for all
            - 500mg IM gluteal injection days 1, 15, 29, and then every 28 days until disease progression or toxicity
        - Side effects
            - Fairly well tolerated overall
            - Fatigue, hot flashes, _____ _____, increased AST/ALT
            - Injection site reaction/discomfort/medication leakage
        - Interactions
            - No significant interactions

Aromatase Inhibitors (AI)

- Mechanism of Action
    - Inhibits aromatase
- Drugs in Class
    - Arimidex (anastrozole)
    - Femara (letrozole)
    - Aromasin (exemestane)
- Indications: Neoadjuvant, adjuvant, or metastatic breast cancer treatment in post-menopausal women in ER positive breast cancer
- Side effects
    - Hot flashes, night sweats, fatigue
    - Arthralgias, myalgias
    - Decreased bone density
    - Mood alterations
    - Vaginal dryness, decreased libido
    - Weight _____
    - Increased AST/ALT
- Drug interactions
    - May increase serum concentration of methadone

_____
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    - Exemestane has more interactions, especially strong CYP 3a4 inducers: Anti-seizure medication
- Many schemata of administration depending on indication/use
    - ONLY for post-menopausal women
    - 5-10 years after surgery/chemo in adjuvant setting
    - Neoadjuvant to downsize tumor for optimal surgical results
    - After 1-2 years of Tamoxifen
    - Continuously in the metastatic setting until unacceptable toxicity or progressive disease
    - In conjunction with ovarian suppression in pre-menopausal women
- Arimidex
    - Nonsteroidal
    - 1mg daily
- Femara
    - Nonsteroidal
    - 2.5mg daily
- Aromasin
    - Steroidal and irreversibly binds to enzymes
    - 25mg daily

Aromatase Inhibitors with CDK 4/6 inhibitors

- CDK 4/6 inhibitors: Reduce proliferation of breast cancer cell lines by preventing progression from G1 to S cell cycle phase
- CDK 4/6 inhibitors used in conjunction with AIs to inhibit tumor growth
- Very effective combination for recurrent/metastatic ER positive breast cancer with efficacy rates similar to chemotherapy
- Three drugs now available: Palbociclib, ribociclib, and abemaciclib

Management of Anti-Estrogen Side Effects

- Decreased bone density
    - Encourage weight bearing exercise
    - Calcium, vitamin D supplements
    - DEXA scans every 2 years
    - Medications like Fosamax, Boniva, Reclast, Prolia
- Arthralgias/myalgias
    - Encourage exercise and regular activity
    - Ibuprofen, acetaminophen, COX 2 inhibitors
- Weight gain
- Mood alterations
- Hot flashes
    - Effexor, gabapentin
    - Yoga, layering clothing, avoiding alcohol
- Cardiac events
    - Monitor in conjunction with PCP

AIs vs. SERMs

- Effectiveness
  - Decreased risk of breast cancer recurrence and mortality with AIs
- Side effects
  - Bone density: Worse with AI
  - Musculoskeletal: Worse with AI
  - Thromboembolic disease: Worse with Tamoxifen
  - Uterine effects: Worse with Tamoxifen

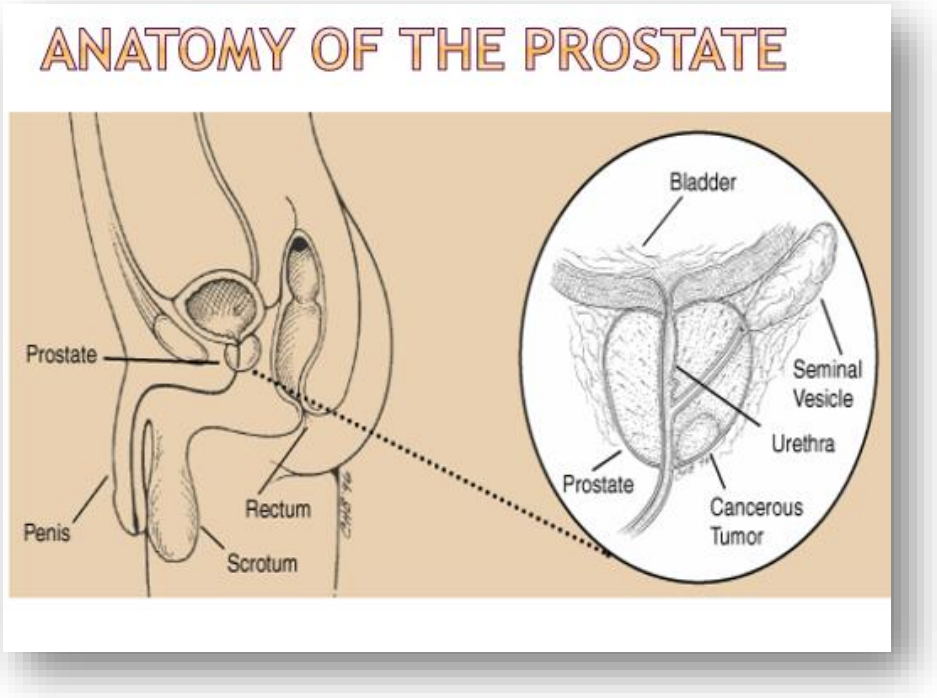
Overview of Treatment

- Premenopausal
  - Tamoxifen alone
  - LHRH agonist/ovarian suppression with AI
- Postmenopausal
  - SERMs, SERDs, AIs
- Adjuvant
  - SERMs, AIs, LHRH agonists or ovarian suppression
- Metastatic/Recurrent disease
  - SERMS, SERDS, AIs, LHRH agonists
- Men
  - Tamoxifen

Hormonal Therapy: Prostate Cancer

Treatment Options for Prostate Cancer

- Hormonal therapy options
  - Mechanism of action
  - Indications
  - Side effects
  - Dose and Administration
  - Drug interactions



Epidemiology

- Estimates in 2024: 299,010 new cases, 35,250 deaths from prostate cancer
- Most commonly diagnosed cancer in men, (1 out of 8 men)
- Second leading cause of death from cancer in men (1 out of 44 men)

Age

- More common after age 65
  - Mean age = 66

The risk factors of prostate cancer include

A. Being of African descent
B. Being under 50 years of age
C. Having a first-degree relative who has been diagnosed with prostate cancer
D. A and C

Risk Factors

- Age: Six out of ten > 65 years old
- Race/Ethnicity: African American > Whites > Asians > Hispanics
- Geography: North America, Northwest Europe, Caribbean
- Family History: Risk multiplies with family history
- Gene Changes: BRAC1, BRAC2, Lynch syndrome
- Diet: Red meat, high-fat diary, calcium, vitamin E
- Obesity: Higher risk, more aggressive form
- Smoking: Not enough data
- Workplace exposures: Toxic combustion products
- Inflammation: Prostatitis
- Sexually transmitted disease (STD)/Vasectomy: Not enough data

Screening recommendation

- Average Risk
  - Age 55-69
  - Digital rectal exam (DRE)
  - Prostate Specific Antigen (PSA)
- High
  - Age 45-50
  - DRE
  - PSA
- Frequency
  - PSA < 2.5 – Every two years
  - PSA > 2.5 – Every year

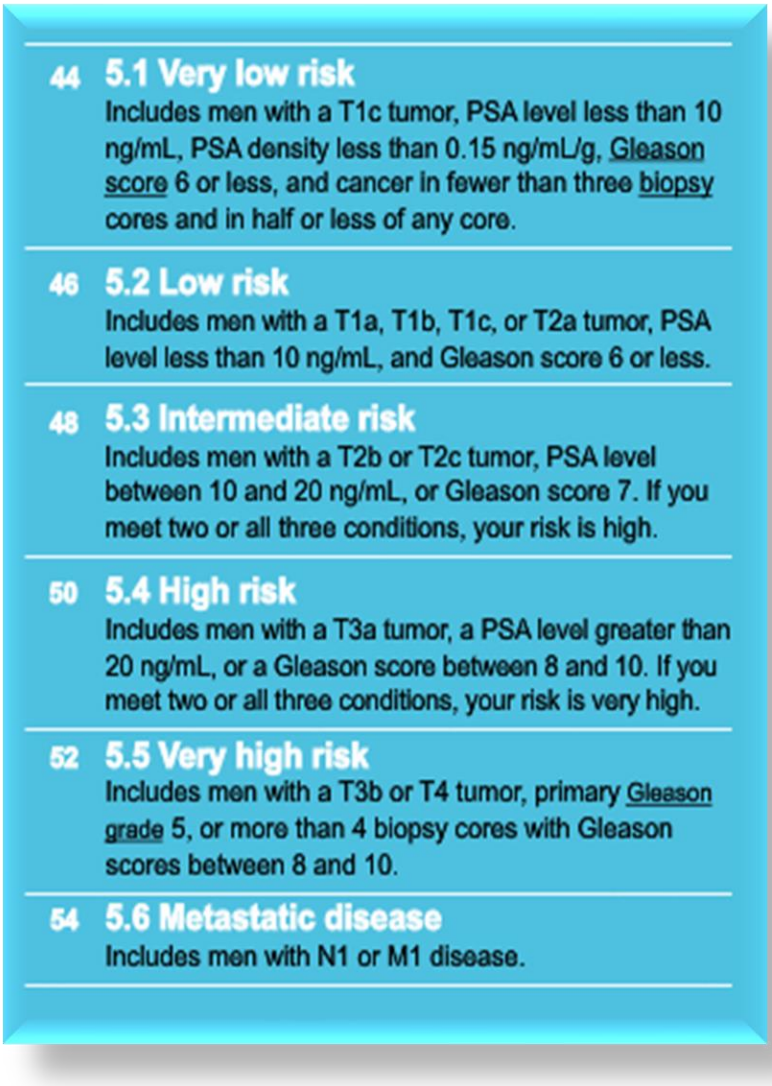
Signs and Symptoms

- Early stage
  - Asymptomatic
- Advanced stage
  - Problem urinating
  - Hematuria
  - Erectile dysfunction
  - Bone pain
  - Weakness, numbness, edema
  - Weight loss

Treatment Options

- Observation
- Surgery
- Radiation
- Hormone therapy
- Chemotherapy

Initial Treatment



Hormone therapy= Androgen Deprivation therapy (ADT)

- Androgen Deprivation Therapy- ADT
    - Lupron, Zoladex, or other agents +/- oral Casodex- to decrease testosterone, which is the energy supply of the cancer cells
- Used as adjuvant therapy for higher risk cancer after prostatectomy
- Used as primary therapy in connection with radiation when surgery is not done
- Used as primary therapy for biochemical recurrence (just increasing PSA) or metastatic disease

Reasons for Hormone Therapy

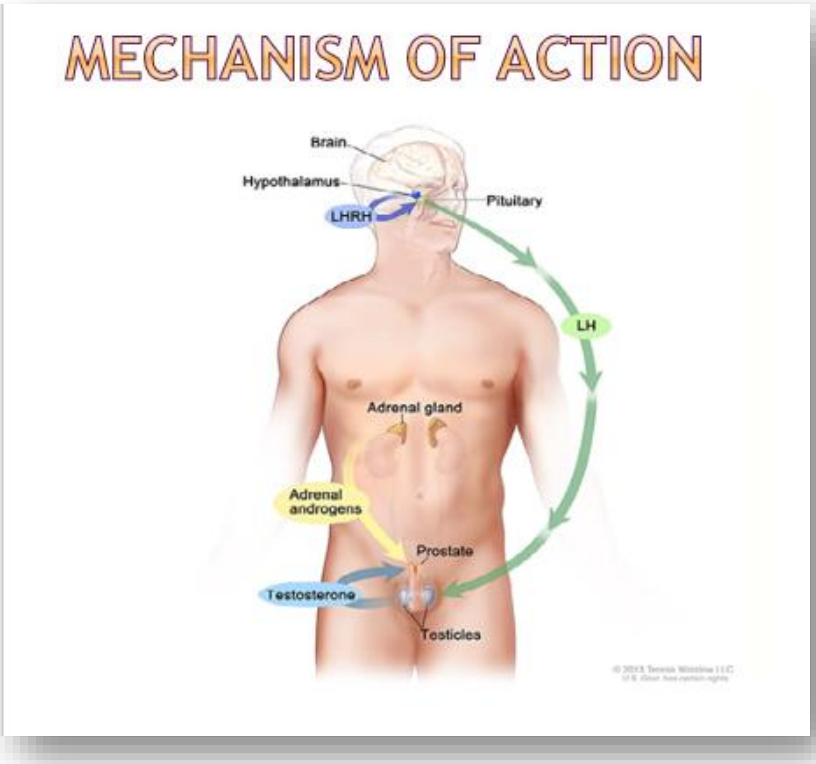
- Localized disease
- Metastatic disease
- Recurrent disease
- Adjuvant therapy

Hormonal Therapy

- Traditional hormone therapy
    - Orchiectomy
    - Luteinizing hormone-releasing hormone (LHRH) analogs
    - Anti-androgens
- New hormone therapy
    - CYP17 blocker
    - Androgen receptor inhibitor
- Other treatments
    - Estrogens
    - Ketoconazole

Traditional Hormone Therapy

- Luteinizing hormone releasing hormone (LHRH) agonists
    - Lupron (Leuprolide)
    - Zoladex (Goserelin)
    - Trelstar (Triptorelin
- LHRH antagonists
    - Firmagon (Degarelix)
- Anti-androgens
    - Eulexin (Flutamide)
    - Casodex (Bicalutamide)
    - Nilandron (Nilutamide)



LHRH Agonists

- First line therapy
- Eliminates 90-95% of androgen production
- Initial 80-90% response rate
- Can cause “flare reaction”
- Take anti-androgen agent to prevent flare reaction

Agent/Dose

- Lupron: Eligard
  - 7.5 mg IM/SQ every month
  - 22.5 mg IM/SQ every three months
  - 30 mg IM/SQ every four months
  - 45 mg IM/SQ every 6 months
- Goserelin (Zoladex)
  - 3.6 mg SQ every 4 weeks
  - 10.8 mg SQ every 12 weeks
- Triptorelin (Trelstar)
  - 3.75 mg IM every 4 weeks
  - 11.25 mg IM every 12 weeks
  - 22.5 mg IM every 24 weeks

LHRH Antagonist

- Firmagon (degarelix)
    - Dose: Loading dose 240 mg SC followed by 80 mg SC monthly
    - Reduce testosterone level quickly
    - Do not cause tumor flare

Side Effects: LHRH Analogs

- Acute
    - Gynecomastia
    - Hot flashes
    - Fatigue
    - Depression
    - Erectile dysfunction
    - Edema
    - Injection site reaction
- Long-term
    - Osteoporosis
    - Obesity
    - Cardiovascular events
    - Insulin resistance
    - Alterations in lipids
    - Increased risk of diabetes

Anti-Androgens

- Oral medications
- Often used with other agents
    - To boost first line therapy
    - To achieve combined androgen blockade (CAB)
- Given for few weeks to prevent flare reaction with LHRH agonists

Dose

- Eulexin: 250 mg PO every 8 hours
- Casodex: 50 mg PO daily
- Nilandron: 300 mg PO daily for thirty days then 150 mg PO daily

Side Effects: Antiandrogens

- Common
    - Hot Flashes
    - Gynecomastia
    - Nausea /vomiting /diarrhea
    - Impotence
    - LFT abnormalities
    - Individual drugs
- Fluamide/Bicalutamide
    - Can increase a risk of bleeding/warfarin
- Nilutamide
    - Vision problems, scarring and inflammation of the lung

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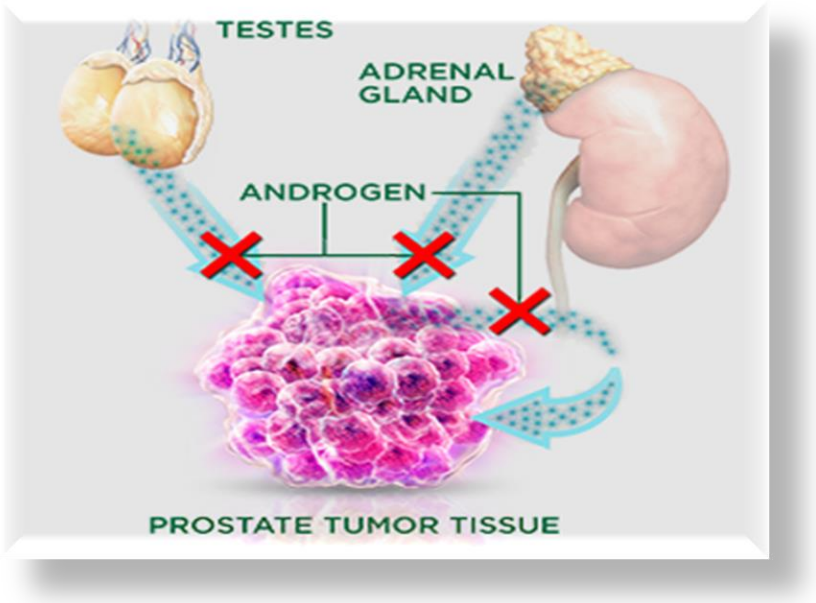
New Hormonal Therapy

- CYP 17 inhibitor
- Androgen receptor inhibitor

Zytiga (abiraterone)
Mechanism of action of Abiraterone



Indication

- Castrate resistant metastatic prostate cancer
- Usually used with LHRH agonist/antagonist
- Also used with initial low volume metastatic hormone sensitive disease

Warnings/Precautions

- Cardiovascular disease
- Hepatic impairment

Dose and Administration

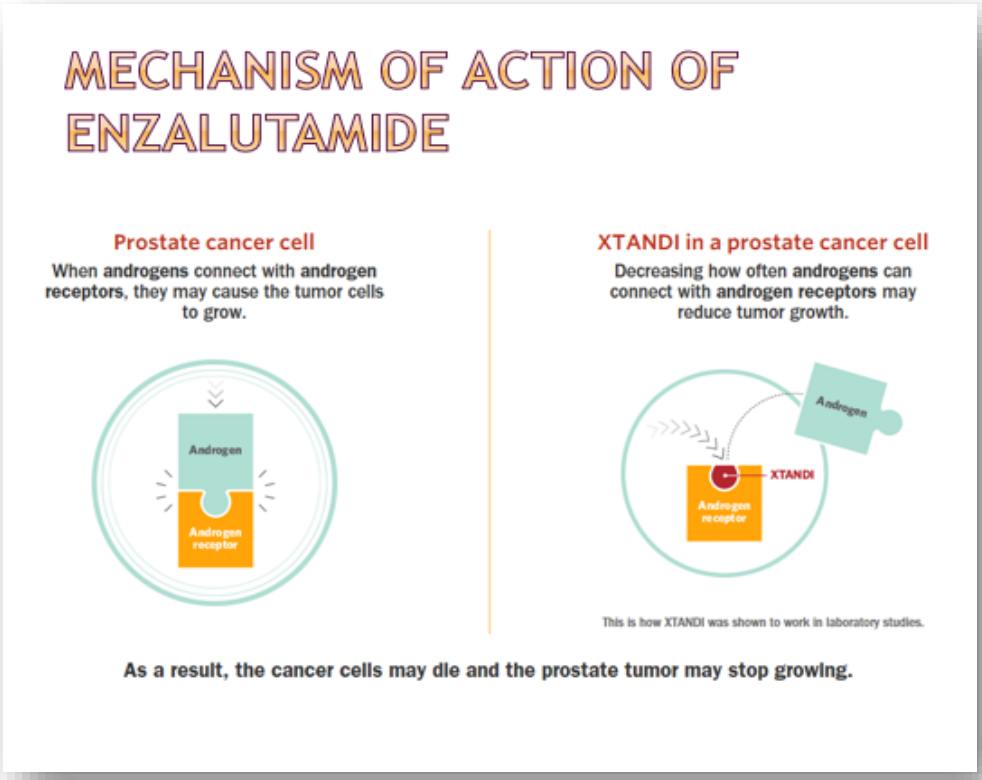
- 1000 mg PO every day with 5 mg predinsone PO twice a day
- At least one hour before meals or two hours after meals

Drug Interactions

- Strong CYP3A4 Inducers: Increase dosing frequency of abiraterone once a day to twice a day
    - Carbamazepine
    - Dexamethasone
    - Fosphenytoin
    - Nafcillin
    - Oxcarbazepine
    - Phenytoin
    - Rifampin

Side Effects of Abiraterone

- Hypokalemia
- Hypertension
- Fluid retention
- Hepatotoxicity
- Fatigue
- Joint swelling/discomfort
- Hot Flashes
- Hypercholesterolemia
- N/V, Diarrhea



Xtandi (enzalutamide)

Indications
- For castrate resistant metastatic prostate Cancer
- Usually used with LHRH agonist
- Also for biochemical recurrence with PSA rising on ADT

Warning and Precautions
- Seizures

Dose and Administration
- 160 mg PO daily
- Take with food

Drug Interactions
- Strong CYP 3A4 Inducers: Increase the dose of enzalutamide to 240 mg
    - Carbamazepine
    - Dexamethasone
    - Fosphenytoin

    - Nafcillin
    - Oxcarbazepine
    - Phenobarbital
    - Phenytoin
    - Rifampin
    - St John's wort
- Strong CYP 2C8 Inhibitors: Reduce dose to 80 mg
    - Gemfibrozil
- Strong CYP 2C8 Inducers
    - Rifampin

Side Effects of Enzalutamide

- Common
    - Back/joint/muscle pain
    - Hypertension
    - Fatigue/joint swelling/discomfort
    - Headache, dizziness
    - Hot flashes
    - Constipation, diarrhea
    - Upper respiratory tract infection
    - Neutropenia

Newest Oral Antiandrogens

Apalutamide (Erleada) 60 mg 4 tabs qd

Darolutamide (Nubeqa) 300 mg 2 tabs bid

Side effects

- Similar side effects to Abiaterone and enzalutamide with the addition of tachycardia, rapid weight gain, dizziness, and bloating

Other Agents

Estrogens: Female Hormones

- Used when first line therapy not working or tolerated
- Diethylstilbestrol (DES)
- Risk of blood clots and breast enlargement

Ketoconazole

- Blocks androgens and cortisol
- 400 mg three times a day
- Use with corticosteroid
- Side effects: Nausea/vomiting, impotence, gynecomastia, dry skin, increased LFTs
- Multiple interactions

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Orgovyx (relugolix)

- New oral GnRH receptor antagonist
- Dosage
    - Loading dose of 360 mg qd on day 1
    - Then 120 mg qd with or without food
- Lowers testosterone quicker (within 15 days) and keeps slightly larger percentage of patients' PSA suppressed
- Similar side effects to GnRH injections but less cardiac events

Chemotherapy

Taxotere

- First line
- 75 mg/m2 every three weeks
- For initial therapy at metastatic diagnosis with ADT is 6 cycles and as additional therapy after oral antiandrogens is 10 cycles

Cabazitaxel

- Second line
- 20 mg/m2 every three weeks

Pluvicto-Lutetium LU 177

Currently has its place in therapy after chemotherapy

- 6 IV infusions 6 weeks apart
- Potential fatigue, dry mouth, nausea, constipation
- Need to have a PSAM PET scan prior- this shows if have prostate specific membrane antigen protein which is required for the small molecules to be taken into the cell and then release alpha particles
- Has contact restrictions for 2-7 days after txs
- Myelosuppression and renal toxicity potentials

Hypersensitivity Reactions and Chemotherapy

Hypersensitivity

- Excessive, undesirable, damaging, discomfort producing, and sometimes _____ reactions produced by the normal _____ system in response to an antigen or allergen
- The types of reaction are divided into four categories based on the mechanisms involved and the time taken for the reaction

Signs and symptoms of anaphylaxis include (Select all that apply)

1. Diaphoresis
2. Fatigue
3. Itching around an intravenous insertion site
4. Pain around the IV insertion site
5. Urticaria

Types of Hypersensitivity Reactions

- Classified as either allergic or non-allergic
    - Allergic responses have a specific immune response mediated by immunoglobulins and/or T-cells
    - Non-Allergic reactions have no specific immune response
- Type I
    - Most common type associated with _____ agents
    - Potential for anaphylaxis
    - Occur after _____ exposure
        - Antibody formation and release of chemical mediators
- Mechanism of action
    - Immediate _____ mediated reaction
    - Mediator release from basophils and mast T-cells

Signs and Symptoms

- _____
- Rash
- N/V
- Flushing
- Urticaria
- Bronchospasm
- _____
- Angioedema
- Anxiety/impending doom

_____
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_____
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Anaphylaxis

- Any reaction that leads to widespread activation of _____ _____ and basophils
    - Activated mast T-cells or basophils subsequently release pro-inflammatory mediators or cytokines, thereby causing the clinical manifestations of allergy
- The goal should be early recognition and appropriate management of anaphylaxis in its milder form, before anaphylactic shock is reached
- Different from other reactions because anaphylaxis is likely to recur despite pre-medications and typically becomes more severe upon re-exposure

Types of Hypersensitivity Reactions

Type	Mechanism of Action	Signs and Symptoms	Examples
I	IgG or IgM antibody-mediated reaction results in antibody-antigen complexes that cause inflammation	Hemolysis	Hemolytic anemia, hemolysis from transfusion
II	Immune complex-mediated reaction cause by antigen-antibody interactions. Complexes form in circulation and deposit in various tissues	Tissue injury; vasculitis, nephritis, arthritis	Systemic lupus, rheumatoid arthritis
IV	Cell-mediated or delayed-type reaction due to sensitized T lymphocytes that interact with antigen	Contact dermatitis, homograft rejection, granuloma formation	Tuberculosis, granulomas, poison ivy

Cytokine Release Syndrome (CRS)

- A _____ inflammatory response due to high circulating levels of inflammatory cytokines released from the immune cells affected by the treatment
- A condition that may occur after treatment with some types of _____, such as monoclonal antibodies and CAR T-cells
- Typical onset: Two – three days
- Typical duration: Seven – eight days
- Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills
    - May be associated with cardiac, hepatic, and/or renal dysfunction
- Serious events may include atrial fabulation, ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, hemophagocytic lymphohistiocytosis macrophage activation syndrome (HLH/MAS)

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Reactions

- Infusion/Anaphylactic
  - Immune-mediated response in a sensitized patient
    - IgE
  - Changes in response to an antigen or foreign substance
  - Allergic
    - Often reacting to vehicle, not drug
- CRS
  - More often occurs with use of biological agents
  - Release of cytokines: From T-cells
  - Non-allergic
- Cytotoxic agents most commonly associated with infusion reactions
  - Taxanes: Paclitaxel, docetaxel
  - Platinum drugs: Carboplatin, oxaliplatin
  - L-asparaginase
  - Etoposide
    - Reaction in the first few minutes to hours after dose
  - Procarbazine
    - Corticosteroid recommended before infusion
  - Monoclonal antibodies
    - Most of these reactions are related to cytokine release rather than murine exposure
    - Reaction is greater during first treatment
- Timing
  - Infusion reactions usually occur during or within a _____ hours of drug infusion
  - A reaction may occur _____ to _____ days after administration, and patients must be adequately informed of symptoms to watch for
- Incidence
  - Overall Incidence rate of severe reactions: _____ - with proper pre-medications and monitoring
  - Overall incidence rate of mild to moderate: _____
  - Varies by drug _____ and diagnosis

Incidence

High Potential	Occasional Potential	Rare Potential
• L-Asparaginase • Cytarabine • Taxanes • Platinum compounds • Procarbazine • Etoposide • Bleomycin • Liposomal	• Anthracyclines	• Cyclophosphamide and ifosfamide • Dacarbazine • 5-FU • Hydroxyurea • Methotrexate • Vincristine and vinblastine

_____
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Biotherapy Drugs Associated with Hypersensitivity Reactions and Cytokine Release Syndrome: Monoclonal Antibodies

Chimeric	Humanized	Fully Human
• Cetuximab • Rituximab	• Alemtuzumab • Bevacizumab • Trastuzumab	• Panitumumab • Nivolumab

Incidence Rates	
Rituxan	77% reaction rate 50% of reactions within initial infusion
Trastuzumab	Up to 40% reaction rate
Cetuximab	16%-19% reaction rate Increased rate in southwest region of U. S.
Platinums (carboplatin and oxaliplatin)	12%-19% reaction rate
Paclitaxel	8%-45% reaction rate
Docetaxel	• 5%-20% reaction rate
Etoposide	• 1%-3% reaction rate • As high as 51% in study of Hodgkin's Lymphoma

True or False?
50% of Rituxan (rituximab) reactions occur during the initial treatment?

Risk Factors

- Drug Risk Factors
  - Class of _____
  - _____ of drug
  - Route of drug
  - _____ at which drug is given
- Cycle number
- Patient Risk Factors
  - Pre-existing allergies/asthma/autoimmune disease
  - High circulating lymphocyte counts (>25,000/mm^3)
  - Gender
  - Age
  - New patient/diagnosis
  - Type of cancer diagnosed
  - Platins
    - _____ number of cycles
    - Extended period of time between cycles
  - Taxanes
    - Early cycles
    - Respiratory dysfunction
    - Obesity

_____
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_____
_____
_____

A patient's risk for anaphylaxis increased when medications are:

A. Given as a single dose
B. Given at a low dose
C. Given intravenously
D. Synthetically prepared

Signs and Symptoms of Infusion Reaction

- _____
- Itching
- Alterations in heart rate and _____
- Dyspnea or chest discomfort
- Back or abdominal pain
- _____ and/or chills and shaking
- Nausea, vomiting, and/or diarrhea
- Skin rash
- Throat _____
- Hypoxia
- Seizures
- Dizziness and/or syncope

Signs and Symptoms of Anaphylaxis

- Cutaneous symptoms
  - _____
  - Urticaria
  - Angioedema: Usually of face, eyelids, or lips
- Respiratory symptoms
  - Repetitive cough
  - Sudden nasal _____
  - Shortness of breath (SOB)
  - Chest tightness
  - Wheeze
  - Sensation of throat closure or choking
  - Change in voice quality: Due to laryngeal edema
  - Hypoxia
- Cardiovascular symptoms
  - Faintness
  - _____ or less often-bradycardia
  - Hypotension or hypertension
  - Loss of conscience
- GI symptoms
  - _____
  - Vomiting
  - Abdominal cramping
  - Diarrhea

_____
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- Neuromuscular symptoms
    - Sense of impending _____
    - Tunnel vison
    - Dizziness, and/or seizure
    - Severe back, chest, or pelvic pain

Onset of Reaction Symptoms

- Platinums
    - Period of sensitization
    - _____ treatments
- Taxanes
    - _____ dose
    - Within 5-10 minutes
- Monoclonal antibodies
    - _____ doses
    - Rituximab

Management and Prevention of Reactions

- Management: _____ the infusion _____
- Stay _____
- Maintain the IV line
    - Begin flushing with compatible IV fluid
- Call for help and obtain a set of vital signs
- Oxygen if necessary
- Call the advanced professional practitioner or physician
- Do not _____ the patient _____
- Evaluate symptoms
- Administer _____ histamine antagonists/corticosteroids/bronchodilators
- Monitor vital signs Q15 minutes for one hour
- Continue or discontinue chemotherapy as ordered
- If the patient becomes unstable
    - Maintain patent airway
    - Place patient in supine position unless contraindicated by respiratory distress
    - Call a condition if symptoms do not resolve or patient is in distress

_____
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Management

- Mild to moderate _____ are considered grades 1 or 2 and do not involve symptoms of anaphylaxis
- These are the most common
- Management involves temporary interruption of the infusion and symptom management
- Treatment of severe infusion reaction (grade 3 or 4) and anaphylaxis requires discontinuation of the drug infusion and immediate treatment with epinephrine and antihistamines
- Rechallenging
    - Physician driven
        - Within 30-60 minutes of acute reaction
        - Next treatment and extra premeds on board
        - Not usually attempted if true anaphylactic event
- Desensitizing
    - _____ dose → _____/goal dose within hours
    - Temporary
    - Allergist supervision and 1:1 nursing care
    - Often in ICU
    - Multiple protocols
        - 12 step, 16 step, etc.
    - Safe and effective way of getting first line treatment

Medications for Infusion Reaction/Anaphylaxis

- Albuterol inhaler for severe _____
- Benadryl 50 mg IVP to relieve _____ and urticaria
- Epinephrine auto-injector 0.3mg/0.3ml IM every 5-15 minute as needed into, mid-outer thigh
- Hydrocortisone 100 mg-250 mg IVP to suppress rebound reaction
- Lorazepam 0.5 mg-4 mg IVP for anxiety
- Methylprednisolone 50-100 mg IVP to suppress rebound reaction
- Pepcid 20 mg IVP Relieve itching and urticaria

Prevention

- Identify risk factors
- Pre-medications
    - Antihistamines
    - Corticosteroids
    - Antiemetics
    - Pepcid
- Atypical premeds if history of reaction
- Extra steroid doses

_____
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When your patient begins to have a reaction, you are to stay calm and do what first?

A. Explain to the patient what is occurring to alleviate anxiety
B. Leave the room to call a physician
C. Remove the IV
D. Stop the infusion

A patient with ovarian carcinoma agrees to participate in a clinical trial involving a new agent with anaphylactic potential. What precautions should the nurse take the first time the drug is given?

A. Administer the agent only in an environment where emergency medication and equipment are available
B. Pre-medicate the patient with diazepam
C. Reject the patient as a candidate for the study
D. Take the vital signs before the agent is administered and every four hours thereafter

Documenting the Incident

- Patient's _____ prior to reaction
- Patient's signs/symptoms during reaction
- All vital signs taken _____ to infusion and ongoing assessment of the patient
- All interventions _____ reaction
- RiskMaster
- Allergy/side effect(s) to the medication
- Patient education
    - Potential for reactions post treatment
    - Seek emergency care at first signs
    - Alert other health care providers and known necessary premeds

Blood Products

Packed Red Blood Cells	Platelets
• Any time during transfusion • Most commonly see rigors/hives/pruritis/fever • Treat appropriately • Do not flush line during subsequent treatments • Larger Benadryl dose and/or addition of steroid	• Usually toward end of transfusion • Most commonly see hives/pruritus • Treat appropriately • Do not flush line during subsequent transfusions • Add steroid as premedication

Emend

- Irritating to vein
- Patients commonly have hypersensitivity
- Give slower through peripheral IV's and first-time doses

_____
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Miscellaneous Chemotherapeutic Agents

Miscellaneous Agents

Leukemia/Lymphoma	MM	Solid Tumors
APL Drugs • ATRA • Arsenic Trioxide IDH1 Inhibitor • Ivosidenib IDH2 Inhibitor • Enasidenib BCL-2 Inhibitor • Venetoclax HDAC Inhibitors • Vorinostat • Belinostat • Romidepsin	IMIDs • Thalidomide • Lenalidomide • Pomalidomide Proteasome Inhibitors • Bortezomib • Carfilzomib • Ixazomib KRAS Inhibitor • Sotorasib • Adagrasib	mTOR Inhibitors • Everolimus • Temsirolimus PI-3 Kinase Inhibitor • Idelalisib • Apelisib • Duvelisib CDK Inhibitors • Palbociclib • Ribociclib • Abemaciclib PARP Inhibitors • Olaparib • Rucaparib • Niraparib • Talazoparib Hedgehog Pathway Inhibitors • Vismodegib • Sonidegib

Acute Promyelocytic Leukemia (APL) Drugs
- All trans retinoic acid – ATRA (Tretinoin)
- Arsenic trioxide (Trisenox)

Tretinoin (all trans retinoic acid – ATRA)
- Indication
  - APL induction, consolidation, maintenance
- Dose, route and administration
  - 45 mg/m2/day PO in two equally divided doses
  - Take with a meal
  - Do not crush capsule
- Miscellaneous
  - t15;17 or PML-RARα must be present in bone marrow cytogenetics
  - Protect from light
  - Handling precaution: Do not handle medication or bodily fluids without gloves
- Dose Adjustments
  - APL differentiation syndrome

- Box warning
    - APL differentiation syndrome, leukocytosis, pregnancy
- Dosage and cost
    - Capsule: 10 mg
    - Each capsule: $30

Tretinoin Common Toxicities

- Fever 83%
- Headache 86%
- Dry skin 77%
- Dry mucous membranes 77%
- Malaise 66%
- Hemorrhage 60%
- Dyspnea 60%
- Infection 58%
- Nausea/vomiting 57%
- Peripheral edema 52%
- Leukocytosis 40%DIC 26%
- GI hemorrhage 34%
- Hypercholesterolemia < 60%
- Hypertriglyceridemia < 60%
- Transaminitis 50-60%
- Otalgia 23%
- Dizziness 20%
- Visual disturbances 17%
- Skin changes 14%

Tretinoin: Unique Toxicities

- Differentiation Syndrome
    - Release of intracellular cytokines from APL cells (25% of patients)
    - Fever, dyspnea, hypotension, edema, acute respiratory distress, weight gain, pleural and/or pericardial infiltrates, musculoskeletal pain, hyperbilirubinemia, hepatic and/or renal failure
    - Treat with steroids immediately
        - Dexamethasone 10mg IV q12h for 3 days
            - 30% mortality without therapy
            - ≤1% with therapy
- Pseudotumor Cerebri
    - ≤1% incidence
    - Papilledema, headache, nausea, vomiting, visual disturbances, intracranial noises, or pulsatile tinnitus
    - Increased incidence with concurrent tetracycline use
    - Treat with steroids
        - Prednisone 0.5 mg/kg daily

Patient Care Considerations

- Educate patients to report all side effects, especially APL differentiation syndrome, promptly
- Monitor CBC with differential, liver function, coagulation profile, cholesterol and triglyceride levels
- Avoid medications and supplements that contain vitamin A or vitamin A derivatives
- Handling precautions – do not handle medication or bodily fluids without gloves
- Avoid in 1st trimester in pregnancy
- Monitoring pregnancy status (1 week prior to treatment and monthly during treatment)
- Recommended to use two reliable forms of contraception during and for 1 month after tretinoin discontinuation, unless abstinence is the chosen method
- Avoid breastfeeding starting one week prior to and during treatment

Arsenic trioxide, ATO (Trisenox)

- Indication
    - APL induction
    - APL relapsed or refractory
- Dose, route and administration
    - 0.15 mg/kg/day IV once daily
    - Administer over 2 hours if acute vasomotor reactions: Flushing, sweating, tachycardia
    - Infuse over 4 hours
- Miscellaneous
    - Prior to administration, verify K > 4 and Mg > 1.8
        - Obtain EKG prior and frequently during treatment
    - Two different concentration solution are available: 10 mg /10 mL or 12 mg / 6 mL
    - Central venous catheter is not required
    - Administer hydroxyurea if WBC > 10,000
- Dose adjustments
    - Renal; hepatotoxicity during treatment; WBC <1000 or platelets <50K; APL differentiation syndrome; QTc prolongation; >Gr 2 nonhematologic

Trisenox Common Toxicities

- Nausea 75%
- Fatigue 63%
- Cough 65%
- Fever 63%
- Headache 60%
- Abdominal pain 58%
- Tachycardia 55%
- Diarrhea 53%
- Dyspnea 53%
- Hypokalemia 50%
- Hyperglycemia 45%
- Insomnia 43%
- Dermatitis 43%
- Arthralgia/myalgia 25-33%
- Leukocytosis 50% / >Gr 3 3%)
- Chest pain 25%Hypotension 25%
- Epistaxis 25%
- Pleural effusion 20%
- Depression 20%
- Transaminitis 13-20%
- Pain at injection site 20%
- Herpes simplex infection 13%
- Blurred vision 10%
- Hyperpigmentation 8%
- Renal failure syndrome 8%
- Otalgia 8%

Toxicities Requiring Modifications

- Differentiation syndrome: Incidence up to 31%
    - Treat with steroids immediately: Dexamethasone 10mg IV q 12h for 3 days
    - Dose reduce 50%, 0.075 mg/kg/day, for 7 days then up titrate
- QTc prolongation: 40% > 500 msec (torsades de pointes 3%)
    - Monitor QTc: Hold arsenic trioxide if QTc > 500 msec
        - Restart when QTc: 450 for men; 460 for women
    - Electrolyte abnormalities 45-50% (replace for K <1.8; Mg <4)
    - Dose reduce 50%, 0.075 mg/kg/day, for 7 days then up titrate
- Encephalopathy $\leq$ 1%
    - Monitor for thiamine deficiency: Replace with IV thiamine
- Leukocytosis: WBC > 10,000/mm3
    - Administer hydroxyurea until WBC < 10,000/mm3
    - Neutropenia: < 1000/mm3 and thrombocytopenia: < 50,000/mm3
        - Dose reduction required
    - Second malignancy

Patient Care Considerations

- Educate patients to report all side effects, especially APL differentiation syndrome promptly
- Monitor CBC with differential, renal function, hepatic function, glucose, and coagulation profile
- Monitor EKG before and during therapy for prolonged QT interval
- Do not administer with other QTc prolonging medications
- Do not start or discontinue meds without notifying provider
- Avoid in pregnancy
- Females should use contraceptives during and for six months after last arsenic trioxide dose
- Males with female partners should use contraceptives, even after vasectomy, during and for three months after last arsenic trioxide dose
- Avoid breastfeeding during and for two weeks after last arsenic trioxide treatment

Which one of the following should be monitored in a patient receiving arsenic trioxide?

A. Daily electrolytes (e.g., K+, Mg++)
B. EKG - QTc interval (at least weekly)
C. Daily CBC
D. All the above

IDH Inhibitor

- Ivosidenib (TIBSOVO)

Ivosidenib (TIBSOVO)

- Mechanism: Inhibits mutant IDH1 enzyme (7% to 14%)
- Indication: Acute myeloid leukemia
    - Newly diagnosed
        - Age ≥ 75 years or if comorbidities that preclude intensive induction chemotherapy
    - Relapse/refractory
        - Susceptible IDH1 mutation detected by approved test
- Dosing and administration
    - PO – 500mg PO daily: > 6 months
    - Administer with or without food: No high fat meals
- Dose adjustments
    - Toxicity: Renal and hepatic insufficiency, not studied
- Box warnings
    - Differentiation syndrome

Ivosidenib – Common Toxicities

- Diarrhea: 34-61%
- Fatigue: 39-50%
- Edema: 32-43%
- Arthralgia: 32-36%
- Myalgia: 18-25%
- Dyspnea: 29% to 33%
- Skin rash: 14-26%
- Fever: 23%
- Dizziness: 21%
- Tumor lysis syndrome (TLS): 8%; > grade 3/4: 6%
- Increased serum creatinine: 23-29%
- Increased uric acid: 29-32%
- Decreased K: 31-43%
- Decreased Na: 39%
- Decreased Mg: 25-38%
- Decreased serum Ca: 25%
- Decreased Phos: 21-25%
- Increased AST: 27-29%
- Increased ALT: 14-15%

Ivosidenib Toxicities Requiring Dose Modifications

- Differentiation Syndrome: 19-25%; grade 3/4: 11-13%
    - Occurs from Day 1 to 3 months. Treat with steroids immediately
        - Dexamethasone: 10mg IV q 12h for 3 days
- QT Prolongation: 21-26% and ventricular arrythmias: < 1%
    - Interrupt ivosidenib treatment if QTc increases to > 480 msec but < 500 msec
        - Restart at 500 mg daily after the QTc interval returns to ≤ 480 msec
    - If QTc increases to >500 msec, interrupt treatment
    - Restart at 250 mg daily after the QTc interval returns to ≤ 480 msec
        - Monitor ECGs at least weekly for 2 weeks
        - Permanently discontinue if there is QTc interval prolongation with signs or symptoms of life-threatening arrhythmia
- Non-infectious leukocytosis: WBC >25,000/mm^3 or absolute WBC increase from baseline of >15,000/$mm^{3,}$ 36-38%; grade 3/4: 7-8%
    - Initiate cytoreduction therapy: Hydroxyurea, or leukapheresis, if clinically indicated
- Grade 3 or higher toxicity
    - Interrupt ivosidenib treatment until resolves to $\leq$ grade 2
    - Resume ivosidenib at 250 mg daily; may increase to 500 mg daily if toxicity resolves to $\leq$ grade 1
    - If $\geq$ grade 3 toxicity recurs, discontinue
- Guillain-Barré syndrome: < 1%, permanently discontinue

IDHI2 Inhibitor: Idhifa (enasidenib)

Enasidenib (Idhifa): Common Toxicities

- Nausea: 50%
- Diarrhea: 43%
- Decrease appetite: 34%
- Vomiting: 34%
- Acute respiratory distress: ≤ 10%
- Pulmonary edema: ≤ 10%
- Decreased Ca: 74%
- Decreased K: 41%
- Increased serum bilirubin: 81%
- Abnormal phosphorus levels: 27%; grade 3/4: 8%
- TLS: 6%

Enasidenib Toxicities Requiring Modifications

- Differentiation syndrome: 14%
  - Occurs from Day 1 to 5 months
  - Treat with steroids immediately: Dexamethasone 10mg IV q 12h for 3 days
- Noninfectious leukocytosis: WBC >30,000/mm^3, 12%; grade 3/4: 6%
  - Initiate cytoreduction therapy: Hydroxyurea
  - Hold if leukocytosis is not improved, then resume 100 mg daily when WBC <30,000/mm^3
- Hepatotoxicity during treatment: Up to 81%
  - Bilirubin > 3 times ULN for ≥ 2 weeks without elevated transaminases or other hepatic disorders
    - Reduce dose to 50 mg daily
    - Resume at 100 mg daily if bilirubin resolves to <2 times ULN
- Grade 3 or higher toxicity (considered to be treatment-related)
  - Hold until toxicity improves to ≤ grade 2
  - Resume at 50 mg daily; may increase to 100 mg daily if toxicity resolves to ≤ grade 1
- If ≥ grade 3 toxicity recurs, discontinue enasidenib

IDH1 and IDH2 Inhibitors: Patient Care Considerations

- Educate patients to report all side effects, especially differentiation syndrome, promptly
- CBC with differential, LFTs, and blood chemistries
  - Baseline and every 2 weeks for at least the first 3 months
- Monitor for signs/symptoms of differentiation syndrome
- Monitor for tumor lysis syndrome
- Pregnancy test: Prior to treatment in females of reproductive potential
  - Effective contraception should be used during therapy and $\underline{\geq}$ 2 months after the last dose
  - Male patients with female partners of reproductive potential should also use effective contraception during therapy and for at least 2 months after the last dose
- Do not breastfeed for at least 2 months after the last dose
- Only available at authorized specialty pharmacies

BCL-2 Inhibitor

- Venetoclax (Venclexta)

Venetoclax (Venclexta)

- Mechanism: Cytotoxic activity in tumor cells which overexpress BCL-2
  - Venetoclax selectively inhibits and binds directly to the BCL-2 protein, displacing pro-apoptotic proteins and restoring the apoptotic process
- Indications
  - Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma
    - Monotherapy and in combination treatment

- Newly diagnosed AML
  - Combination treatment: In combination with azacitidine, decitabine, or low dose cytarabine
- Age ≥ 75 years or with comorbidities that do not allow use of intensive induction chemotherapy
- No box warning

- Tumor lysis syndrome (TLS)
  - Administer prophylactic hydration and anti-hyperuricemics prior to the first dose
  - WBC should be < 25,000/mm^3 prior to initiation of venetoclax
    - Cytoreduction prior to treatment may be required

Dosing Varies by Indication

	CLL	AML
Dosing	Monotherapy • Week 1: 20 mg daily • Week 2: 50 mg daily • Week 3: 100 mg daily • Week 4: 200 mg daily • Week 5: 400 mg daily	Combination therapy • Day 1: 100 mg daily • Day 2: 200 mg daily • Day 3: 400 mg daily • Day 4: 600 mg daily, if needed
Combination Therapy	Venetoclax in combination until disease progression or unacceptable toxicity: • With obinutuzumab: Cycle 1, day1 o Initiate venetoclax increase on cycle one day 22 of 28-day cycle o Continue until the end of cycle 12 • With rituximab: Begin rituximab after increasing complete on week 5 and thereafter o 400 mg daily o Continue for up to 24 months	Venetoclax in combination until disease progression or unacceptable toxicity • With azacitidine or decitabine o Max 400 mg daily • With low-dose cytarabine o Max 600 mg daily
Dose Adjustment	Concomitant strong or moderate CYP3A inhibitors or P-gp inhibitors • >75% for strong CYP3A inhibitors • >50% for moderate CYP3A inhibitors or P-gp inhibitors Severe hepatic impairment, Child-Pugh class C: Reduce dose by 50%	

Venclexta Drug-Drug Interactions

- p inhibitors
  - Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
- Moderate CYP3A inhibitors
  - Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
- Strong CYP3A inhibitors
  - Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole*, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole
- Moderate CYP3A4 inducers
  - Bosentan, efavirenz, etravirine, phenobarbital, primidone
- Strong CYP3A4 inducers
  - Apalutamide
  - Carbamazepine
  - Enzalutamide
  - Mitotane
  - Phenytoin
  - Rifampin
  - St. John's wort

Venclexta Toxicities

- Increased AST: 53%
- Diarrhea: 43%
- Nausea: 42%
- Upper respiratory tract infection: 36%
- Fatigue: 32%
- Musculoskeletal pain: 29%
- Edema: 22%
- Cough: 22%
- Fever: 18%
- Headache: 18%
- Abdominal pain: 18%
- Skin rash: 18%
- Dizziness: 14%
- Pneumonia: 14%
- Febrile neutropenia: 6%
  - ≥ Gr 3: 6%
- Leukopenia: 89%
  - > Gr 3/4: 42%
- Neutropenia: 50% to 87%
  - Gr 3: 45-63%
  - Gr 4: 33%
- Lymphocytopenia: 11-74%
  - Gr 3: 7-40%; Gr 4: 9%
- Anemia: 33-71%
  - ≥ Gr 3: 18-26%
- Thrombocytopenia: 29-64%
  - Gr 3: 20-31%; Gr 4: 15%)
- Tumor lysis syndrome (TLS)
  - 2-3-week ramp-up phase 13%
  - 5-week ramp-up phase: 2%
- Hyperuricemia: 10%
- Hypocalcemia: 16-87%
- Hyperkalemia: 17-59%
- Hypophosphatemia: 45%
- Hyponatremia: 40%
- Hyperglycemia: 67%

Patient Care Considerations

- Determine whether venetoclax should initiated in inpatient or outpatient setting
- Review patient's home medications for drug interactions
- Order appropriate venetoclax dosage and supply based on ramp-up dosing schedule
    - Available as 10 mg, 50 mg, and 100 mg tablets
    - NOTE: The "CLL/SLL Starting Pack" should not be used for AML patients
- Start allopurinol or other xanthine oxidase inhibitor at least 2-3 days before first dose
- Instruct patient to begin oral hydration (1.5-2 L/day) 2 days before the first dose
- Contact patient PRIOR to scheduled treatment appointment to verify the following:
    - Patient received venetoclax supply
    - Patient stopped taking any interacting medications as instructed (if applicable)
    - Patient started taking allopurinol and oral hydration as instructed
    - Patient will bring venetoclax and a meal with them to clinic appointment

HDAC Inhibitors

- Vorinostat (Zolinza)
- Belinostat (Beleodaq)
- Romidepsin (Isodax)

Vorinostat (Zolinza)

- Indication
    - Cutaneous T-cell lymphoma
    - Lymphoma: Relapsed or refractory
- Route of Administration
    - PO Take with food
- Dosing and schedule
    - 400 mg daily
- Dose adjustment
    - Hepatic
    - Grade 4 anemia or thrombocytopenia
- Box warning
    - None
- Dosage forms and cost
    - 100 mg capsule
    - $150 per capsule

Belinostat (Beleodaq)

- Indication
    - Peripheral T-cell lymphoma
    - Lymphoma: Relapsed or refractory
- Route of administration
    - IV 30-minute infusion using 0.22-micron inline filter
- Dosing and schedule
    - 1000 mg/m2 on D1-5: 21-day cycle

- Dose adjustment
  - UGT1A1*28: 750 mg/m2
  - Platelets < 25k
  - Absolute neutrophil count (ANC) < 500
  - Any > grade 3 nonhematologic toxicity
- Box warning
  - None
- Dosage forms and cost
  - 500 mg vial
  - $2882 per vial

Isodax (romidepsin)

- Indication
  - Cutaneous T-cell lymphoma
  - Peripheral T-cell lymphoma
- Route of administration
  - IV over four hours
- Dosing and schedule
  - 14 mg/m^2 on day 1, 8, 15, of a 28-day cycle
- Dose adjustment
  - Hepatic
  - Febrile neutropenia
  - Any > grade 3 nonhematologic toxicity
- Box warning
  - None
- Dosage and cost
  - 10 mg vial
  - $3838 per vial

Side Effects	Vorinostat	Belinostat	Romidepsin
Hyperglycemia	8-69%	-	< 52%
Peripheral edema	13%	20%	6-10%
Proteinuria	51%	0%	0%
Increased serum creatinine	16-47%	> 2%	-
Transaminitis	-	-	2-28%
QTc prolongation	3-4%	11%/≥ Gr 3 -4%	< 10%
VTE – DVT/PE	1%/5%	0%	< 10%
Fever	11%	35%	20-47%
Fatigue	52%	37%	77%
Skin rash	-	20%	-
Squamous cell carcinoma	3.5%	-	-
Dyspnea	-	22%	13-21%
Infection	< 1%	2-3%	< 54%

Alopecia	19%	-	-
Diarrhea	52%	23%	12-40%
Nausea	41%	42%	56-86%
Vomiting	15%	29%	34-52%
Anemia	14%/≥ Gr 3- 2.3%	32%/11%	< 72%/ ≥ Gr 3- 11-28%
Thrombocytopenia	26%/≥ Gr 3- 3%	16%/7%	< 66%/ ≥ Gr 3- 24-36%
Dizziness	15%	29%	-
Hypotension	10%	10%/≥ Gr 3 – 3%	7-23%
Headaches	12%	15%	15-34%
Injection site pain	-	14%	-
Electrolyte abnormalities	-	12% (K)	< 52% (Mg, Ca, K, Na, Phos, uric acid, albumin

Vorinostat: Patient Care Considerations

- Monitor CBC and chemistries every two weeks for the first two months of therapy, then monthly
- Monitor hepatic function
- Monitor for signs of dehydration and treat all pre-existing electrolyte abnormalities
- Handling precautions: Do not handle medication or bodily fluids without gloves
- Females should use contraceptives for six months after last vorinostat dose
- Males with female partners should use contraceptives for three months after last vorinostat dose
- Avoid breastfeeding during and for one week after last vorinostat dose

Belinostat: Patient Care Considerations

- Monitor CBC and hepatic and renal function
- Monitor for signs/symptoms of dehydration and correct all pre-existing electrolyte abnormalities
- Monitor for skin toxicity
- Monitor liver function tests before treatment and before the start of each subsequent cycle
- Genetic counseling - Homozygous for the UGT1A1*28 allele
- Females should use contraceptives for six months after last belinostat dose
- Males with female partners should use contraceptives for three months after last belinostat dose
- Avoid breastfeeding during and for two weeks after last belinostat dose

Romidepsin: Patient Care Considerations

- Monitor CBC and electrolytes (Ca, Mg, K, Phos)
    - Ensure K and Mg are normal before administering
- Consider monitoring EKG in patients with:
    - History of cardiovascular disease (also congenital long QT syndrome) and/or are taking concurrent medications that can prolong QT interval

- Risk for increased toxicities with concurrent use with strong CYP3A4 inhibitors
- Avoid use with rifampin and strong CYP3A4 inducers – decreased efficacy
- Handling precautions: Do not handle bodily fluids without gloves
- Monitor for infections
- Pregnancy test seven days prior to romidepsin treatment
- Females should use contraceptives for one month after last romidepsin dose
- Males with female partners should use contraceptives for 1 months after last romidepsin dose
- Avoid breastfeeding during and for 1 week after last romidepsin dose

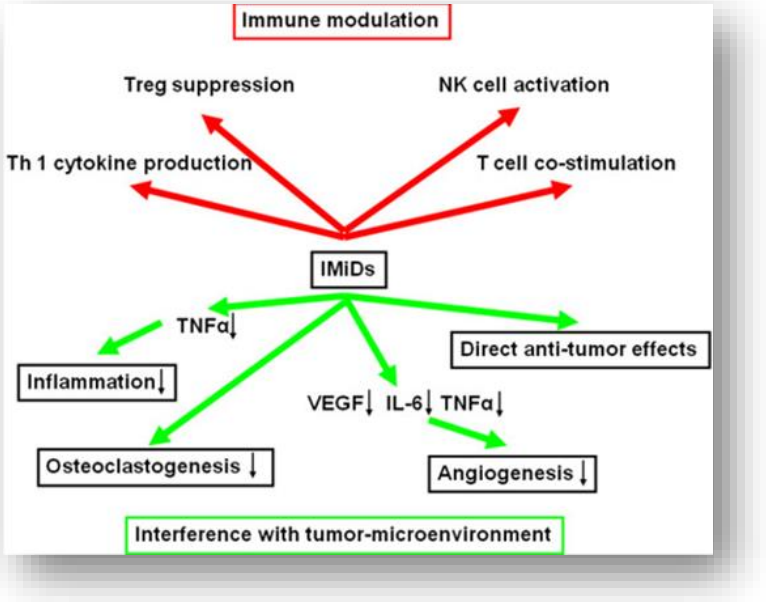
Immunomodulatory Agents: IMiDs: Immunomodulatory imide drugs

- Thalidomide (thalidomide)
- Enalidomide (lenalidomide)
- Pomalidomide (pomalidomide)

Risk Evaluation Mitigation Strategy (REMS)

- Patient and prescriber MUST complete monthly survey before drug can be dispensed
- Patient, pharmacy, and physician must all be enrolled in Thalidomide, Revlimid, or Pomalyst REMS program
    - Celgeneriskmanagement.com 1-888-423-5436
- Women of childbearing potential must have pregnancy test monthly

Mechanism of Action



Thalidomide

- Indication
  - Multiple myeloma (MM)
    - New diagnosis
    - Relapse/refractory
  - Also use in non-malignancy
- Administration
  - Oral: Bedtime, > 1hr after evening meal
  - Swallow capsules whole with water
- Dosing in combination with dexamethasone
  - 200 mg daily
- Dosing adjustments
  - ANC ≤750/mm3
  - Dermatologic reactions
  - Grade 3 or 4 adverse events
  - Non-hematologic toxicity
- Box warning
  - Thromboembolic events
  - Pregnancy
- Dosage forms and cost
  - Capsule: 50, 100, 150, 200 mg
  - $379 each capsule

Lenalidomide

- Indications
  - Multiple Myeloma
    - New diagnosis
    - Relapse/refractory
  - Myelodysplastic syndrome (MDS)
  - Lymphoma
- Administration
  - Oral with or without food
  - Swallow capsule whole
- Dosing in combination with dexamethasone
  - 25 mg daily on days 1 to 21 days of a 28-day cycle
- Dosing adjustments
  - Renal impairment: Creatinine clearance < 60 mL/min
  - Hematologic
  - Non-hematologic toxicity
- Box warning
  - Thromboembolic events
  - Pregnancy
- Dosage forms and cost
  - Capsule: 2.5, 5, 10, 15, 20, 25 mg
  - $1042 each capsule

Pomalidomide

- Indication
  - Multiple Myeloma
    - New diagnosis
    - Relapse/refractory
- Administration
  - Oral without regard to meals
  - Swallow capsule whole with water
- Dosing in combination with dexamethasone
  - 4 mg daily on days 1 to 21 of 28-day cycles
- Dosing adjustments
  - Strong CYP1A2 Inhibitors
  - Hepatic impairment
  - Hematologic
  - Non-hematologic toxicity
- Box warning
  - Thromboembolic events
  - Pregnancy
- Dosage forms and cost
  - Capsule: 1, 2, 3, 4 mg
  - $1042 each capsule

Other Indications

- Thalidomide
  - Leprosy
  - AIDs-related aphthous stomatitis, chronic graft-versus-host disease, amyloidosis, Waldenström macroglobulinemia
- Lenalidomide
  - Low or Intermediate 1-risk MDS (del 5q)
  - Mantle cell lymphoma (MCL)
  - Marginal zone lymphoma
  - Follicular lymphoma
  - Chronic lymphocytic leukemia (relapsed/refractory), diffuse large B cell lymphoma, amyloidosis
- Pomalidomide
  - Kaposi sarcoma

Side Effects	Thalidomide	Lenalidomide	Pomalidomide
Drowsiness	≤ 38%	20%	-
Dizziness	≤ 4%	20%	22%
Headache	≤ 13%	9-20%	15%
Peripheral neuropathy	≤ 10%	5-10%	22%
Constipation	≤ 4%	13-24%	22%
Diarrhea	-	39-49%	35%
Fatigue	≤ 8%	11-34%	< 58%
Myalgias	Not defined	7-99%	12%
Fever	-	21-23%	23%
Thromboembolic events	3-4%/22.5%	3-6%/26%	4%/17%
Peripheral edema	≤ 4%	16-20%	25%
URI	Not defined	11-15%	37%
Increased serum creatinine	-	Not defined	19%
Rash	≤ 4%	8-36%	21%
Neutropenia	Not defined	49-61%/ ≥ Gr 3-43-54%	53%/ ≥ Gr 3-48%
Thrombocytopenia	Not defined	24-62%/ ≥ GR 3-13-50%	26%/≥ Gr 3-22%

IMiDs: With steroids and other agents and Venous Thromboembolism (VTE) Risk

- Thalidomide, lenalidomide or pomalidomide monotherapy: VTE risk < 5%
- Thalidomide or lenalidomide plus low-dose dexamethasone: VTE risk is 12-14%
- Thalidomide or lenalidomide plus high-dose dexamethasone: VTE risk > 20%
  - Pomalidomide plus high-dose dexamethasone is slightly less: VTE risk 17%

VTE Risk and Anticoagulation

- Low Risk: Aspirin 81mg vs no anticoagulation required
- Standard Risk: Aspirin > warfarin vs low-molecular-weight heparin (LMWH)
- High Risk: Warfarin vs LMWH

_____
_____
_____
_____
_____

- Direct Oral Anticoagulants (DOACs): Limited data with prophylaxis dosing

Anticoagulation

- Decrease VTE risk to ≤ 10%
- Continue as long as receiving thalidomide or lenalidomide

IMiDs: Multiple Myeloma

Patient Care Considerations

- Notify provider if skin rash develops
- Monitor for s/s of thromboembolic events
- Do not donate blood during treatment or for 1 month after stopping treatment
- Precautions: do not handle medication or bodily fluids without gloves
- Education about risk for birth defects with males and females
    - Need to use double barrier methods of contraception
- Thalidomide specific
    - Bowel regimen to prevent constipation
    - Administer at bedtime
- Lenalidomide specific
    - Monitor CBC (hold for ANC <1000 and/or platelets < 30,000)
    - Increased risk of secondary malignancy (e.g., AML)
- Pomalidomide specific
    - Monitor CBC, LFTs, and serum creatinine
    - Liver metabolism CYP1A2 and CYP3A4: Need to watch for drug interactions
    - Smoking may also reduce efficacy of pomalidomide

Which one of the following is not true regarding thalidomide and/or lenalidomide?

A. Patient and provider must enroll in the REMS programs
B. Warfarin (INR goal = 2-3) is appropriate Venous thromboembolism (VTE) prophylaxis for a patient receiving bortezomib, thalidomide and dexamethasone
C. Significant peripheral neuropathy can occur from treatment
D. All patients receiving lenalidomide monotherapy require VTE prophylaxis

Proteasome Inhibitors

- Bortezomib (Velcade)
- Carfilzomib (Kyprolis)
- Ixazomib (Ninlaro)

Velcade (bortezomib)

- Indication
    - New diagnosis
    - Relapsed or refractory MM or mantle cell lymphoma (MCL)
- Type of inhibitor
    - Reversible

- Route of administration
  - IVP 3-5 secs
  - Subcutaneous injection: Abdomen or thigh
- Dosing and scheduling
  - 1.3 mg/m2 range 1 to 1.5 mg/m2 on D1, 4, 8, and 11 of 21 day cycle
  - Doses separated by > 72 hrs
- Dose Adjustments
  - Hepatic
  - Platelets <30k
  - ANC <750
  - Any > grade 3 nonhematologic toxicity
- Dosage and cost
  - 3.5 mg vial
  - $1827

Carfilzomib (Kyprolis)

- Indication
  - Relapse/refractory MM
- Type of inhibitor
  - Irreversible
- Route of Administration
  - IV 10 to 30 minutes
- Dosing and Schedule
  - C1: 20 mg/m2
  - C2-CX: 27 alternate 56 or 70 mg/m2 on D1,2,8,9,15, and 16 of 28 day cycle
    - Hydrate prior and after
- Dose adjustments
  - Hepatic; renal
  - Platelets < 10K
  - ANC <500

Ixazomib (Ninlaro)

- Indication
  - After one line of treatment
- Type of inhibitor
  - PO: > 1h prior to and > 2hr after meals
- Dosing and schedule
  - 4 mg weekly on D1,8, and 15 of a 28-day cycle
- Dose Adjustments
  - Hepatic; renal
  - Platelets < 30k
  - ANC <500
  - Any > grade 3 nonhematologic toxicity

- Dosage form and cost
    - Capsule: 2, 3, 4, mg
    - $5190

Side Effects	Bortezomib	Carfilzomib	Ixazomib
Fatigue	7-52%	40-52%	-
Neutropenia	5-27%	19-21%	67%
Anemia	12-23%	42-49%	-
Thrombocytopenia	Up to 52%	32-54%	78%
Peripheral neuropathy	IV: 35-54%/SC:37%	< 20%/≥ Gr 3 – 1%	28%
Neuralgia	23%	-	-
Hypotension	8-9%	-	-
Hypertension	6%	15-42%	-
Chest pain	-	3-21%	-
Peripheral edema	7%	20%	25%
Back pain	1-17%	12-21%	21%
Upper respiratory infection	11-15%	19-21%	21%
Fever	8-23%	30-58%	-
Skin rash	12-28%	-	-
Dyspnea	15-23%	34-58%	-
Nausea	16-52%	35-54%	26%
Vomiting	9-29%	17-33%	22%
Diarrhea	19-52%	25-27%	42%
Constipation	18-34%	21%	34%
Dizziness	10-18%	13%	-
Injection site reaction	IV 5%, SC 6%	-	-
Hepatotoxicity	Case reports	-	<1%
Increases serum creatinine	-	17-25%	-
Renal insufficiency	-	10%	-
Headache	14-26%	24-33%	-
Eye disease	-	-	26%
Blurred vision	-	<10%	6%

Which sites are preferred for bortezomib administration?

A. Gluteal and abdomen (rotating)
B. Thigh and abdomen (rotating)
C. Deltoid and thigh (rotating)
D. Abdomen (rotating)

Bortezomib: Patient Care Considerations

- Monitor CBC and hepatic function
- Monitor blood pressure and EKG/cardiac function
- Assess for peripheral neuropathy at baseline and every visit

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- For subcutaneous injection, rotate injection sites
- Do not take or start new medications with consulting provider
    - Avoid CYP3A4 inhibitors or inducers and grapefruit juice
- Avoid green tea and green tea extracts ascorbic acid (do not 12 hrs before or after) – reduce efficacy
- Females - use contraceptives for 7 months after last bortezomib dose
- Males with female partners should use contraceptives for 4 months after last bortezomib dose
- Avoid breastfeeding during and for 2 months after last bortezomib dose

Carfilzomib: Patient Care Considerations

- Monitor CBC and hepatic and renal function
- Monitor blood pressure and EKG/cardiac function
    - Hypertension should be controlled prior to beginning carfilzomib and monitored continually during treatment
- Infusion-related reaction (within 24 hours of infusion)
- Use a lower starting dose with mild to moderate hepatic impairment
- Females should use contraceptives for 6 months after last bortezomib dose
- Males with female partners should use contraceptives for 3 months after last bortezomib dose
- Avoid breastfeeding during and for 2 weeks after last bortezomib dose

Ixazomib: Patient Care Considerations

- Monitor CBC and hepatic and renal function
- Monitor gastrointestinal and dermatologic toxicity
- Assess for peripheral neuropathy at baseline and every visit
- Monitor for peripheral edema
- If a dose is missed, then administer only if the next scheduled dose is $\geq$72 hours away
- If vomiting occurs, do not repeat the dose
- Handling precautions – do not handle medication without gloves
    - Avoid skin or eye exposure (wash or flush immediately)
    - Females should use contraceptives for at least 90 days after last dose
    - Avoid breastfeeding during and for 90 days after last ixazomib dose

mTOR Inhibitors

- Temosirolimus (Torisel)
- Everolimus (Afinitor)

Temsirolimus

- Indication
    - Advanced renal cell carcinoma
- Dosing, route, and administration
    - 25 mg IV over 30-60 minutes every week
        - Vial contents must be diluted with the enclosed diluent before diluting in 250 mL of 0.9% NaCl

- Premedication
    - Diphenhydramine 25-50 mg, thirty minutes before treatment

- Dosing adjustments
    - Hepatic
    - ANC < 1000
    - Platelets < 75k
        - Any grade 3 nonhematologic toxicity
- Contraindications
    - Moderate to severe hepatic impairment
- Box warning
    - None
- Dosage forms and cost
    - 25 mg/ml
    - $1910

Everolimus

- Indication
    - 10 mg PO once daily
    - Take with or without food
    - Do not chew, crush, or break
    - Tablets to make oral suspension are not interchangeable
- Premedication
    - None
- Dosing adjustments
    - Hepatic
    - ANC <500
    - Platelets < 50K
        - Grade 2 nonhematologic toxicity
    - Neutropenic fever
    - Pneumonitis
    - Stomatitis
    - Metabolic toxicity
- Dosage forms and costs
    - Tablets: 2.5, 5, 7.5, 10 mg Afinitor tablets
    - $738 per 10 mg tablet

Side Effects	Temsirolimus	Everolimus
Skin rash	47%	21-59%
Nail disease	14%	5-22%
Peripheral edema	35%	13-39%
Chest pain	16%	5%
Headache	15%	< 30%
Mucositis	41%	-
Vomiting	19%	15-29%
Diarrhea	27%	14-50%

Abdominal pain	21%	5-36%
Dysgeusia	20%	5-19%
Stomatitis	20%	44%/≥ grade three 4-9%
Decreased hemoglobulin	94%/≥ grade three < 15%	41-92%/≥ grade three < 15%
Decreased neutrophils	19%/≥ grade three 5%	14-46%/≥ grade three <9%
Thrombocytopenia	40%/≥ grade three < 1%	19-45%/> grade three 9%
UTI	15%	9-31%
Infections	20%/≥ grade three 3%	37-74%
Dyspnea	28%	20-24%
Pneumonia	8%	6-19%
Fever	24%	20-31%
Increased Alk Phos	68%/≥ grade three 3%	32-74%
Increased AST	38%/≥ grade three 2%	23-67%
Increased serum creatinine	57%/≥ grade three 3%	5-50%
Increased glucose	89%/≥ grade three 16%	-
Increased cholesterol	87%/≥ grade three 2%	66-85%
Hypertriglyceridemia	83%/≥ grade 44%	27-73%
Hypophosphatemia	49%/≥ grade three 18%	9-49%
Hyperglycemia	26%	13-75%
Hypocalcemia	-	37%
Hypokalemia	21%/≥ grade three 5%	23-27%
Hyperbilirubinemia	8%	3%
VTE	2%	< 1%
Hypertension	7%	4-13%
GI hemorrhage/perforation	1%	3%
Wound healing impairment	1%	< 1%

Temsirolimus Patient Care Considerations

- Monitor CBC, glucose, lipid profile, renal and hepatic function
- Monitor for GI toxicity, respiratory status, infection and hemorrhage
- Monitor for hypersensitivity reactions throughout entire infusion (Polysorbate 80)
- Avoid concomitant strong CYP3A4 inducers and/or inhibitors
    - Avoid grapefruit and grapefruit juice
- Use with caution in perioperative period due to risk of abnormal wound healing
- Handling precautions – do not handle bodily fluids without gloves
- Females should use contraceptives for three months after last temsirolimus dose
- Males with female partners should use contraceptives for three months after last temsirolimus dose
- Avoid breastfeeding during and for 3 weeks after last temsirolimus treatment

Everolimus Patient Care Considerations

- Monitor CBC, glucose, lipid profile, renal and hepatic function
- Monitor for GI toxicity, respiratory status, infection and hemorrhage
- Monitor for hypersensitivity reactions throughout entire infusion (Polysorbate 80)
- Avoid concomitant strong CYP3A4 inducers and/or inhibitors

    - Avoid grapefruit and grapefruit juice
- Use with caution in perioperative period due to risk of abnormal wound healing
- Handling precautions – do not handle medication or bodily fluids without gloves
- Can cause infertility
    - Females: menstrual irregularities, secondary amenorrhea, and increased LH and FSH / males: azoospermia and oligospermia
- Females should use contraceptives for two months after last everolimus dose
- Males with female partners should use contraceptives for 1 months after last dose
- Avoid breastfeeding during and for two weeks after last everolimus treatment

KRAS Inhibitor

- Sotorasib (LUMAKRAS)
- Adagrasib (KRAZATI)

Sotorasib

- Indication
    - Non-small cell lung cancer, locally advanced or metastatic, KRAS G12C mutated (1 prior therapy)
- Dosing route and administration
    - 960 mg PO daily
    - Take with or without food
    - Avoid with PPIs and H2 receptor antagonists. If cannot avoid, administer sotorasib 4 hrs before or 10 hrs after antacid
- Dose adjustments
    - Hepatic (tx-related); Nonhematologic (Nausea; Vomiting; Diarrhea; Pulmonary); Drug Interactions
- Dosage form and cost
    - Tablet: 120 mg: $106 per tablet

Adagrasib

- Indication
    - Non-small cell lung cancer, locally advanced or metastatic, KRAS G12C mutated (1 prior therapy)
- Dosing route and administration
    - 600 mg PO BID
    - Take with or without food
    - Antiemetic required
- Dose adjustments
    - Hepatic (tx-related);QTc prolongation; Nonhematologic (Gr 3/4; Nausea; Vomiting; Diarrhea; Pulmonary);
- Dosage form and cost
    - Tablet: 200 mg: $148 per tablet

Side Effects	Sotorasib	Adagrasib
Diarrhea	42%	70%
Nausea / vomiting	26% / 17%	69% /56%
Peripheral edema	15%	32%
Fatigue	26%	59%
Skin rash	15%	-
Increased CPK	-	50%
Musculoskeletal pain	35%	41%
Urinary Protein	29%	-
Cough	20%	24%
Dyspnea	16%	35%
Pneumonia	12%	24%
Pneumonia	12%	24%
Interstitial Lung Disease	<1%	4.1%
Pneumonitis	<1%	2%
Anemia	43% / ≥Gr 3 <1%	3%
Lymphocytopenia	48% / ≥Gr 3 2%	64% / ≥Gr 3 25%
Thrombocytopenia	-	27%
Prolonged PTT	23% / / ≥Gr 3 2%	-
Renal insufficiency	-	36%
Hepatotoxicity	25%	37%
↑ ALT	38%	46%
↑ AST	39%	52%
↑ Alk Phos	33%	-
↓ Ca ++	35%	-
↓ Na +	28%	-
↓ Mg ++	-	26%
↓ K+	-	26%

Sotorasib: Patient Care Considerations

- Monitor hepatic function tests prior to initiation, every 3 weeks for 3 months, and then monthly
- Monitor for interstitial lung disease/pneumonitis
- Extensive drug-drug interactions (requires dose adjustment)
- CYP3A4 substrate (major)
- Induces CYP 3A4 (moderate)
- Monitoring pregnancy status prior to initiation. There are no recommendations regarding monitoring pregnancy status or use of contraceptives
- Avoid breastfeeding during and for 1 week after last sotorasib dose

Adagrasib: Patient Care Considerations

- Monitor hepatic function tests prior to initiation, every month for 3 months
- Monitor for interstitial lung disease/pneumonitis
- Monitor electrolytes & fluid status (GI toxicity – nausea, vomiting, diarrhea)

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- Monitor for ECGs at baseline and as clinically needed or with addition of other QTc prolonging medications
- Avoid CYP3A4 inhibitors and inducers
- Adagrasib can cause infertility
- Monitoring pregnancy status prior to initiation. There are no recommendations regarding monitoring pregnancy status or use of contraceptives
- Avoid breastfeeding during and for 1 week after last adagrasib treatment

PI-3 Kinase Inhibitors
- Idelalisib (Zydelig)
- Alpelisib (Pigray)
- Duvelisib (Copiktra)

Idelalisib
- Classification
  - PI3K Isoform Specific
- Indication
  - Relapsed CLL, SLL, and Follicular B-cell NHL
- Dosing route and administration
  - 150 mg PO twice daily
  - Take with or without food
- Miscellaneous
  - Specialty Pharmacy
  - Medication Guide
  - Severe hypersensitivity
- Box warnings
  - Diarrhea
  - Hepatic
  - Pneumonitis
  - Infection
  - GI perforation
- Dose adjustments
  - Hepatic: Treatment related
  - ANC < 500
  - Platelets < 25K
  - Diarrhea
- Dosage forms and cost
  - Tablets: 100, 150 mg
  - $225 each tablet

Alpelisib
- Classification
  - PI3K Isoform Specific
- Indication
  - Breast cancer: HR+/HER2-/PIK3CA mutated

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- Dosing route and administration
    - 300 mg PO once daily with fulvestrant
    - Take with food
- Miscellaneous
    - Therapy pack tablets
- Dosing adjustments
    - Hepatic treatment-related
    - ANC < 500
    - Platelets < 25K
    - Nonhematologic
- Dosage forms and cost
    - Tablets: 50, 150, 200 mg
    - Therapy Pack: 200, 250, 300
    - $700 each therapy pack

Duvelisib

- Classification
    - Pan-PI3K Inhibitor
    - (PI3K-δ & PI3K-γ)
- Indication
    - Relapsed or refractory CLL/SLL (after 2 prior therapies)
- Dosage and administration
    - 25 mg PO BID
    - Take with or without food
- Dosing adjustments
    - Hepatic (tx-related); dermatologic; diarrhea or colitis; ANC <500; Plts <25K; infection; CMV; PJP; pneumonitis; moderate or strong CYP3A inducers / strong CYP3A inhibitors
- Box warning
    - Infections, diarrhea or colitis, cutaneous reactions and pneumonitis
- Dosage form and cost
    - Tablets: 15 mg, 25 mg: $566 per tablet

Side Effects	Durelisib	Idelalisib	Alpelisib
Fatigue	25-29%	30%	42%
Hypertension	-	-	-
Peripheral edema	11-14%	10%	15%
Alopecia	-	10%	15%
Skin rash	27-31%	21%	52%
Diarrhea	<57%/> grade 3 25%	47%/≥ grade 3: 3%	58%/≥ grade 3: 3%
Nausea/vomiting	24%/16%	29%/15%	45%/27%
Stomatitis	14%	-	30%
Hyperglycemia	-	59%	65%
Hypertriglyceridemia	-	62%	-
Anaphylaxis	-	< 1%	0.7%
Severe dermatologic reaction	5%	< 1%	< 1%
Lower respiratory tract infection	10-18%	12%	-
Pneumonia	21-27%	15-25%	-
Pneumonitis	5%	4%	2%
Serious infection	31-38%	21%	< 1%
Neutropenia	34-67%/≥ grade 3: 18-49%	60%/≥ grade 3: 31%	42%/≥ grade 3: 4%
Decreased hemoglobulin	20-55%/≥ grade 3: 11-20%	28%/≥ grade 3: 6%	-
Thrombocytopenia	17-43%/≥ grade 3: 6-16%	26%/≥ grade 3: 6%	14%/≥ grade 3: 1%
Lymphocytopenia	21%/≥ grade 3 3-9%	-	52%/≥grade 3: 8%
Abdominal pain	16-18%	26%	17%
Hepatotoxicity	-	14%	-
Increased ALT/AST	42% 37%	35%/25%	44%/-
Increased serum creatinine	24-29%	-	67%

Idelalisib: Patient Care Considerations

- Patient should be provided a medication guide and counseled about idelalisib
- Monitor CBC every two weeks for six months
- Monitor liver function every two weeks for three months, then monthly for 3 months, at least every 3 monthly thereafter
- Monitor for infections, sepsis/pneumonia, and opportunistic infections, pneumocystis carinii pneumonia (PCP), viral
- Monitory for s/s diarrhea/colitis, dermatologic toxicity, hypersensitivity (anaphylaxis), GI, and respiratory pneumonitis
- Do not take or start any new medications or supplements
    - Drug-drug interactions: CYP 3A inhibitors and inducers
- If miss a dose and it is > 6 hours from normal dosing time, skip the dose and wait for the next scheduled dose
- Monitoring pregnancy status (prior to, during, and for 1 month after last dose)

- Females should use contraceptives during and for 1 month after last idelalisib dose
- Males with female partners should use contraceptives during and for 3 months after last idelalisib dose
- Avoid breastfeeding during and for 1 month after last idelalisib dose

Alpelisib: Patient Care Considerations

- Monitor fasting glucose prior to, once weekly for 2 weeks, then monthly as clinically indicated
    - HbA1c prior to and every 3 months during treatment as indicated
- Monitor for s/s of diarrhea, skin reactions, hypersensitivity, hyperglycemia, respiratory symptoms
- Do not take or start any new medications or supplements
    - Drug-drug interactions: CYP 3A inducers, BCRP inhibitors, or CYP 2C9 substrates
- If miss a dose and it is > 9 hours from normal dosing time, skip the dose and wait for the next scheduled dose
- Handling precautions: Use gloves to handle alpelisib
- Monitoring pregnancy status: Prior to treatment, during treatment, and for 1 week after discontinuation
    - Embryofetal toxicity
- Females should use contraceptives during and for 1 week after last alpelisib dose
- Males with female partners should use contraceptives during and for 1 week after last dose
- Avoid breastfeeding during and for 1 week after last alpelisib dose

Duvelisib: Patient Care Considerations

- Patient should be provided a medication guide and counseled about duvalisib
- Monitor CBC (every 2 weeks for 2 months (if have Gr 3 or 4, then weekly)
- Monitor liver function and for pancreatitis (amylase, lipase)
- Monitor for infections (sepsis/pneumonia) and opportunistic infections (PCP, CMV)
- Monitory for s/s diarrhea/colitis, dermatologic toxicity (SJS, TEN), and respiratory (pneumonitis)
- If miss a dose and it is > 6 hours from normal dosing time, skip the dose
- Handling precautions – use gloves to handle duvelisib
- Fetal harm may occur
- Females should use contraceptives during and for 1 month after last duvelisib dose
- Avoid breastfeeding during and for 1 month after last duvalisib dose

CDK4/6 Inhibitors

- Palbociclib (Ibrance)
- Ribociclib (Kisqali)
- Abemaciclib (Verzenio)

Palbociclib

- Indication: Breast Cancer HR+/HER2-
  - 1st line - postmenopausal
  - 2nd line
- Dosing, route and administration
  - 125 mg PO once daily for 21 days of a 28-day cycle
  - Same time each day
  - Do not chew, crush, or break
- Miscellaneous
  - Specialty pharmacy
  - Tablets with or without food
  - Capsules with food
- Dosing adjustments
  - Severe hepatic
    - Grade 3 hematologic toxicity
  - Strong CYP3A inhibitors
- Dosage forms and cost
  - Capsules: 75, 100, 125mg
  - Tablets: 75, 100, 125 mg
  - $913 each tablet or capsule

Ribociclib

- Indication
  - Breast Cancer (HR+/HER2-)
  - 1st line - postmenopausal
  - 2nd line
- Dosing, route and administration
  - 600 mg PO once daily for 21 days of a 28-day cycle
  - Take in AM, preferred
  - Do not chew, crush, or break
- Miscellaneous
  - Tablet therapy packs for 200, 400, 600 mg dose
  - Take with or without food
- Dosing adjustments
  - Mod to severe hepatic
  - Renal
  - > grade 2 hepatobiliary
  - > grade 2 pulmonary
  - > grade 3 neutropenia
  - QTc > 480
  - Strong CYP3A inhibitors
  - > grade 3 nonhematologic
- Dosage forms and cost
  - Therapy pack 200, 400mg
    - $404 each 200 mg tablet
  - Therapy pack 600 mg
    - $337 each 200 mg tablet

Abemaciclib

- Indication
  - Breast Cancer HR+/HER2-
  - 1st line postmenopausal
  - 2nd line
- Dosing, route, and administration
  - 150 mg PO twice daily
  - 200 mg PO twice daily
  - Same time each day
  - Do not chew, crush, or break
- Miscellaneous
  - Specialty Pharmacy
  - Tablets-with or without food
- Dosing adjustments
  - Severe hepatic
  - > grade 3 hepatotoxicity
  - > grade 3 hematologic toxicity
  - Strong CYP3A inhibitors
  - > grade 2 diarrhea
  - > grade 2 pulmonary
  - > grade 3 nonhematologic
- Dosage forms and cost
  - Tablet: 50, 100, 150, 200mg
  - $330 each tablet

Potential Drug-Drug Interactions

	Palbociclib	Ribociclib	Abemaciclib
Drug-drug interactions	• CYP 3A inhibitors • CYP 3A inducers • CYP 3A substrates • Grapefruit juice	• CYP 3A inhibitors • CYP 3A inducers • CYP 3A substrates • QTc prolonging agents • Grapefruit juice • Pomegranate	• CYP 3A inhibitors • CYP 3A inducers • Grapefruit juice

Side Effects	Palbociclib	Ribociclib	Abemaciclib
Neutropenia	80%/≥ grade 3: 55%	78%/≥ grade 3: 55%	88%/≥ grade 3:27%
Anemia	24%/≥ grade 3: 5%	19%/≥ grade 3: 1%	28%/≥ grade 3: 6%
Thrombocytopenia	16-23%	10%	415/ Grade 3 2%
Infections	60%	35-42%	31%
Diarrhea	26%	35%	90% Grade 3 20%
Nausea	35%	31-52%	64% Grade 3 5%
Vomiting	19%	29%	35% Grade 3 2%
Rash	18%	17%	14%
Alopecia	18-33%	19-33%	12%
Fatigue	37%	37%	40%
Increased ALT/AST	6-43%/ 8-52%	46%/ 49%	31%/ 30%
QTc prolongation	-	7.5%/≥ grade 3: 3%	-
Increased Serum Cr	-	20-65%	99%

Patient Care Considerations

- Monitor CBC (with differential) and hepatic function
    - Baseline, every two weeks for the first two cycles, then prior to each cycle thereafter
- Monitor for signs and symptoms of diarrhea/dehydration, VTE, infection, and interstitial lung disease/pneumonitis
- Do not start or take new medications without notifying health provider
    - Avoid CYP 3A4 inhibitors and inducers
- For ribociclib, monitor electrolytes and EKG/cardiac function
    - Avoid concomitant administration with other QTc prolonging agents
- Pregnancy test prior to treatment
- Females should use contraceptives during and for three weeks
    - Three months for palbociclib after last dose
- Avoid breastfeeding during and for ≥ three weeks after last dose

PARP Inhibitors

- Olaparib (Lynparza)
- Rucaparib (Rubraca)
- Niraparib (Zejula)
- Talazoparib (Talzenna)

Olaparib

- Indication
    - Early breast cancer: High risk, HER-2, germline BRCA mutated
    - Met breast HER2- /BRCA mutated
    - Advanced ovarian: BRCA mutated or homologous recombination deficient positive
        - Maintenance
    - Recurrent ovarian: Maintenance
    - Metastatic pancreatic, BRCA mutated: maintenance

    - Metastatic prostate: Castration resistant /homologous recombination repair gene mutated
- Dosing route and administration
    - Tablets: 300 mg PO twice daily
    - Take with or w/o food
    - Do not chew, crush, dissolve, or divide tablets
- Miscellaneous
    - Specialty Pharmacy
    - Medication Guide
    - Nausea/vomiting more common if taken on empty stomach
- Dosing adjustments
    - CYP3A inhibitors and inducers
    - Renal
    - Nonhematologic
- Dosage forms and cost
    - Tablets: 100, 150 mg
    - $169 per tablet

Rucaparib

- Indication
    - Advanced ovarian cancer: BRCA mutated
        - > Two lines treatment
    - Recurrent ovarian cancer
        - Maintenance
    - Metastatic prostate cancer: Castrate-resistant/BCRA mutated
- Dosing, route and administration
    - 600 mg PO twice daily
    - Take with or w/o food
- Miscellaneous
    - Moderately emetogenic
        - May need antiemetic
- Dosing adjustment
    - Prolonged hematologic
        - > 4 weeks
- Dosage forms and costs
    - Tablets: 200, 250, 300 mg
    - $173 per tablet

Niraparib

- Indication
    - Advanced or recurrent (BRCA mutated) ovarian, fallopian tube, or primary peritoneal cancer
        - Maintenance or >3 lines of chemotherapy
- Dosing route and administration
    - Maintenance: 300 mg PO once daily
        - >77 kg or platelets > 150K

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    - 200 mg PO once daily
        - < 77 kg or platelets < 150K
    - Metastatic: 300 mg PO once daily
    - Antiemetic recommended
- Miscellaneous
    - Moderately emetogenic
        - May need antiemetic
    - Maintenance dose depends on weight
        - < or > 77 kg and platelets < or >150K
- Dosing adjustments
    - ANC < 1000
    - Platelets < 100K
    - Any > grade 3 nonhematologic
- Dosage forms and adjustments
    - Capsule: 100 mg
    - $733 each capsule

Talazoparib

- Indication
    - Locally advanced or metastatic breast cancer HER2-/BRCA mutated
    - Metastatic prostate: Castration resistant
- Dosing, route, and administration
    - 1 mg PO once daily
    - Take with or w/o food
    - Swallow capsule whole
- Dosing adjustments
    - P-gp inhibitors
    - Renal insufficiency
    - Hgb <8
    - ANC < 1000
    - Platelets < 50K
        - Any > grade 3 nonhematologic toxicity
- Dosage forms and costs
    - Capsule: 0.25, 1 mg
    - $721 each 1mg
    - $240 each 0.25mg

Side Effects	Olaparib	Rucaparib	Niraparib	Talazoparib
Fatigue	< 67%	< 73%	51-61%	62%
Headache	7-26%	22%	26%	33%
Dizziness	7-20%	15%	18%	17%
Alopecia	-	-	-	25%
Skin rash	5-15%	45%	10%	-
Nausea/vomiting	45-77%/20-40%	79%/37%	74%/40%	49%/25%
Diarrhea	18-37%	34%	20%	22%
Constipation	23-28%	39%	40%	-
Abdominal pain	45%	< 46%	33%	54%
Increased glucose	-	-	66%	54%
Decreased calcium	-	-	-	28%
Increased cholesterol	-	39%	-	-
Anemia	23-44% ≥ grade 3: 7-21%	41%/≥ grade 3: 21%	52%/≥ grade 3: 31%	90%/≥ grade 3: 39%
Neutropenia	12-19%/≥ grade 3: 6-9%	20%/≥ grade 3: 8%	30%/≥ grade 3: 20%	68%/≥ grade 3: 17%
Thrombocytopenia	4-14%/≥ grade 3: 1%	35%/≥ grade 3: 5%	66%/≥ grade 3: 38%	55%/≥ grade 3: 11%
Increased AST/ALT	-	< 67%/< 59%	< 36%/< 28%	37%/33%
Increased ALK phos	-	37%	46%	36%
Increased serum creatinine	3-45%	96%	40%	-
Secondary AML/MDS	< 1.5%	<7%	<7%	<1%
Back pain	14%	-	18%	-
Insomnia	-	19%	27%	-
Hypertension	-	-	20%/≥ grade 3: 9%	-
Dysgeusia	9-21%	40%	10%	10%
URI	<36%	29%	-	

Olaparib: Patient Care Considerations

- Test for genetic mutation or biomarker status with approved companion diagnostic test
- Patient should be provided a medication guide and counseled about olaparib
- Monitor CBC (baseline and monthly) and renal function
- Monitor s/s of AML/MDS and pneumonitis
- If a dose is missed or vomited, do not give an additional dose
    - Administer dose at the next scheduled time
- Do not start or take new medications without notifying health provider
    - Avoid strong CYP3A inhibitors and inducers

- Handling precautions
    - Do not handle medication without gloves
- Monitoring pregnancy status prior to treatment, during treatment, and for 6 months after discontinuation
    - Embryo-fetal death
- Females should use contraceptives during and for 6 months after last olaparib dose
- Males with female partners should use contraceptives during and for 3 months after last olaparib dose
- Avoid breastfeeding during and for 1 month after last olaparib treatment

Rucaparib: Patient Care Considerations

- Test for genetic mutation or biomarker status with approved companion diagnostic test
- Monitor CBC
    - Baseline and monthly
- Monitor signs and symptoms of AML/MDS
- If a dose is missed or vomited, do not give an additional dose
    - Administer dose at the next scheduled time.
- Do not start or take new medications without notifying health provider
    - Substrate for CYP1A2, CYP3A, CYP2C9, CYP2C19
- Handling precautions
    - Do not handle medication without gloves
- Monitoring pregnancy status prior to treatment, during treatment, and for 6 months after discontinuation
    - Embryo-fetal death
- Females should use contraceptives during and for 6 months after last rucaparib dose
- Males with female partners should use contraceptives during and for 3 months after last rucaparib dose
- Avoid breastfeeding during and for two weeks after last rucaparib treatment

Niraparib: Patient Care Considerations

- Monitor CBC weekly for first month, then monthly for next eleven months
- Monitor BP and heart rate weekly for the first two months, then monthly for first year
- Monitor signs and symptoms of AML/MDS
    - If a dose is missed or vomited, do not give an additional dose: Administer dose at the next scheduled time
    - Handling precautions: Do not handle medication without gloves
- Monitoring pregnancy status prior to treatment, during treatment, and for 6 months after discontinuation
    - Embryo-fetal death
- Females should use contraceptives during and for six months after last niraparib dose
- Avoid breastfeeding during and for one month after last niraparib dose

Talazoparib: Patient Care Considerations

- Monitor CBC and renal function
- Monitor signs and symptoms of AML/MDS
    - If a dose is missed or vomited, do not give an additional dose: Administer dose at the next scheduled time
- Do not start or take new medications without notifying health provider
- Avoid P-gp inhibitors: Increases talazoparib exposure
    - Handling precautions: Do not handle medication without gloves
- Monitoring pregnancy status prior to treatment, during treatment, and for 7 months after discontinuation
    - Embryo-fetal death
- Females should use contraceptives during and for seven months after last dose
- Males with female partners should use contraceptives during and for four months after last dose
- Avoid breastfeeding during and for and month after last talazoparib treatment

Hedgehog Pathway Inhibitors

- Vismodegib (Erivedge)
- Sonidegib (Odomzo)

Vismodegib

- Indication
    - Metastatic or locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those not candidates for surgery or radiation therapy
- Dosing, route, and administration
    - 150 mg PO once daily
    - Take with or without food
    - Do not chew or crush
    - Antiemetic required
- Miscellaneous
    - Erivedge Access Solutions program
    - Specialty pharmacy
    - Must dispense medication guide
- Dosing adjustments
    - None
        - Intolerable toxicity withhold up to eight weeks for resolution
- Box warning
    - Embryofetal toxicity
- Dosage form and cost
    - Capsule: 150 mg
    - $490 each capsule

Sonidegib

- Indication
  - Metastatic or locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those not candidates for surgery or radiation therapy
- Dosing, route and administration
  - 200 mg PO once daily
  - Administer on an empty stomach > one hour before or two hours after a meal
  - High fat meal increases concentration 7-8-fold
- Miscellaneous
  - Verify pregnancy status prior to treatment
  - Obtain serum creatine kinase and renal function prior treatment
  - Must dispense medication guide
- Dosing adjustment
  - Creatine kinase elevation > 2.5 x ULN
- Box warning
  - Embryofetal toxicity
- Dosage form and cost
  - Capsule: 200 mg :$474 each capsule

Side Effects	Vismodegib	Sonidegib
Headache	-	15%
Decreased appetite	25%	23%
Abdominal pain	-	18%
Weight loss	45%	30%
Dysgeusia	55%	46%
Increased LFTs	-	19%
Increased amylase	-	16%
Increased serum lipase	-	43%
Pruritis	-	10%
Hyperglycemia	-	51%
Amenorrhea	30%	< 1%
Azotemia	grade 3: 2%	-
Fatigue	40%	41%
Alopecia	64%	53%
Nausea	30%	39%
Diarrhea	29%	32%
Anemia	-	32%
Lymphocytopenia	-	28%/≥ grade 3: 3%
Increased creatinine phosphokinase	38%	61%/≥ grade 3: 8%
Muscle spasm	72%	54%/grade 3: 8%
Musculoskeletal pain	-	32%/grade 3: 1%
Increased serum creatinine	-	32%/grade 3: 1%
Myalgia	-	19%
Arthralgia	16%	-

Vismodegib: Patient care considerations

- Patient should be provided a medication guide and counseled about vismodegib
- Monitor CBC and comprehensive metabolic panel baseline and every 4 weeks
- Monitor liver function and perform skin examination routinely during therapy
    - Cutaneous squamous cell cancer (cuSCC) cases have been reported
- Monitoring pregnancy status one week prior to treatment, monthly during treatment, and for 24 months after discontinuation
    - May cause severe birth defects and embryo-fetal death
- Females should use contraceptives during and for 24 months after last dose
- Males with female partners should use contraceptives during and for three months after last vismodegib dose
- Avoid breastfeeding during and for 24 months after last vismodegib treatment
- Blood donations
    - Wait $\geq$ seven months
- Sperm donations
    - Wait $\geq$ three months

Sonidegib: Patient Care Considerations

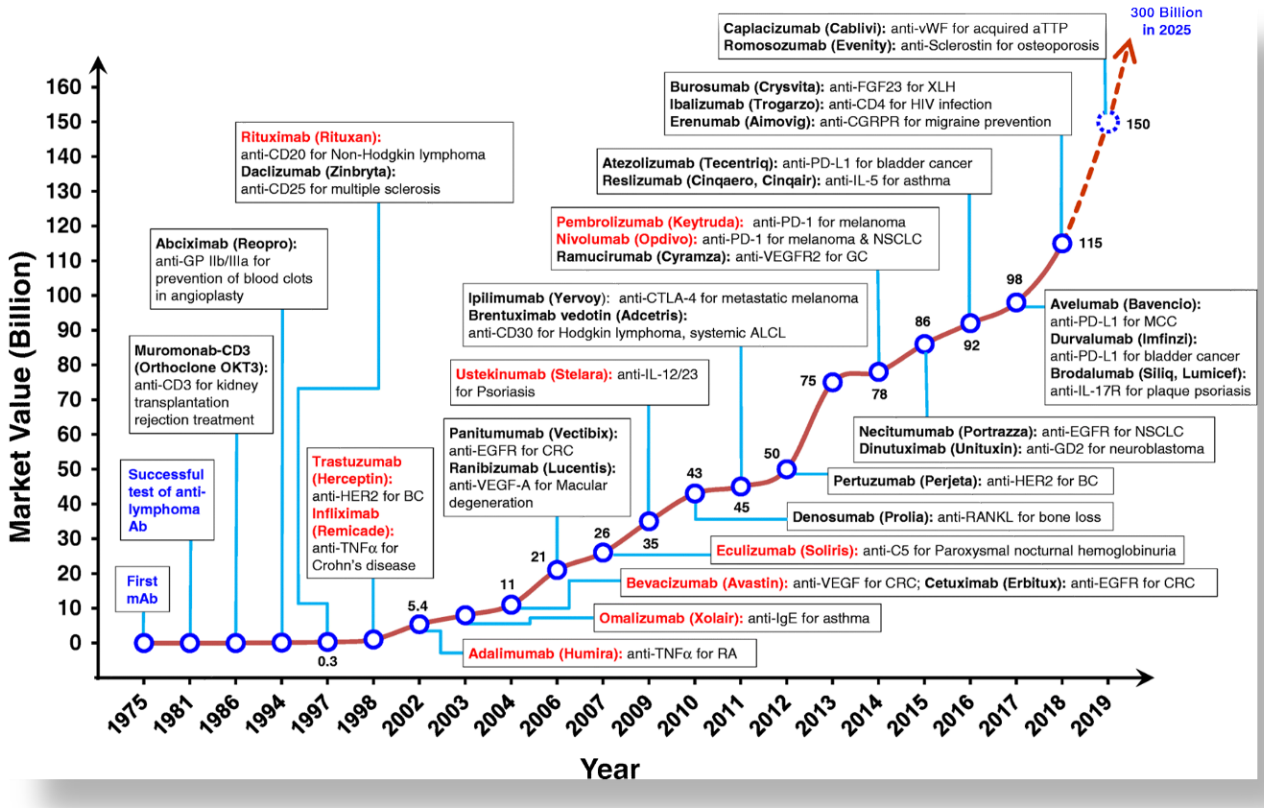
- Patient should be provided a medication guide and counseled about sonidegib
- Monitoring serum creatine kinase (CK)
- Monitor serum creatinine baseline and periodically during treatment
- Monitor liver function
- Monitor for signs/symptoms of musculoskeletal toxicity
- Monitoring pregnancy status one week prior to treatment, monthly during treatment, and for 24 months after discontinuation
    - May cause severe birth defects and embryo-fetal death
- Females should use contraceptives during and for 20 months after last sonidegib dose
- Males with female partners should use contraceptives, even after vasectomy, during and for eight months after last sonidegib dose
- Avoid breastfeeding during and for 20 months after last sonidegib treatment
- Blood donations
    - Wait $\geq$ 20 months
- Sperm donations
    - wait $\geq$ 8 months
- Amenorrhea
    - May last at least 18 months

The Role of Monoclonal Antibodies in Hematology/Oncology Part One

FYIs

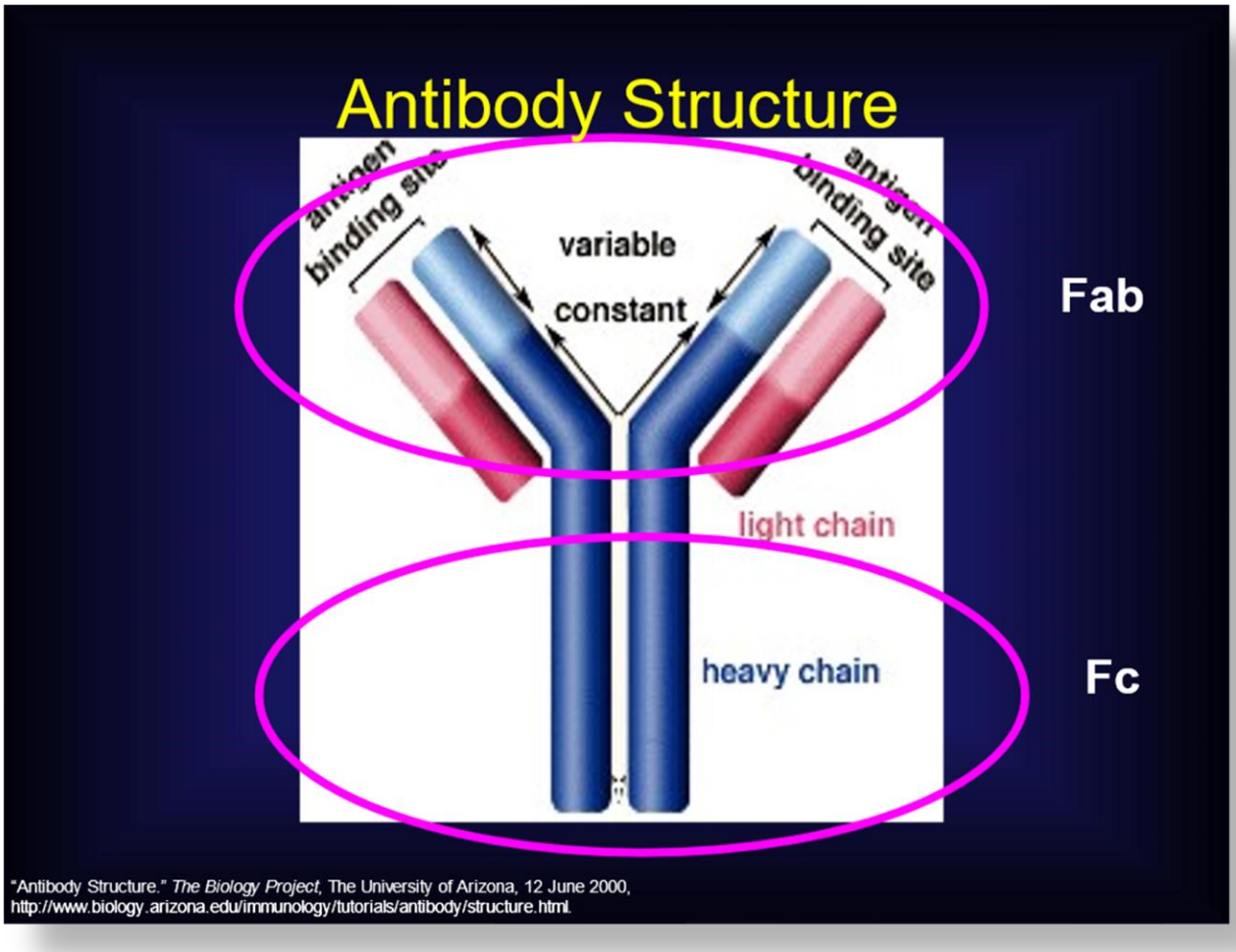
- To date, there are >100 FDA approved monoclonal antibody therapeutics in the United States
- Our focus will be on the most common monoclonal antibodies used therapeutically in oncology
- Dosing, indications, warnings, etc. are constantly being updated as new data becomes available
    - For the most up to date information, reference the current package insert available for each drug and/or institution specific policies

US FDA-approved monoclonal antibodies on the market



What are Antibodies?

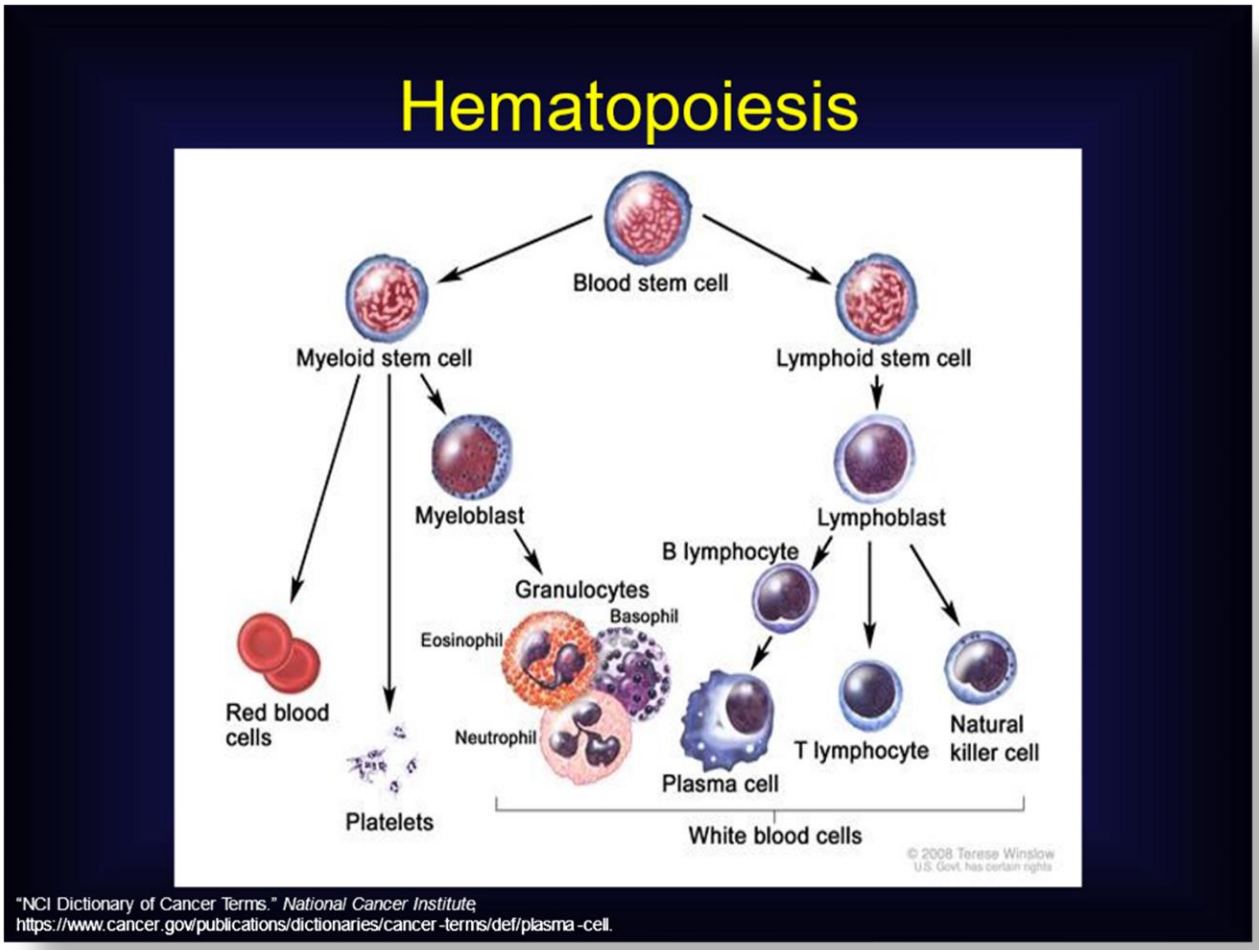
- Proteins produced mainly by plasma cells and used by the immune system to neutralize pathogens
- Monoclonal antibodies – Made by identical immune cells that are all clones of a unique parent cell and thus bind to a common epitope (the part of an antigen that is recognized by the antibody)
- Polyclonal antibodies – Bind to multiple epitopes and are usually made by several different plasma cell (antibody secreting immune cell) lineages



Function of Antibodies

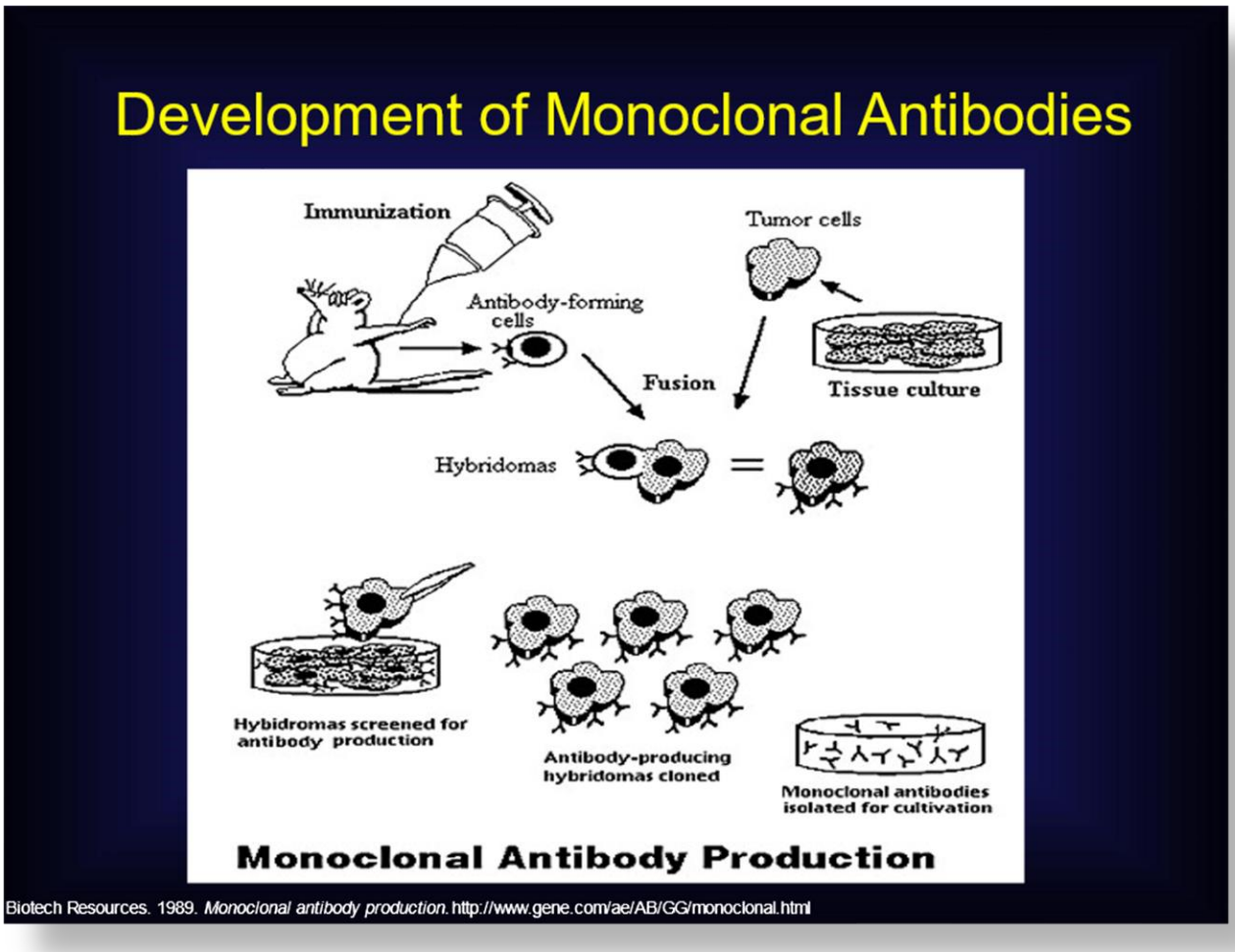
- Protect host organism
- Bind and neutralize toxins
- Activate immune system
  - Lyses target cells
  - Initiation of cellular response on natural killer cells, monocytes, and macrophages

- Different isotypes and subclasses differ in ability to activate this response
  - IgA, IgD, IgE, IgG, IgM



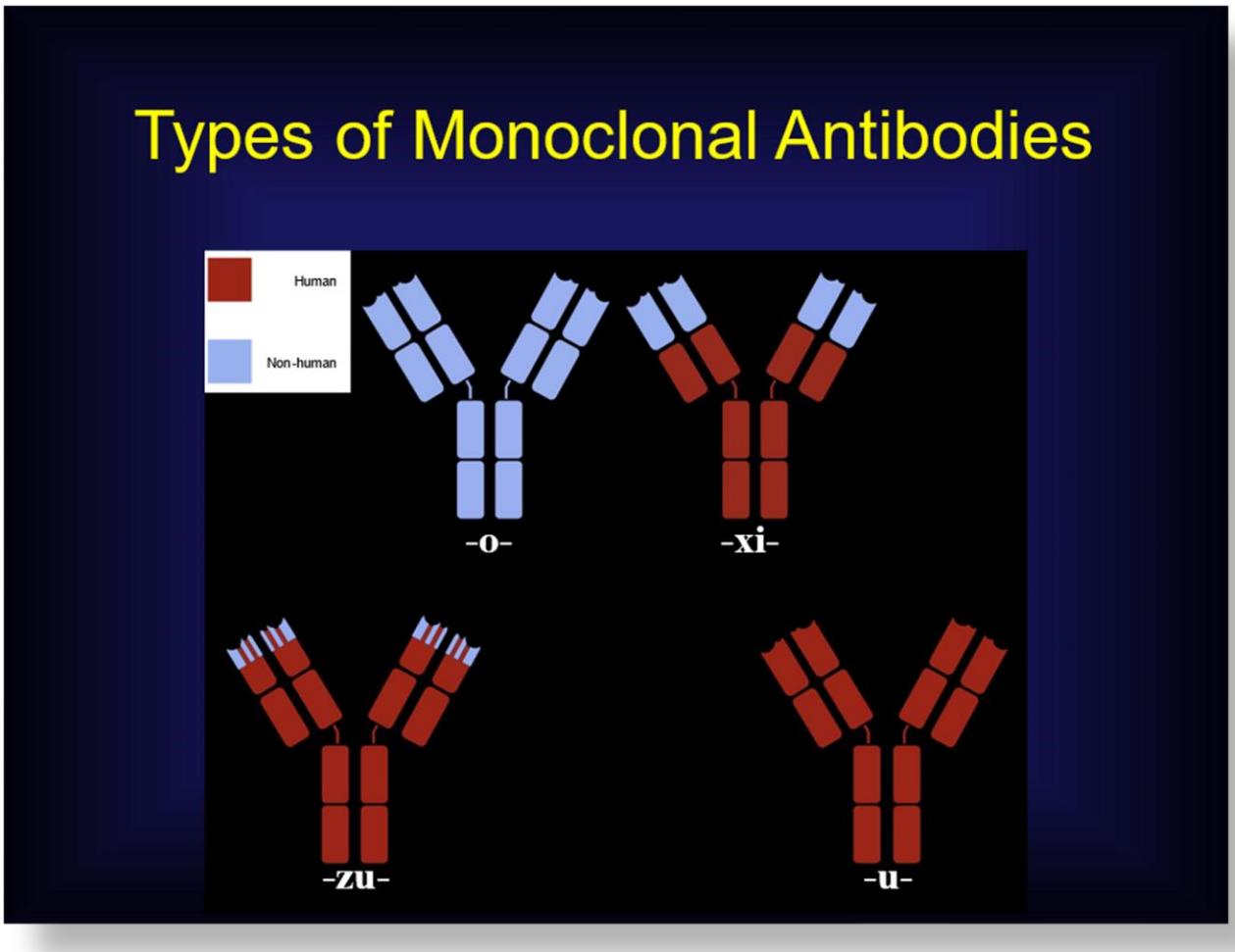
Improving Selectivity of Cancer Treatment

- Direct activity against therapeutic targets
- Limit adverse drug effects through specific targets
- Examples of targeted therapy
  - Low molecular weight compounds (TKI)
  - Monoclonal antibodies (mAb)



Types of Monoclonal Antibodies

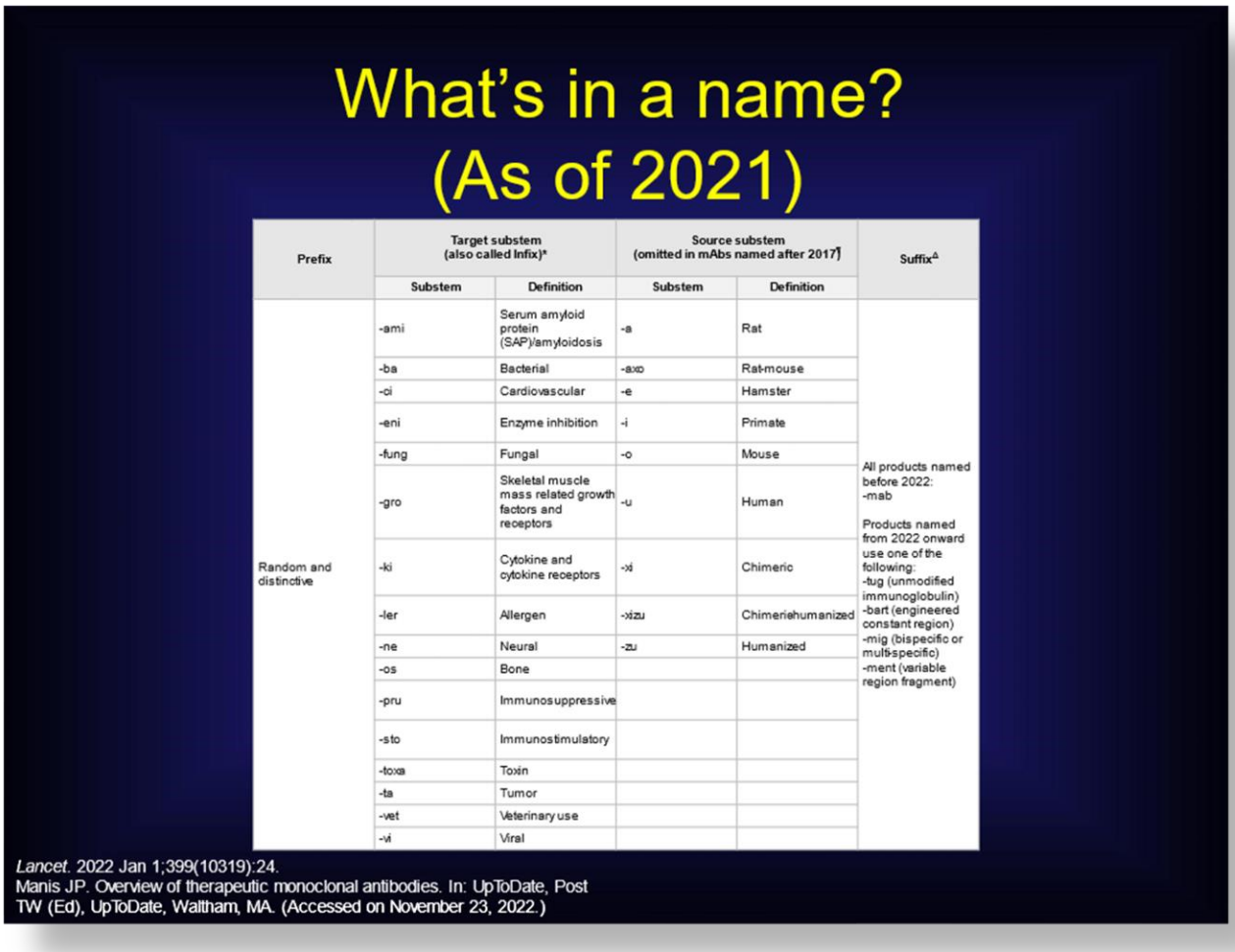
- Murine antibodies
  - Recognized by host immune system
  - Allergic reactions
- Chimeric: Human/mouse
  - Constant domains replaced by human
- Humanized
  - Antibodies that are 95% human
- Fully human
  - No mouse portion


Types of Monoclonal Antibodies
Human
Non-human
-o-
-xi-
-zu-
-u-

What's in a name? (Prior to mid-2017)

Abbreviation	Antibody Source	Example
-mo	Mouse	Moxetumomab pasudotox
-xi	Chimeric	rituximab
-zu	Humanized	trastuzumab
-mu	Human	panitumumab

Monoclonal antibodies are named by combining a Prefix + Target + Source + Suffix (usually –mab)



Monoclonal Antibody Part 1: Lecture Outline by Drug Class

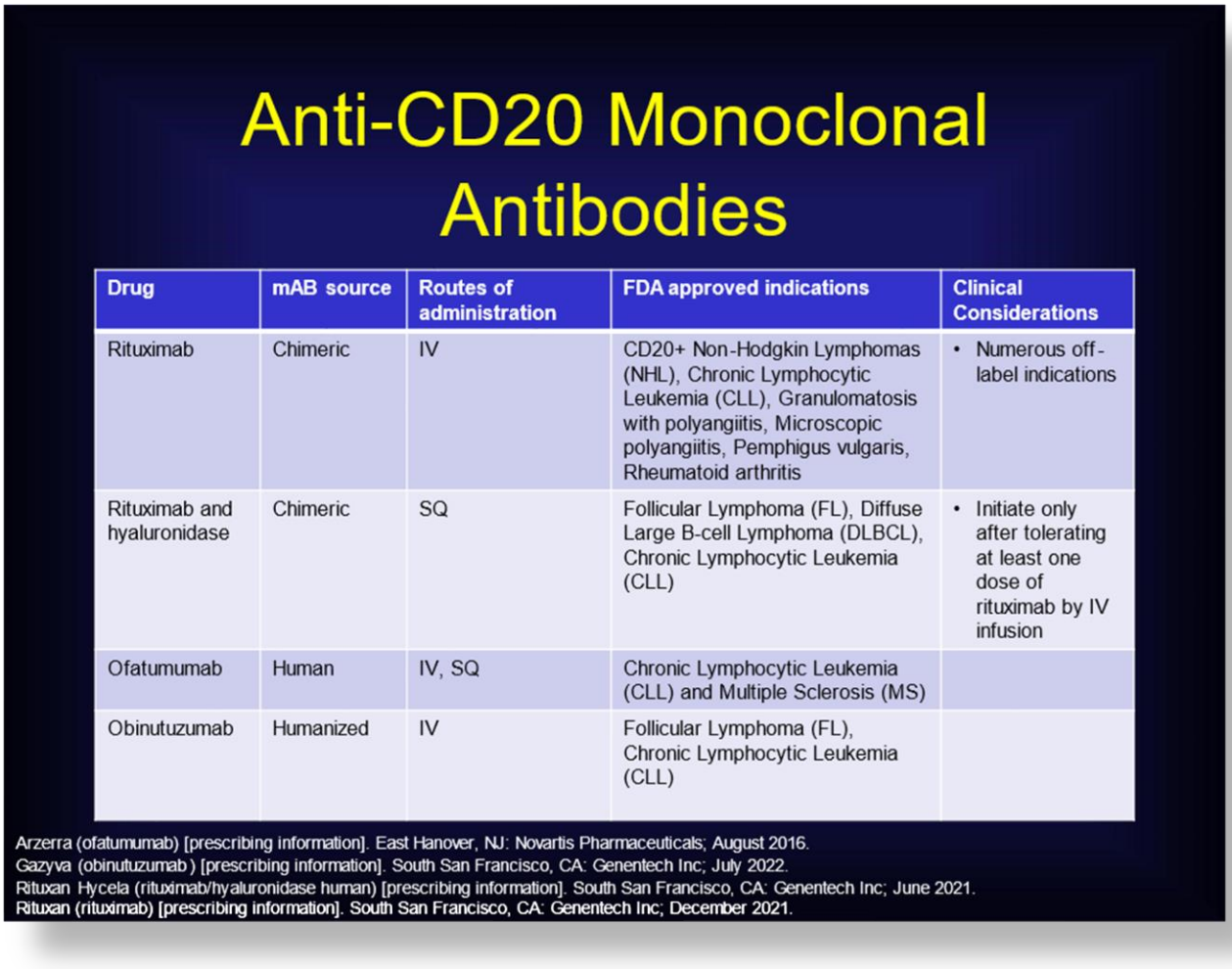
- **<u>CD20-Directed Monoclonal Antibodies</u>**
- CD19-Directed Monoclonal Antibodies
- HER2-Directed Monoclonal Antibodies
- VEGF-Directed Monoclonal Antibodies
- EGFR-Directed Monoclonal Antibodies
- Nectin-4-Directed Monoclonal Antibodies
- RANKL-Directed Monoclonal Antibodies

CD20-Directed Monoclonal Antibodies

Mechanism of Action

- Directed against CD20 antigen
  - Expressed on the surface of most B-cells

        - Regulates cell cycle initiation
        - Good target for many B-cell malignancies
    - Causes cytotoxicity



Warnings and Precautions

- Tumor Lysis Syndrome (TLS)
- Hepatitis B reactivation
    - Monitor HBsAg and HBcAb
- Bowel obstruction/perforation
- Cytopenias
- Immunization response
- Hypersensitivity/infusion reactions
- Infection

- Mucocutaneous reactions
- Cardiovascular effects
- Progressive Multifocal Leukoencephalopathy (PML)
    - Rare, progressive, demyelinating CNS disease from JC virus

Reaction Incidence: Hypersensitivity/infusion reactions

Drug	Incidence (with first exposure/infusion)
Rituximab	>50%
Ofatumumab	44%
Obinutuzumab	67%

Hypersensitivity/Infusion Reactions

- Fevers, chills, rigors, hypotension, bronchospasm, angioedema, rash, headache, dyspnea, sweats, nausea, rhinitis, urticaria
- Tend to occur earlier in infusion
- Initial infusions require pre-medications and must be titrated
- Initial infusions started at a low rate and increased incrementally over time as patient tolerates drug to prevent infusion reactions
- Most reactions are brief and resolve completely when the infusion is stopped
- Decreases with subsequent infusions
- Frequent monitoring of vital signs during infusion

EXAMPLE: Management of Rituximab Reactions

- Pre-medications
    - Diphenhydramine 50 mg IVP
    - Acetaminophen 650 mg PO
    - +/- corticosteroid
- Meperidine, epinephrine, corticosteroids, bronchodilators, IV saline PRN
- Interrupt infusion for reactions and manage symptoms accordingly
    - Once symptoms resolved, most patients can resume at 50% rate at which the reaction occurred

Rituximab Administration

- Administration
  - First infusion: 50 mg/hour, can escalate in 50 mg/hr increments every 30 minutes to a max of 400 mg/hr
  - Subsequent infusions: 100 mg/hr and can increase 100 mg/hr every 30 minutes to a max of 400 mg/hr
- Infusion related events
  - Slow or discontinue IV infusion
  - Monitor vital signs

Rituximab Rapid Infusion Administration

- First dose standard
- If initial infusion tolerated without ≥ grade 3 infusion reaction, proceed to rapid infusion for doses up to 1000 mg
- For Rapid Infusion (90 minutes)
  - Mix in total volume of 250 mL and initiate infusion at 100 mL/hr x 30 minutes
  - If no reaction, infuse remaining rituximab at a rate of 200 mL/hr

Audience Response Question: All of the following target CD20 except:

A. Rituximab
B. Ofatumumab
C. Obinutuzumab
D. Trastuzumab

Monoclonal Antibody Part 1 Lecture Outline by Drug Class

- CD20-Directed Monoclonal Antibodies
- **CD19-Directed Monoclonal Antibodies**
- HER2-Directed Monoclonal Antibodies
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- EGFR-Directed Monoclonal Antibodies
- Nectin-4-Directed Monoclonal Antibodies
- RANKL-Directed Monoclonal Antibodies

CD19-Directed Monoclonal Antibodies

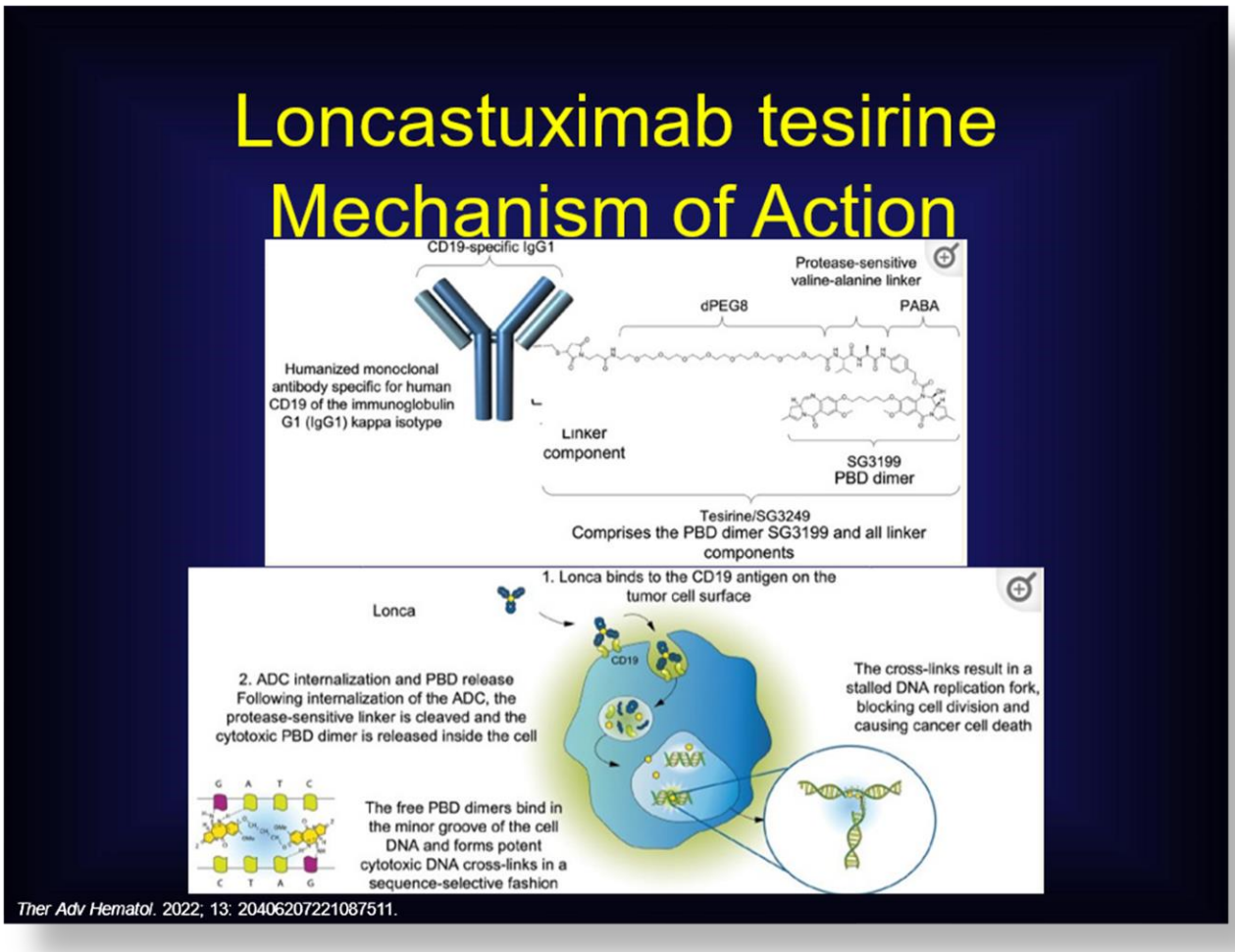
CD19

- Expressed on the surface of most B-cells
  - Aids in B-cell activation
    - Functions as an adaptor protein to recruit cytoplasmic signaling proteins to the membrane
    - Works within the CD19/CD21 complex to decrease the threshold for B cell receptor signaling pathways

Anti-CD19 Monoclonal Antibodies

Drug	mAB source	Routes of administration	FDA approved indications	Clinical Considerations
Loncastuximab tesirine	Humanized	IV	Large B-cell lymphoma	• Antibody-drug conjugate • Irritant with vesicant-like properties; avoid extravasation. Monitor infusion site during administration • Premedicate with dexamethasone 4 mg PO or IV BID for 3 days beginning the day before infusion to reduce incidence of edema/effusions • For patients with BMI ≥35 kg/m^2, the dose should be calculated based on an adjusted body weight (AdjBW). The following formula was used in the clinical trial and is recommended in the manufacturer's labeling: AdjBW in kg = 35 kg/m^2 × (height in meters)^2
Tafasitamab	Humanized	IV	Diffuse Large B-cell lymphoma	• Pre-medications required for first 3 infusions (6% incidence of infusion reactions) • Only approved in combination with lenalidomide

Zynlonta (loncastuximab tesirine) [prescribing information]. Murray Hill, NJ: ADC Therapeutics America; October 2022.
Monjuvi (tafasitamab) [prescribing information]. Boston, MA: Morphosys US Inc; June 2021.



Warnings and Precautions

- Bone marrow suppression
- Dermatologic toxicity
- Infection
- Extravasation (Loncastuximab tesirine)
- Photosensitivity (Loncastuximab tesirine)
- Infusion reactions
- Effusion/edema (Loncastuximab tesirine>tafasitamab)
    - Loncastuximab tesirine
        - Pleural effusion :10%; grade 3/4: 2%
        - Edema: 28%; grade 3/4: 3%

Monoclonal Antibody Part 1 Lecture Outline by Drug Class

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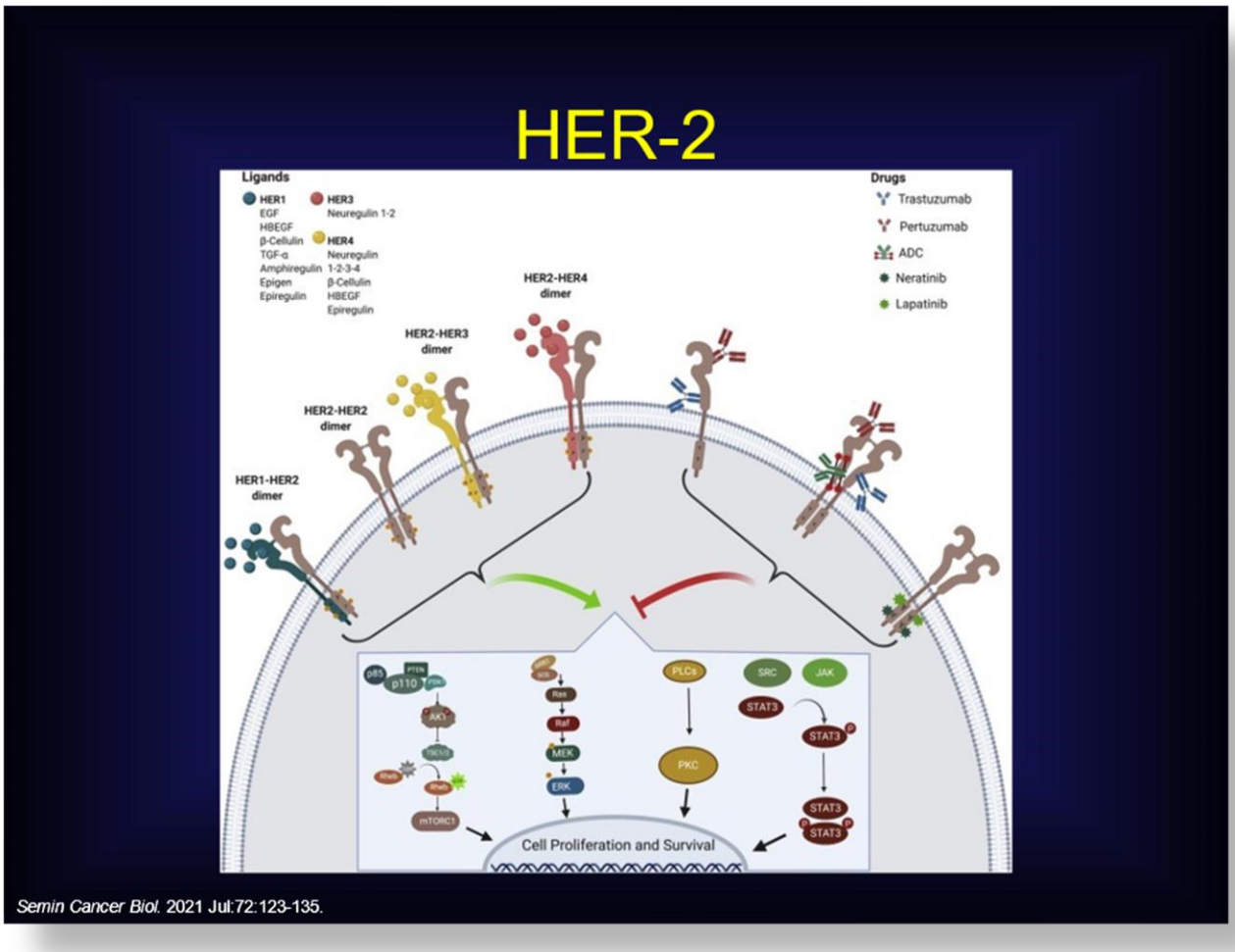
- RANKL-Directed Monoclonal Antibodies

HER2-Directed Monoclonal Antibodies

HER-2/*neu*

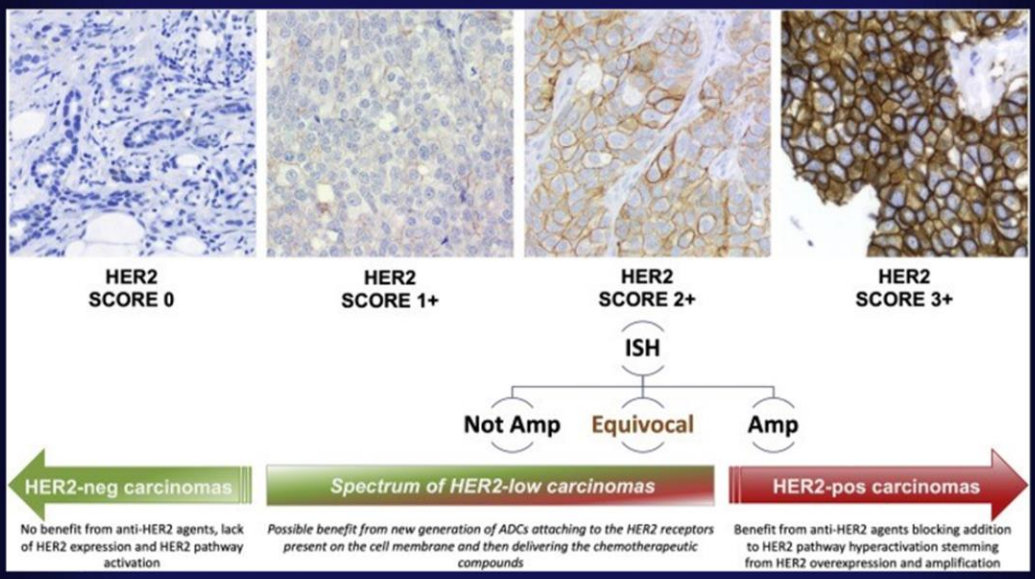
- Member of the tyrosine kinase family that includes EGFR
- Accounts for 15-20% of newly diagnosed breast cancers
- Generally more aggressive if HER2 overexpressed, however targeted therapy available



HER-2/*neu*

- Immunohistochemical technique (3+)
- Fluorescence *in situ* hybridization
    - FISH testing for all IHC 2+
- Overexpressed in ovarian, gastric, colorectal, endometrial, lung, bladder, prostate, salivary gland tumors

HER-2 Testing by IHC



Semin Cancer Biol. 2021 Jul:72:123-135.

Anti-HER2 Monoclonal Antibodies

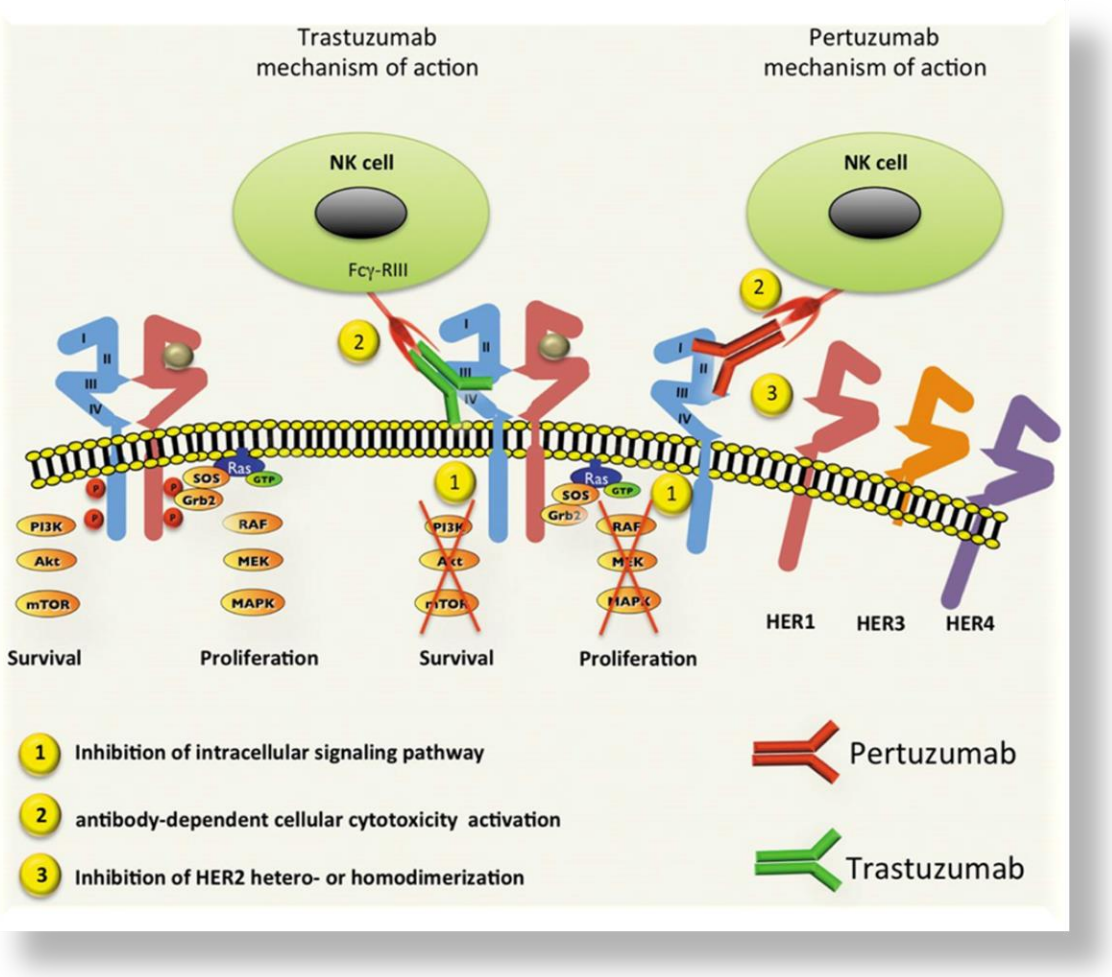
Drug	mAB source	Routes of administration	FDA approved indications	Clinical Considerations
Trastuzumab	Humanized	IV	HER2+ breast cancer, HER2+ gastric cancer	Binds to different domain of HER2 (subdomain IV) than pertuzumab
Trastuzumab and hyaluronidase	Humanized	SQ	HER2+ breast cancer	SQ formulation of trastuzumab (dosing is NOT interchangeable)
Pertuzumab	Humanized	IV	HER2+ breast cancer	Binds to different domain of HER2 (subdomain II) than trastuzumab; generally given in combination with trastuzumab

*Check label to ensure appropriate product is administered (conventional trastuzumab products and ado -trastuzumab emtansine, fam - trastuzumab deruxtecan, pertuzumab / trastuzumab/hyaluronidase, or trastuzumab/hyaluronidase are different products and are NOT interchangeable).

Herceptin (trastuzumab) [prescribing information]. South San Francisco, CA: Genentech Inc; February 2021.
Perjeta (pertuzumab) [prescribing information]. South San Francisco, CA: Genentech Inc; February 2021.
Herceptin Hylecta (trastuzumab and hyaluronidase) [prescribing information]. South San Francisco, CA: Genentech, Inc; February 2019.

Mechanism of Trastuzumab

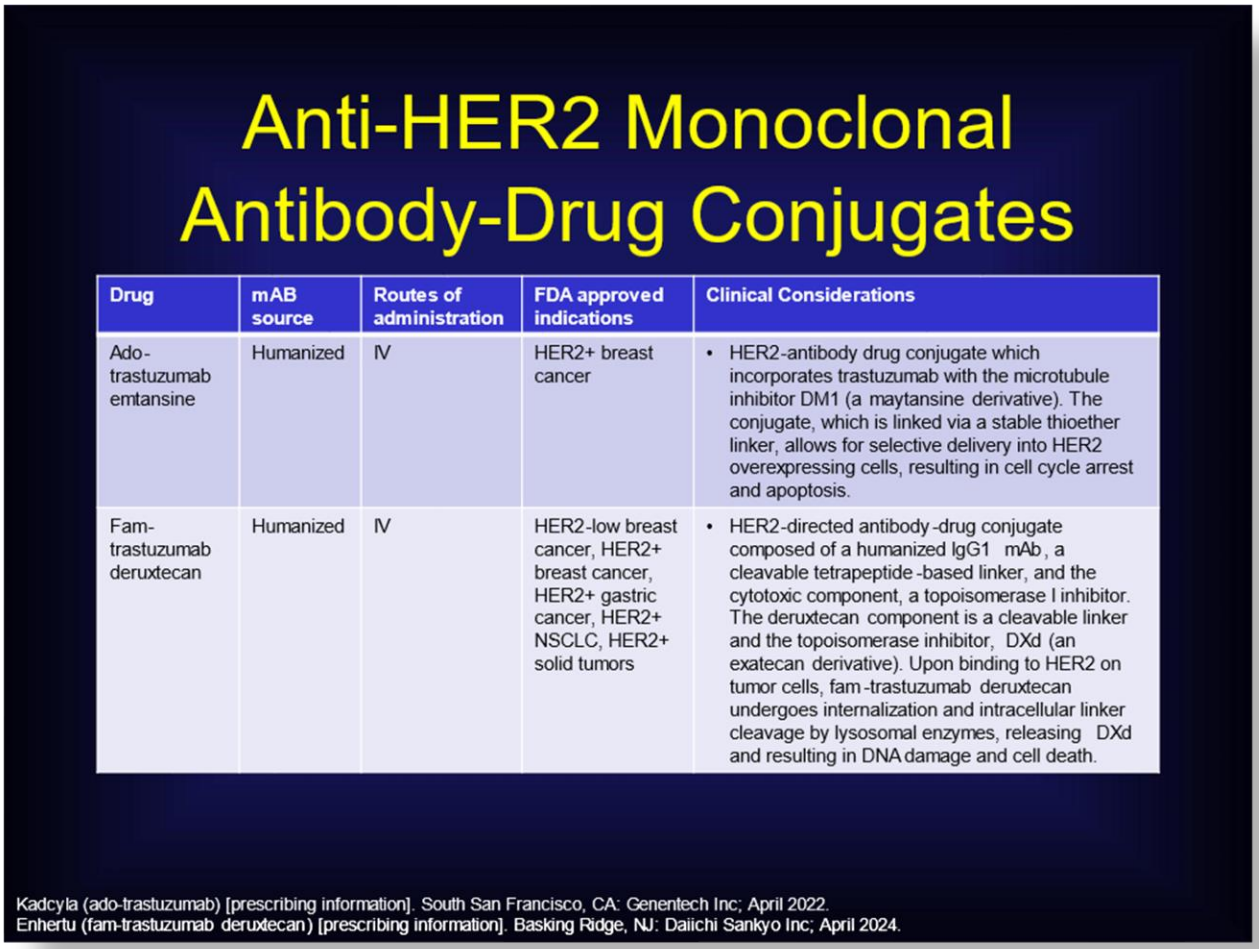
- Binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2)
- Mediates antibody dependent cellular cytotoxicity by inhibiting proliferation of HER-2 overexpressing cells



Warnings and Precautions

- Cardiomyopathy (Black Box Warning)
  - Associated with symptomatic and asymptomatic reductions in left ventricular ejection fraction (LVEF) and heart failure
  - Monitor LVEF via ECHO/MUGA prior to and during treatment
  - Hold/discontinue if clinically significant decrease in LVEF
  - Caution with other cardio-toxic chemotherapy
    - Anthracyclines and cyclophosphamide
- Risk factors
  - Age, cardiac disease, chest radiation, previous anthracycline exposure
- Infusion reactions
  - Observe patients closely during infusion for fever, chills, or other infusion-related symptoms. Treatment with acetaminophen, diphenhydramine, and/or meperidine is usually effective for managing infusion-related events

- Pulmonary toxicity (Trastuzumab)
- Renal toxicity (Trastuzumab)
    - Rare cases of nephrotic syndrome with evidence of glomerulopathy have been reported
- GI adverse events (Pertuzumab)



Ado-trastuzumab emtansine: Warnings and Precautions

- Do not substitute for or with trastuzumab
- Hepatotoxicity
    - Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate

- May lead to reductions in left ventricular ejection fraction (LVEF)
    - Assess LVEF prior to initiation. Monitor and withhold dosing or discontinue as appropriate
- Bone marrow suppression
- Hemorrhage
- Hypersensitivity/infusion-related reactions (1-3%)
- Peripheral neuropathy
- Pulmonary toxicity
- Extravasation reactions: Irritant with vesicant-like properties; avoid extravasation

Fam-trastuzumab deruxtecan: Warnings and Precautions

- Do not substitute for or with trastuzumab
- Bone marrow suppression
- Cardiotoxicity
    - Increased risk of developing left ventricular dysfunction
    - Assess LVEF prior to initiation. Monitor and withhold dosing or discontinue as appropriate
- GI effects
    - Nausea, vomiting, constipation, diarrhea, and stomatitis have been reported
    - Associated with moderate to high emetic potential; antiemetics are recommended for prevention
- Pulmonary toxicity

Monoclonal Antibody Part 1 Lecture Outline by Drug Class

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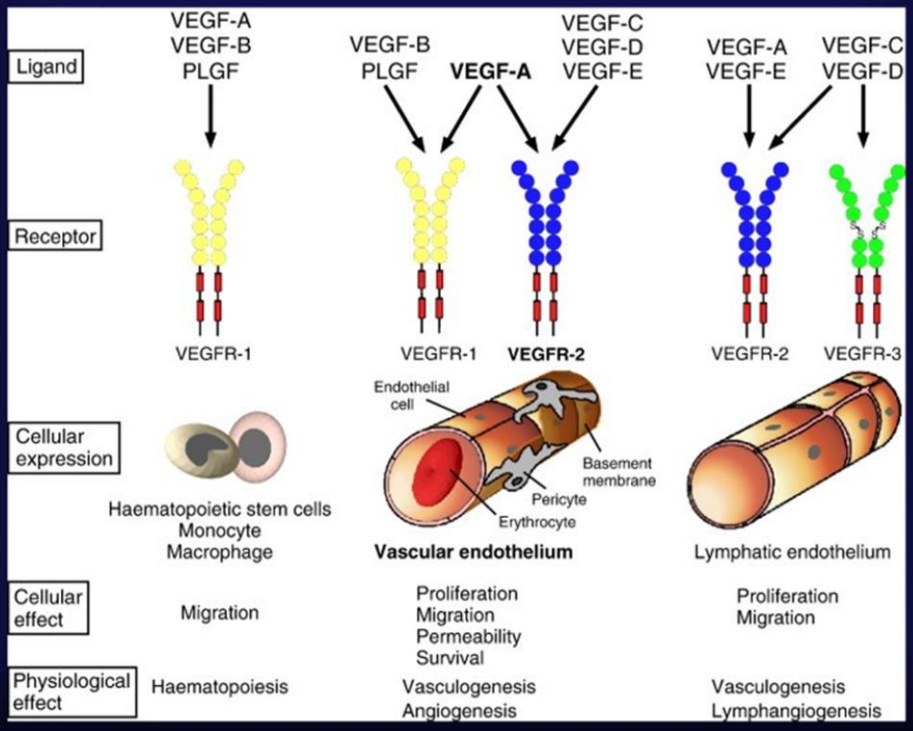
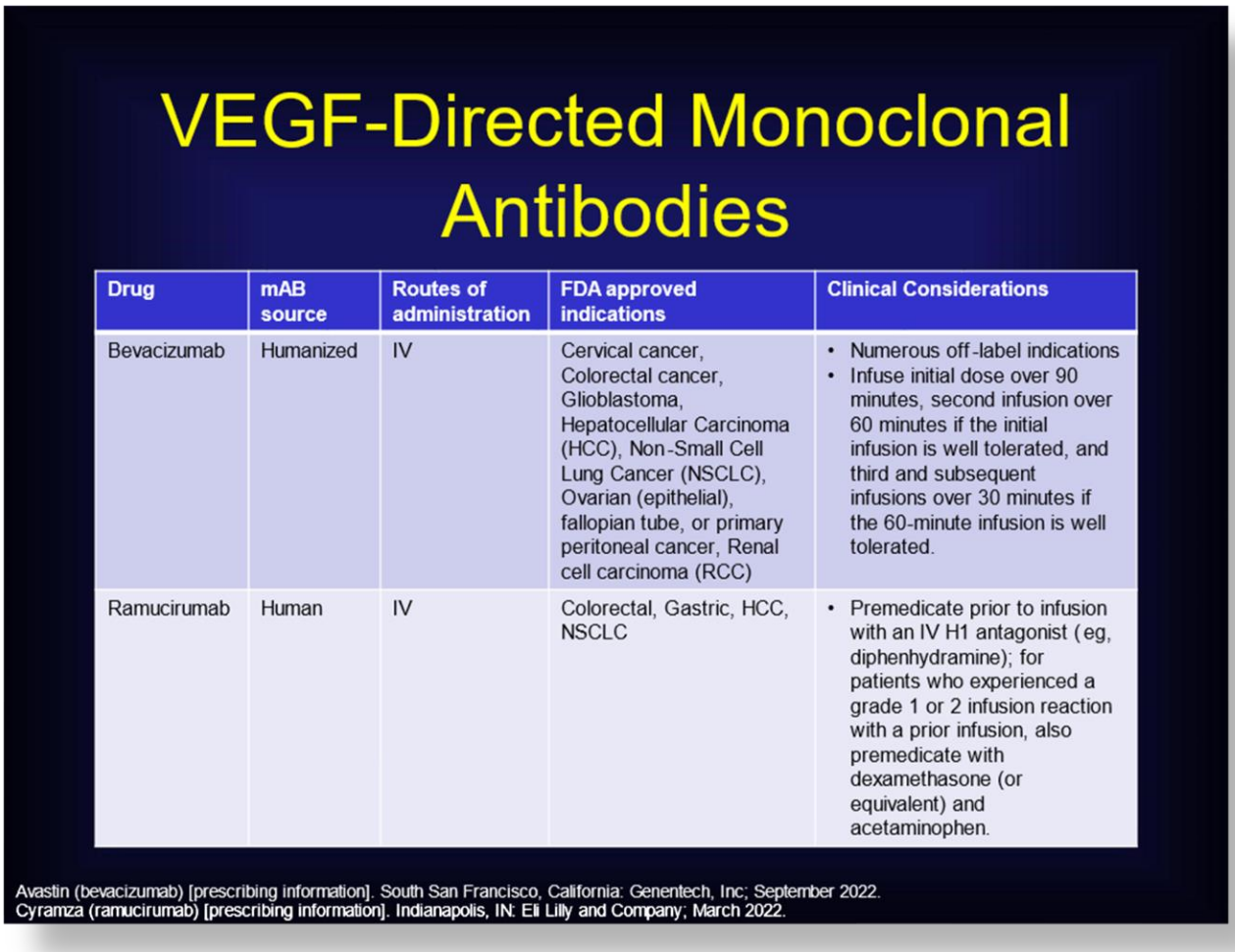
- Nectin-4-Directed Monoclonal Antibodies
- RANKL-Directed Monoclonal Antibodies

VEG-F Location and Function



Cell Signal. 2007 Oct;19(10):2003-12. Epub 2007 Jun 12.



Mechanism of Bevacizumab

- Binds to vascular endothelial growth factor (VEGF) and inhibits the interaction of VEGF to Flt1 and KDR receptors on surface of endothelial cells
- Prevents proliferation of endothelial cells and formation of new blood vessels
    - Blocks angiogenesis

Mechanism of Ramucirumab

- Recombinant human IgG1 monoclonal antibody that binds to VEGFR2 and blocks binding of VEGFR ligands VEGF-A, VEGF-C, VEGF-D
- Inhibits proliferation and migration of endothelial cells and inhibits angiogenesis

Warnings and Precautions

- GI perforation/fistula
    - Abdominal pain, constipation, vomiting

- Wound healing complications
  - Withhold for at least 28 days prior to elective surgery
  - Resume only after wound is adequately healed (bevacizumab held for at least 28 days after major surgery; ramucirumab held for at least 14 days after major surgery)
- Necrotizing fasciitis (bevacizumab)
  - Cases have been reported, usually secondary to wound healing complications, GI perforation or fistula formation
- Hemorrhage
- Thromboembolism
- Hypertension
- Heart failure
- Hepatotoxicity (ramucirumab)
- Thyroid disfunction (ramucirumab)
- Proteinuria/nephrotic syndrome
- Reversible posterior leukoencephalopathy syndrome (RPLS)
- Osteonecrosis of the jaw (bevacizumab)
  - Increased risk when used in combination with bisphosphonates and other antiresorptive agents
- Infusion reactions
  - Pre-medications are recommended prior to ramucirumab (reactions tend to occur with the first or second dose); Reduce rate for grade 1/2; permanently discontinue for grade 3/4
  - Infusion reactions uncommon with bevacizumab

Audience response Question: mAbs that impact the role of VEGF are commonly known to cause which of the following?

A. Colitis
B. Poor Wound Healing
C. Rash
D. Tumor Lysis Syndrome

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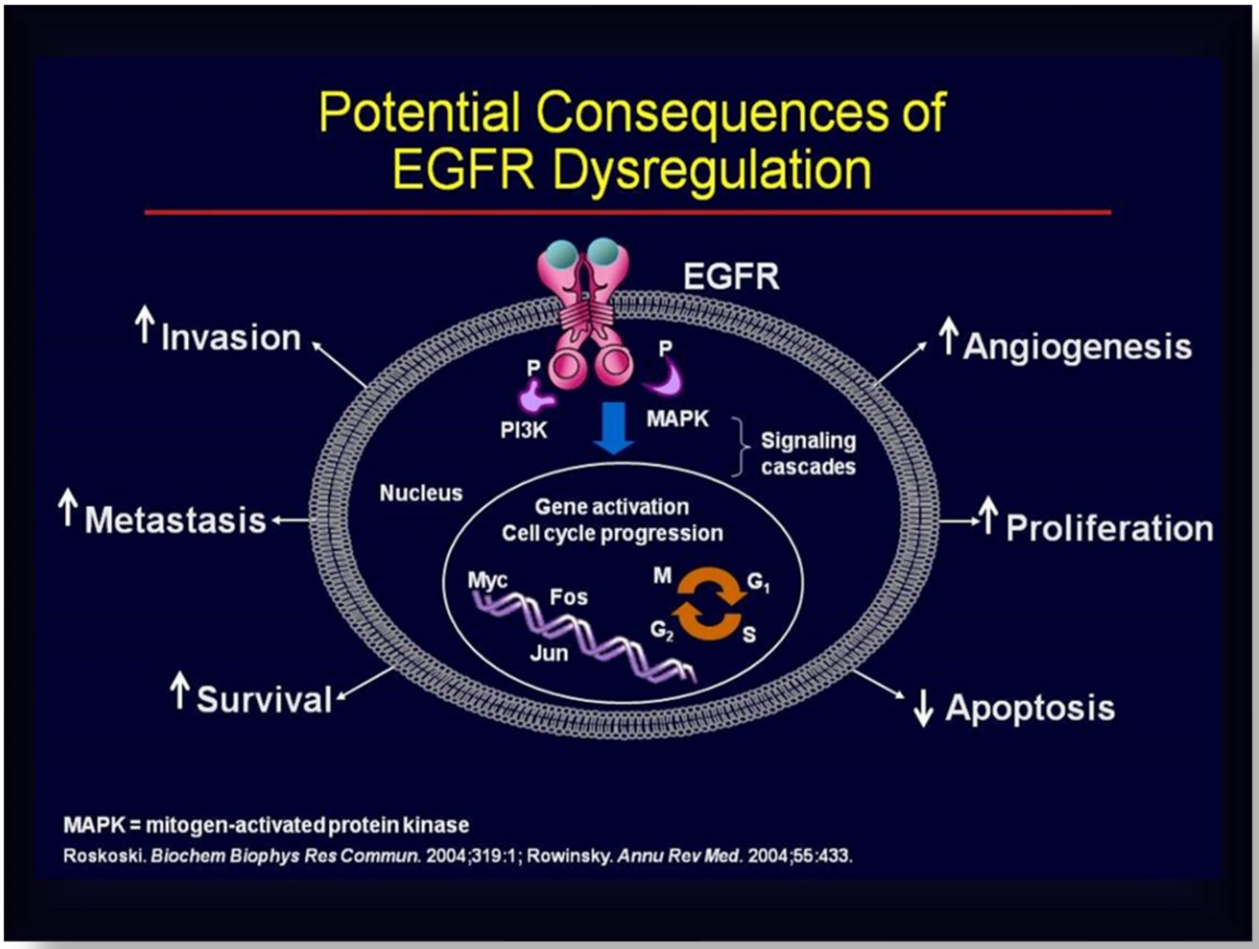
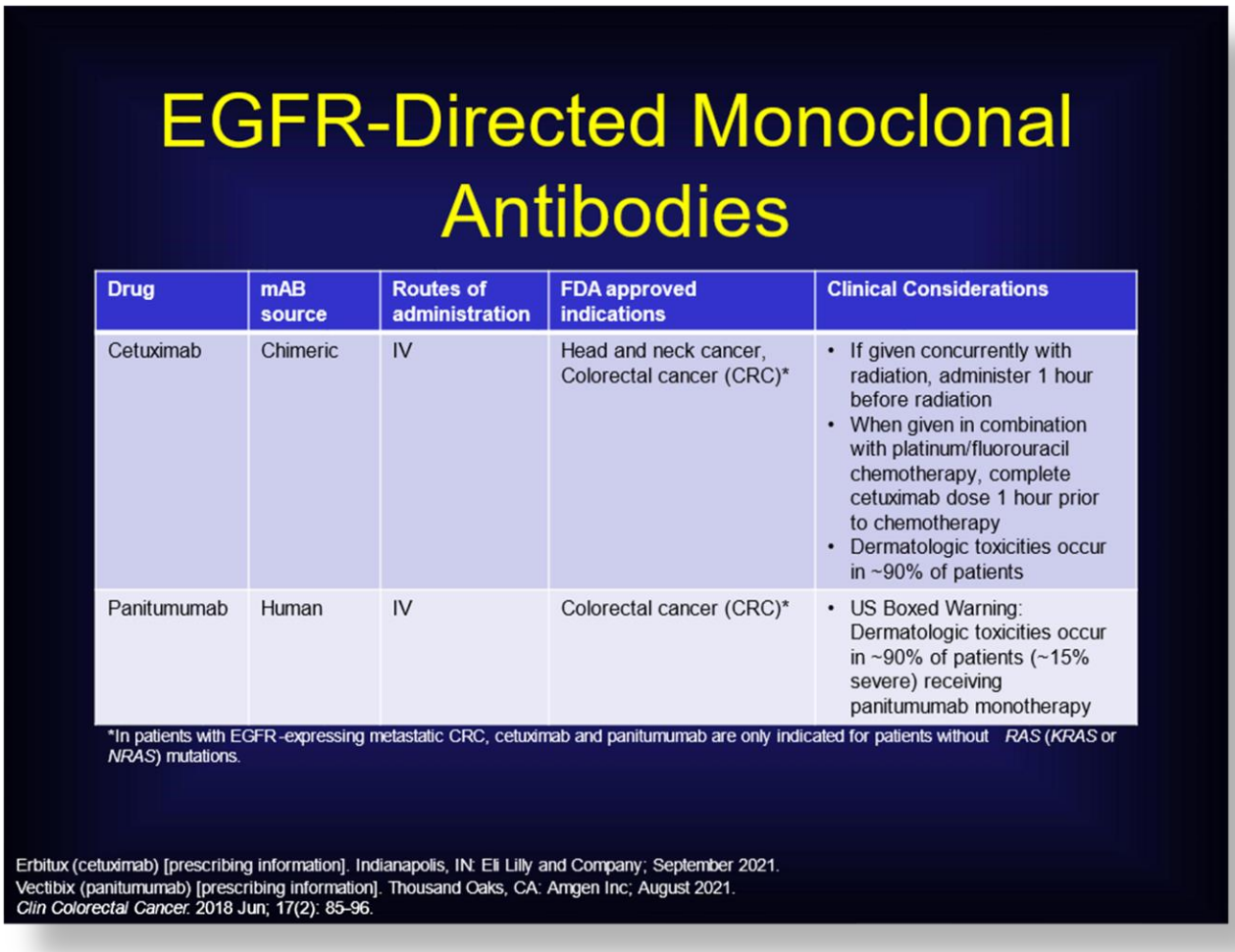
- **EGFR-Directed Monoclonal Antibodies**
- Nectin-4-Directed Monoclonal Antibodies
- RANKL-Directed Monoclonal Antibodies

EGFR-Directed Monoclonal Antibodies: Mechanism of Action

- Binds to EGFR and blocks growth factor binding and receptor activation
- Blocks phosphorylation and activation of receptor-associated kinases
    - Inhibits growth and survival of tumor cells that over-express EGFR

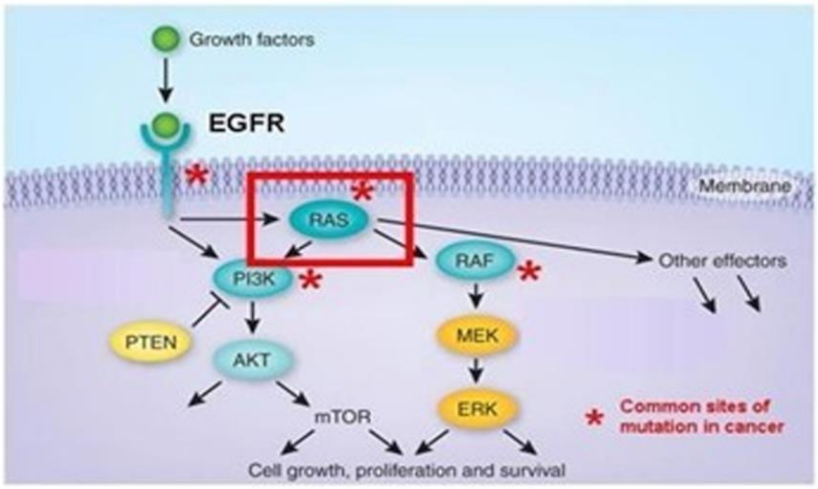




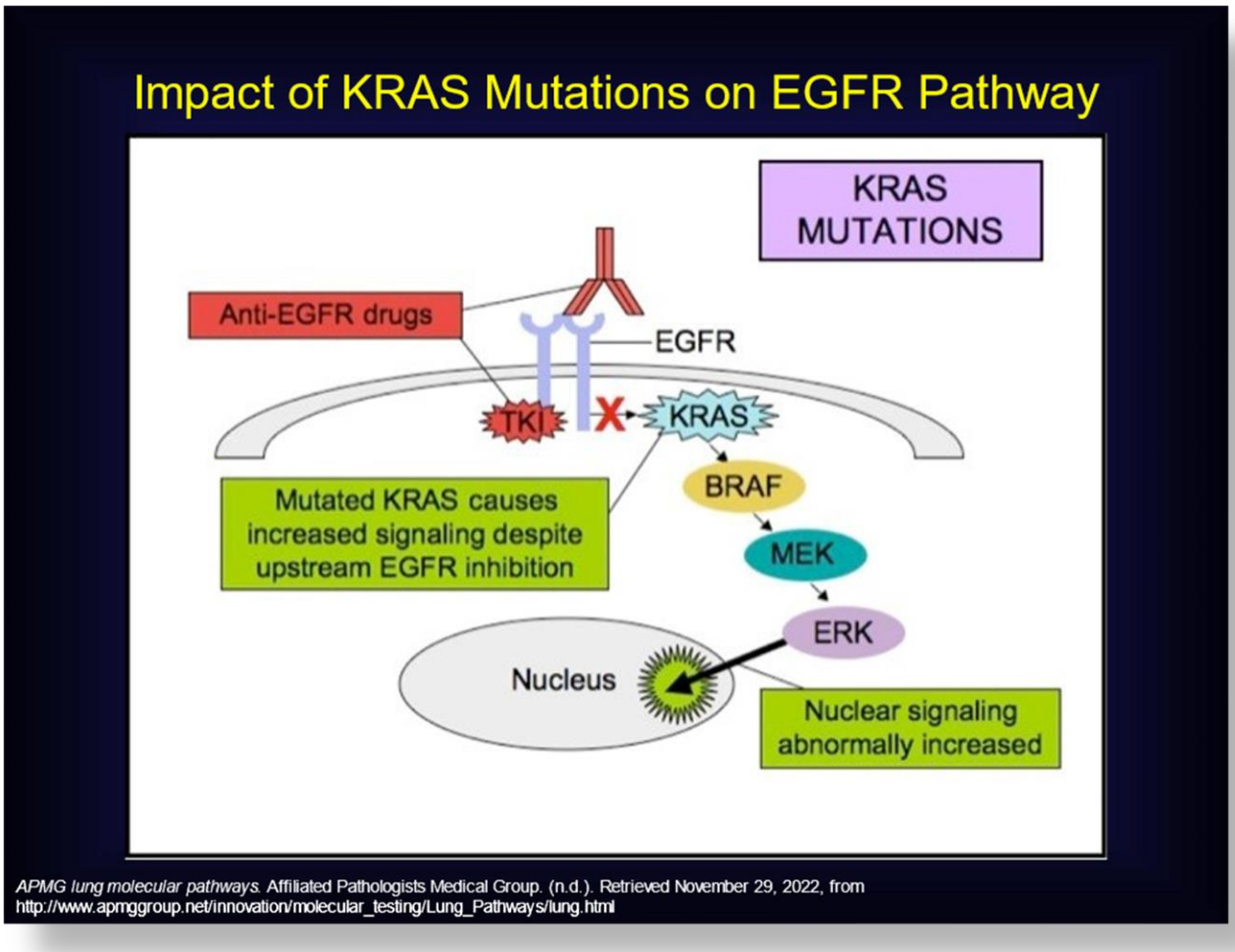
Cetuximab Indications

- Metastatic colorectal cancer, *KRAS* mutation-negative, EGFR-expressing, as monotherapy, in patients intolerant to irinotecan-based chemotherapy
- Metastatic colorectal cancer, *KRAS* mutation-negative, EGFR-expressing, as monotherapy in patients who failed both irinotecan- and oxaliplatin-based regimens
- Metastatic colorectal cancer, *KRAS* mutation-negative, EGFR-expressing, in combination with irinotecan, in patients refractory to irinotecan-based chemotherapy
- Metastatic colorectal cancer, *KRAS* mutation-negative, EGFR-expressing, first-line therapy, in combination with FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin)
- Metastatic colorectal cancer, BRAF V600E mutation-positive, in combination with encorafenib, after prior therapy

Impact of RAS on EGFR Pathway



http://healthcare.sourcebioscience.com/drug-development/market/kras



Warnings and Precautions

- Infusion related reactions
  - More common with cetuximab (~18%; severe <2%) than panitumumab (3%-4%; severe ≤1%)
    - Pre-medication for cetuximab
    - H1 antagonist (diphenhydramine) IV, 30-60 minutes prior to the first dose
    - Pre-medication for subsequent doses is based on clinical judgement with consideration of reaction to the initial infusion
    - Observe patient for 1 hour after infusion
- Dermatologic toxicities
  - Acneiform rash
- Pulmonary toxicity
- Electrolyte abnormalities
  - Monitor Mg, K, Ca weekly during treatment and for ≥ 8 weeks after completion

- Diarrhea
- Cardiopulmonary arrest (cetuximab)
    - Occurred in patients with squamous cell carcinoma of the head and neck receiving cetuximab with radiation therapy or a cetuximab product with platinum-based therapy and fluorouracil
- Ocular toxicity (panitumumab)
    - Keratitis, ulcerative keratitis, and corneal perforation have occurred

Cetuximab Dose Adjustments

Adverse reaction	Severity	Dosage modification
Dermatologic toxicity and infectious sequelae (eg, acneiform rash, mucocutaneous disease)	First occurrence, grade 3/4	Delay cetuximab infusion 1 -2 weeks. If improvement, continue cetuximab at 250 mg/m2. If no improvement, discontinue cetuximab.
	Second occurrence, grade 3/4	Delay cetuximab infusion 1 -2 weeks. If improvement, continue cetuximab at 200 mg/m2. If no improvement, discontinue cetuximab.
	Third occurrence, grade 3/4	Delay cetuximab infusion 1 -2 weeks. If improvement, continue cetuximab at 150 mg/m2. If no improvement, discontinue cetuximab.
	Fourth occurrence, grade 3/4	Permanently discontinue cetuximab.
Electrolyte imbalance		Replete electrolytes as clinically indicated.
Infusion reaction	Grade 1/2	Reduce the cetuximab infusion rate by 50%.
	Grade 3/4	Immediately and permanently discontinue cetuximab.
Pulmonary toxicity	Acute onset or worsening pulmonary symptoms	Delay cetuximab infusion 1 -2 weeks; if improvement, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks, discontinue cetuximab.
	Interstitial lung disease (confirmed)	Permanently discontinue cetuximab.

Erbitux (cetuximab) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; September 2021.

Panitumumab Dose Adjustments

Adverse reaction	Severity	Dosage modification
Dermatologic or soft tissue toxicity	Grade 3 toxicity (first occurrence)	Withhold 1-2 doses; if reaction improves to <grade 3, resume therapy at initial dose.
	Grade 3 toxicity (second occurrence)	Withhold 1-2 doses; if reaction improves to <grade 3, resume therapy at 80% of initial dose.
	Grade 3 toxicity (third occurrence)	Withhold 1-2 doses; if reaction improves to <grade 3, resume therapy at 60% of initial dose.
	Grade 3 toxicity (fourth occurrence), grade 3 toxicity that does not recover to <grade 3 after withholding 1-2 doses, or grade 4 toxicity	Permanently discontinue.
Infusion reaction	Grade 1 or 2	Reduce infusion rate by 50% for duration of infusion.
	Grade 3 or 4	Stop infusion; consider permanent discontinuation (depending on severity or persistence of reaction).
Pulmonary toxicity	Acute onset or worsening pulmonary symptoms	Interrupt treatment.
	Interstitial lung disease (confirmed)	Permanently discontinue treatment.
Electrolyte depletion		Replete as clinically appropriate.
Ocular toxicity (acute or worsening keratitis, ulcerative keratitis, or corneal perforation)		Interrupt or discontinue treatment.

Vectibix (panitumumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; August 2021.

Audience response Question: Which of the following is a major side effect to monitor and prevent regarding mAbs targeting EGFR?

A. Colitis
B. Rash
C. Tumor Lysis Syndrome
D. Hypertension

Monoclonal Antibody Part 1 Lecture Outline by Drug Class

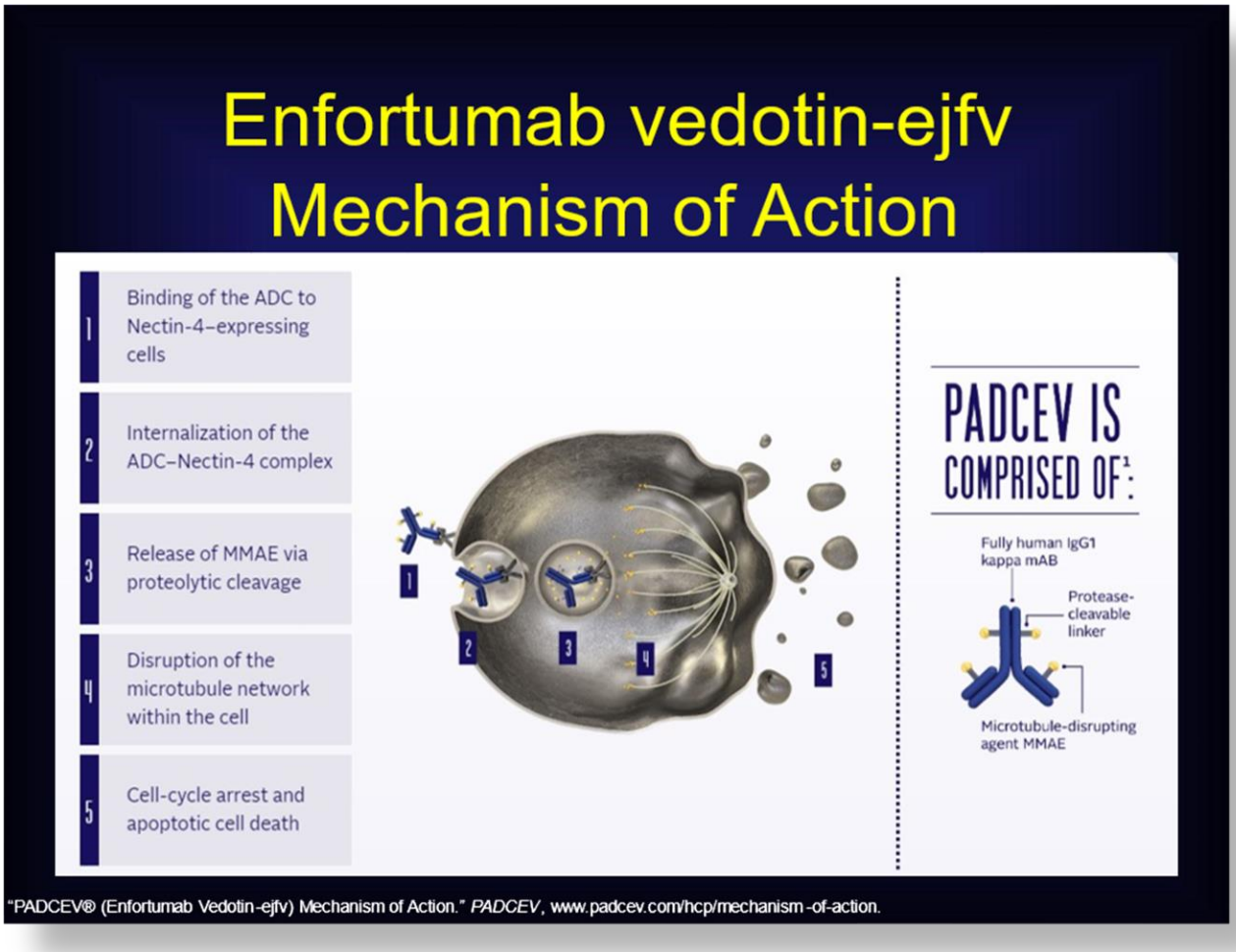
- CD20-Directed Monoclonal Antibodies
- CD19-Directed Monoclonal Antibodies
- HER2-Directed Monoclonal Antibodies
- VEGF-Directed Monoclonal Antibodies
- EGFR-Directed Monoclonal Antibodies
- **Nectin-4-Directed Monoclonal Antibodies**
- RANKL-Directed Monoclonal Antibodies

Nectin-4

- Adhesion protein located on cell surfaces
- Highly expressed in urothelial carcinoma as well as breast, gastric, and lung cancers

Enfortumab vedotin-ejfv

- Antibody drug conjugate (ADC) directed at Nectin-4
- Contains an IgG1 anti-Nectin-4 antibody conjugated to a microtubule-disrupting agent, monomethyl auristatin E (MMAE)
    - MMAE is attached to the antibody via a protease cleavable linker. The ADC binds to Nectin-4 expressing cells to form a complex which is internalized within the cell. Released MMAE binds to the tubules and disrupts the cellular microtubule network, inducing cell cycle arrest and apoptosis of Nectin-4 expressing cells.
- FDA approved for urothelial cancer



Warnings and Precautions

- Extravasation
  - May be an irritant
  - Extravasation reactions may be delayed – Erythema, swelling, increased temperature, and pain worsened until 2 to 7 days after extravasation and resolved within 1 to 4 weeks of peak
- Dermatologic toxicity
  - Severe skin reactions (grades 3/4) reported in 10% of treated patients
  - Median time to onset of severe skin reactions = 0.6 months (range: 0.1-8 months)
- Hyperglycemia
  - Diabetic ketoacidosis has been observed
  - Therapy interruption is warranted for blood glucose >250 mg/dL
  - Risk factors include higher BMI and higher baseline HbA1c

Warnings and Precautions

- Ocular effects
  - Most ocular effects involve the cornea and include keratitis, blurred vision, limbal stem cell deficiency, and other effects associated with dry eye syndrome
  - Median time to onset is 1.7 months
- Peripheral neuropathy
  - Occurred in nearly half of patients treated in clinical trials
  - Usually low grade/manageable
  - Therapy interruption, dosage reduction, and/or permanent discontinuation may be warranted, depending on the severity
  - Complete resolution occurred in 11% of patients; 89% of patients had residual neuropathy (at the time of their last evaluation)
  - Median time to onset of grade ≥2 peripheral neuropathy = 4.9 months
- Pneumonitis/interstitial lung disease
  - Median time to onset = 2.9 months

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- EGFR-Directed Monoclonal Antibodies
- Nectin-4-Directed Monoclonal Antibodies
- **RANKL-Directed Monoclonal Antibodies**

RANKL-Directed Monoclonal Antibodies

Denosumab

- Fully human monoclonal antibody
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor
- Binds to transmembrane or soluble protein RANKL on the surface of osteoclasts preventing receptor activation
- Formation, function, and survival of osteoclasts are inhibited→decreased bone resorption and increased bone mass and strength in the cortical and trabecular bone
- Indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors and multiple myeloma (Xgeva ®)
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (Xgeva ®)
- Improve bone mass among patients at high risk for fracture who receive androgen deprivation therapy for non-metastatic prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer (Prolia®)

Dosage and Administration

- Bone metastases/Multiple Myeloma (prevention of skeletal related events) (Xgeva ®)
  - Administer 120 mg SQ q4 weeks
  - Upper arm, upper thigh, or abdomen
- Hypercalcemia of malignancy (Xgeva ®)
  - Administer 120 mg SQ q4 weeks
  - During the first month, give an additional 120 mg on days 8 and 15
  - Upper arm, upper thigh, or abdomen
- Improve bone mass (Prolia®)
  - Administer 60 mg SQ q6 months

Denosumab

- Correct hypocalcemia prior to initiation of denosumab
- Supplement calcium 1000 mg PO QD and vitamin D $\geq$ 400 IU PO QD
- Dental exam prior to and during treatment to monitor for osteonecrosis of the jaw

The Role of Monoclonal Antibodies in Hematology/Oncology: Part 2

Monoclonal Antibody Part 2 Lecture Outline by Drug Class

- **Checkpoint Inhibitors: PD-1/PD-L1 Inhibitors**
- Checkpoint Inhibitors: CTLA-4 Inhibitors
- CD30-Directed Monoclonal Antibodies
- CD38-Directed Monoclonal Antibodies
- SLAM7-Directed Monoclonal Antibodies
- CD33-Directed Monoclonal Antibodies
- CD22-Directed Monoclonal Antibodies
- CD79b-Directed Monoclonal Antibodies
- CCR4-Directed Monoclonal Antibodies
- IL-6 Receptor-Directed Monoclonal Antibodies

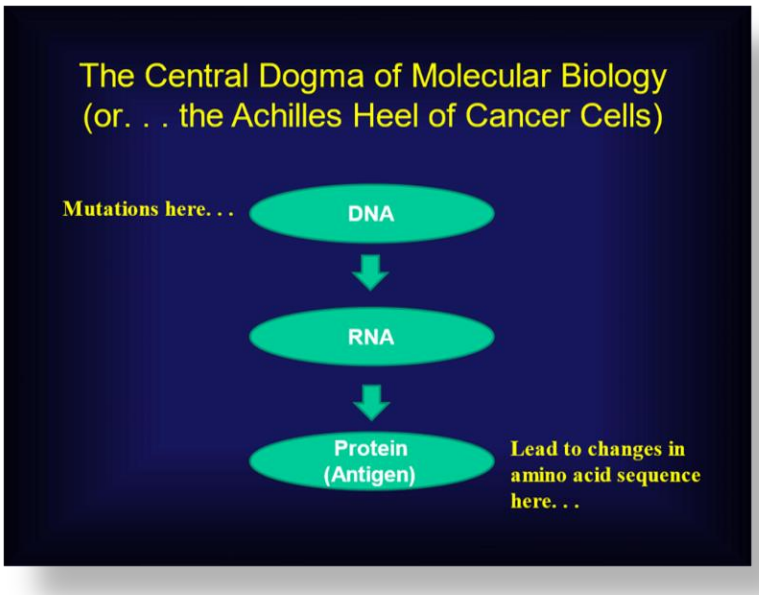
Checkpoint Inhibitors: PD-1/PD-L1 Inhibitors

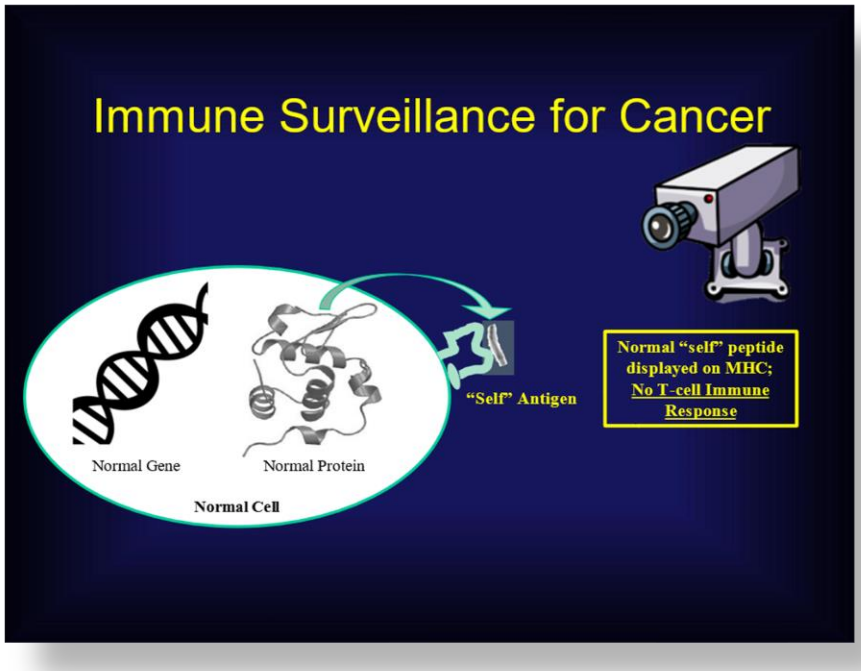
Self-Reactive T-cells are Deleted Early in T-cell Development

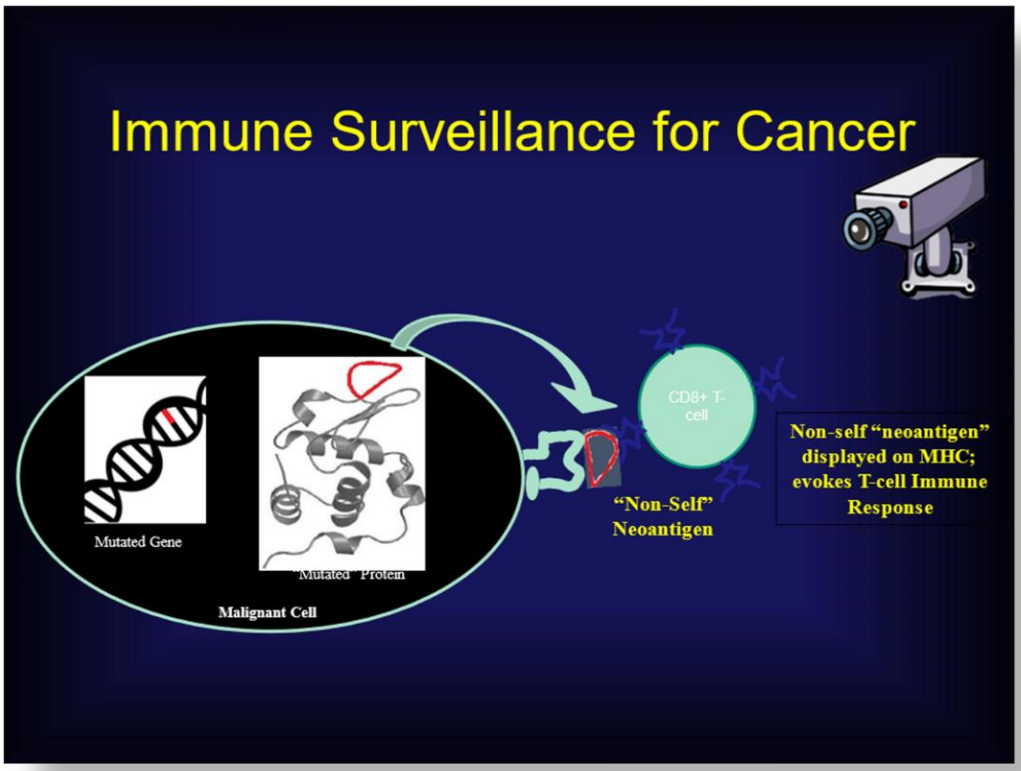
- T-cells develop in the thymus
- Self-reactive T-cells are destroyed during T-cell development
- T-cell repertoire only recognizes foreign (non-self) antigens
    - Infectious organisms and viruses
    - Pre-cancerous and malignant cells

Cancer Cells are. . . Different

- Cancer cells are derived from “self” tissue but can be recognized as “non-self” by the immune system
- Cancer occurs via changes in the genetic code (mutations) which occasionally leads to changes in amino acid sequence of proteins
    - These “altered” peptides are displayed by tumor cells
    - Can be recognized by T-cells as non-self


The Central Dogma of Molecular Biology
(or. . . the Achilles Heel of Cancer Cells)
Mutations here. . .
DNA
RNA
Protein
(Antigen)
Lead to changes in
amino acid sequence
here. . .


Immune Surveillance for Cancer
Normal Gene
Normal Protein
Normal Cell
"Self" Antigen
Normal "self" peptide
displayed on MHC;
No T-cell Immune
Response



Cancer Cells are *Different* than Normal Cells

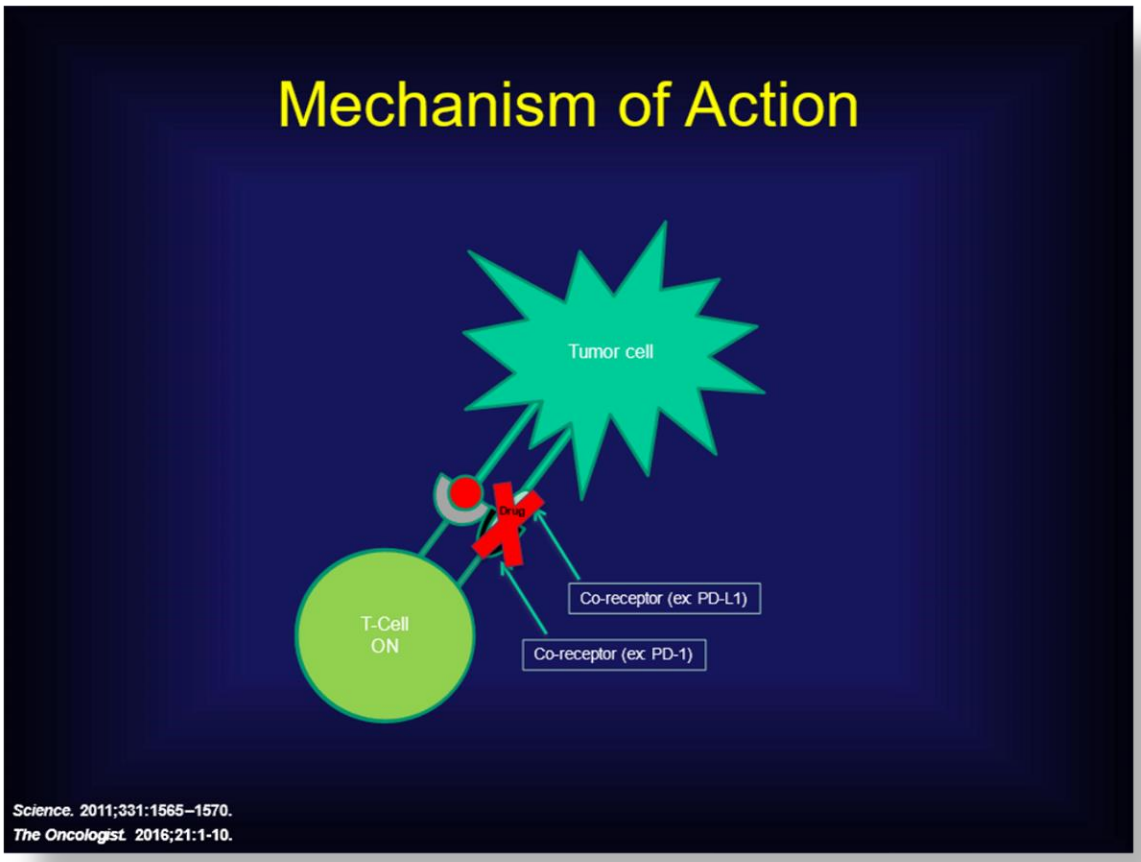
Why do Immune Checkpoints Exist?

- Prevent complications from "unchecked" activation of the immune system
  - Autoimmune diseases
  - Overzealous response to infection (e.g. sepsis)

What are PD-1 and PD-L1?

- Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production
- Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T cell immune surveillance of tumors

PD-L1 Expression Allows Cancer Cells to "Disguise" Themselves to Avoid Destruction



FDA Approved PD-1/PD-L1 Inhibitors

PD-1 Inhibitors

- Pembrolizumab (2014)
- Nivolumab (2014)
- Cemiplimab (2018)
- Dostarlimab (2021)
- Retifanlimab (2023)
- Toripalimab (2023)

PD-L1 Inhibitors

- Atezolizumab (2016)
- Avelumab (2017)
- Durvalumab (2017)

PD-1 Inhibitor Indications

Cancer	Pembrolizumab	Nivolumab	Cemiplimab
Melanoma	x	x	
Non-Small Cell Lung Cancer (NSCLC)	x	x	x
Malignant Pleural Mesothelioma		x	
Head and Neck Squamous Cell Cancer (HNSCC)	x	x	
Classical Hodgkin Lymphoma (cHL)	x	x	
Primary Mediastinal Large B-cell Lymphoma (PMBCL)	x		
Urothelial Carcinoma	x	x	
Endometrial Carcinoma	x		
Microsatellite Instability-High (MSI-H) or Mismatch Repair-Deficient (dMMR) Cancer	x	x (colorectal)	
Tumor Mutational Burden-High Cancer	x		
Gastric Cancer	x	x	
Esophageal Cancer	x	x	
Cervical Cancer	x		
Hepatocellular Carcinoma (HCC)	x	x	
Merkel Cell Carcinoma (MCC)	x		
Renal Cell Carcinoma (RCC)	x	x	
Breast Cancer, Triple Negative	x		
Cutaneous Squamous Cell Carcinoma (SCC)	x		x
Biliary Tract Cancer	x		
Basal Cell Carcinoma (BCC)			x

Dostarlimab indications	Retifanlimab indications	Toripalimab indications
Advanced Endometrial Cancer (dMMR or MSI-H)	Merkel Cell Carcinoma	Nasopharyngeal Carcinoma
Recurrent or Advanced dMMR Solid Tumors		

Atezolizumab indications	Avelumab indications	Durvalumab indications
Alveolar Soft Part Sarcoma	Urothelial Carcinoma	Small Cell Lung Cancer
Non-Small Cell Lung Cancer	Merkel Cell Carcinoma	Non-Small Cell Lung Cancer
Small Cell Lung Cancer	Renal Cell Carcinoma	Hepatocellular Carcinoma
Melanoma		Biliary Tract Cancer
Hepatocellular Carcinoma		

Monoclonal Antibody Part 2 Lecture Outline by Drug Class

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- **Checkpoint Inhibitors: CTLA-4 Inhibitors**
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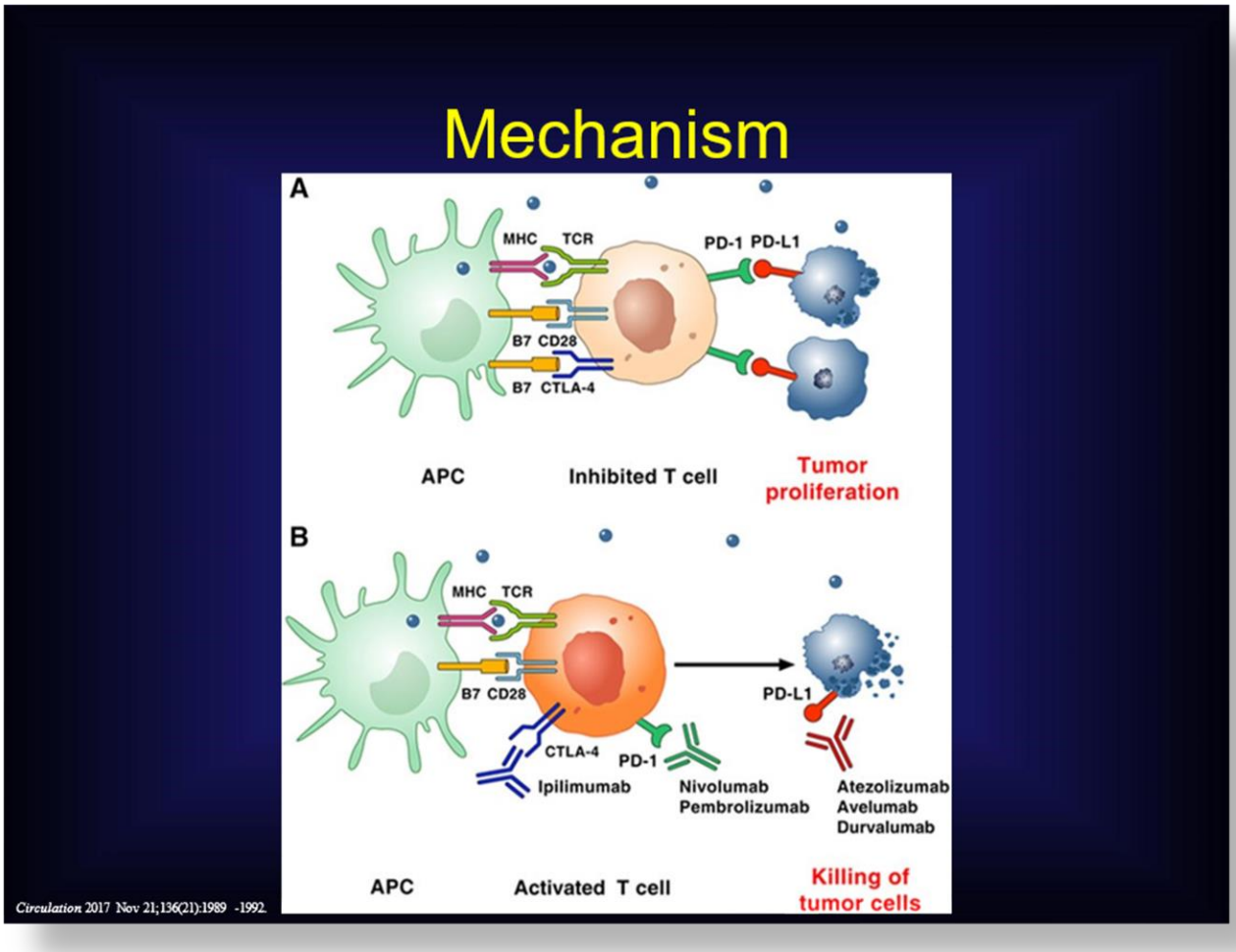
- CCR4-Directed Monoclonal Antibodies
  IL-6 Receptor-Directed

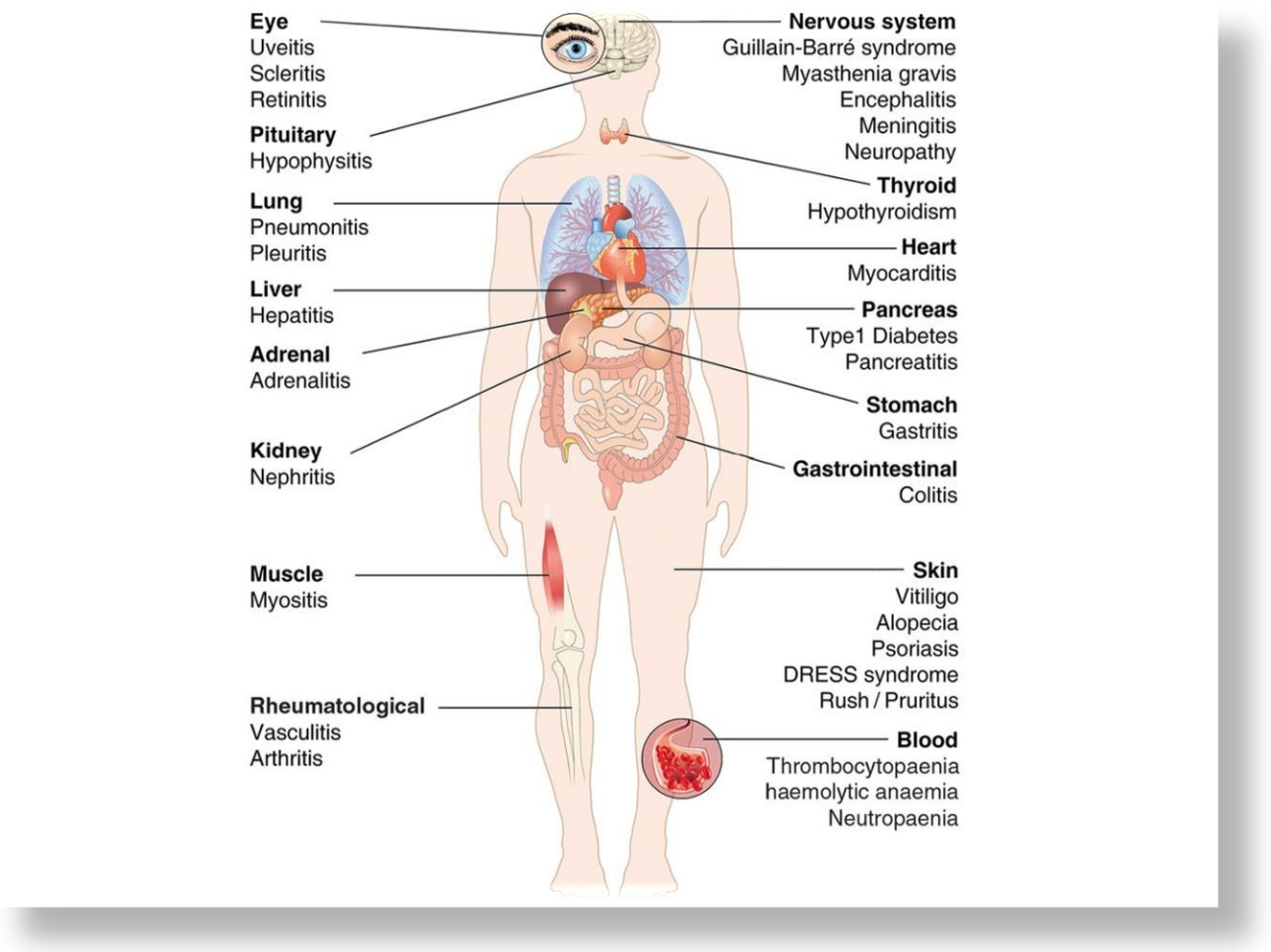
Checkpoint Inhibitors: CTLA-4 Inhibitors



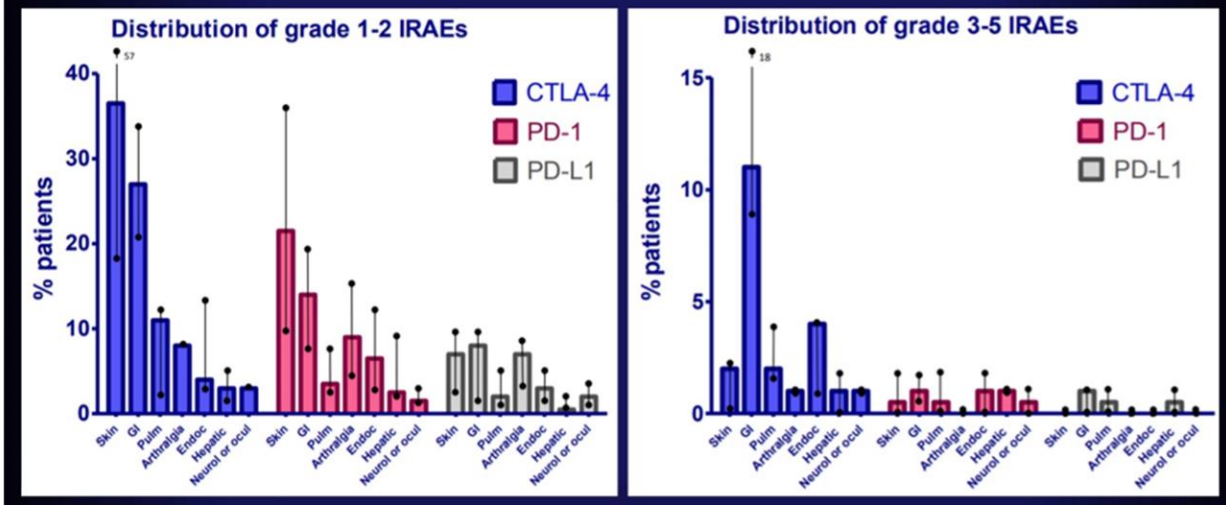
Drug	mAB source	Routes of administration	FDA approved indications	Clinical Considerations
Ipilimumab	Human	IV	Colorectal cancer (MSI-high or dMMR), Esophageal cancer, HCC, Malignant pleural mesothelioma, Melanoma, NSCLC, RCC	•When given in combination with nivolumab, infuse nivolumab first, followed by ipilimumab. •When given in combination with nivolumab and platinum-based doublet chemotherapy, infuse nivolumab first, followed by ipilimumab, and then the platinum-based doublet chemotherapy. •Most FDA approved indications are for 4 cycles of ipilimumab in combination with nivolumab, followed by nivolumab monotherapy.
Tremelimumab	Human	IV	HCC, NSCLC	•When given in combination with durvalumab, administer tremelimumab first. •Only approved in combination with durvalumab •In NSCLC, tremelimumab is given in combination with durvalumab and platinum-based chemotherapy. Tremelimumab is administered for a total of up to 5 doses; the tremelimumab schedule is dependent on cycle number.

Management of Checkpoint Inhibitor Toxicity

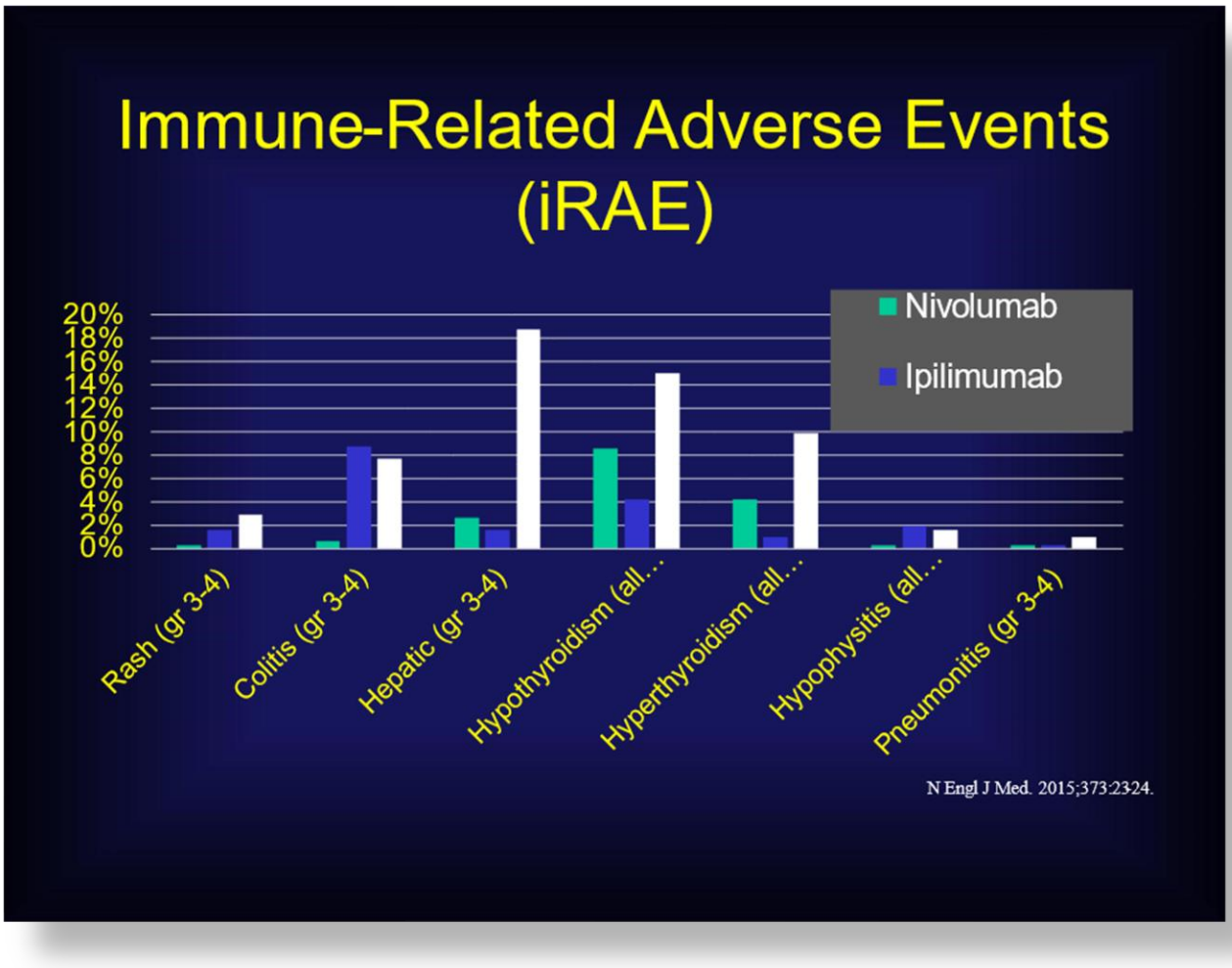
Warnings and Precautions: Immune-mediated adverse reactions



Incidence of iRAEs



European Journal of Cancer. 2016;54:13948.



Monitoring

- Physical exam and review of systems prior to each dose
- LFTs and bilirubin at baseline and each dose
- Thyroid function tests at baseline and each dose
- Serum chemistries and adrenocorticotropic hormone (ACTH) prior to each dose
- Serum creatinine (baseline and periodic)
- Diarrhea, abdominal pain, blood/mucus in stool
- Rash, pruritus, other signs of dermatologic toxicity
- Other immune-mediated endocrinopathies

General Management Principles

- Refer to package insert and product website for details
- Accurate grading (NCI CTCAE)
- Decide whether to hold/discontinue checkpoint inhibitor
- Consider corticosteroids
  - Additional immunosuppression if poor response
- Provide supportive care
  - GI prophylaxis
  - Glucose management
  - Bone health
  - PJP prophylaxis

NCI CTCAE v 5.0 Grading of iRAE: Overview

- Grade 1: Mild; asymptomatic, clinical/diagnostic observation only, no intervention indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL*
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4: Life-threatening consequences; urgent intervention indicate
- Grade 5: Death related to AE

General Management Criteria

- Grade 1
  - Monitor closely
  - Continue checkpoint inhibitor cautiously
- Grade 2
  - Topical steroids, if applicable or Prednisone 0.5-1 mg/kg/day
  - Suspend checkpoint inhibitor; consider resuming when resolves to $\leq$ grade 1
- Grade 3-4
  - IV corticosteroids: Prednisone 1-2 mg/kg/day equivalent
  - Hospitalization may be indicated
  - Permanently discontinue checkpoint inhibitor in most cases
  - Consult specialist if indicated: Dermatology, gastroenterology, endocrinology, pulmonology

GI Adverse Effects: Colitis

- Signs and/or symptoms
  - Diarrhea
  - Abdominal pain
  - Mucus or blood in stool
  - Fever
  - Peritoneal signs
  - Ileus

- Work-up
  - Blood tests (CBC, CMP, ESR, CRP)
  - Stool tests (ova/parasites, c diff)
  - CT scan
  - Consider colonoscopy with biopsy and CMV testing
- Colitis Management
  - Consider GI consult and/or surgery consult; peritoneal signs
  - Grade 1: <4 stools/day above baseline
    - Monitor closely
    - Symptomatic treatment- loperamide and/or diphenoxylate/atropine
  - Grade 2: 4-6 stools/day above baseline; duration >5 days
    - Prednisone 1 mg/kg/day equivalent
  - Grade 3-4: ≥7 stools/day above baseline
    - Consider hospitalization
    - IV corticosteroids: 1-2 mg/kg/day prednisone equivalent
    - If no response in 3-5 days, infliximab* 5 mg/kg IV q 2 weeks

Hepatic Adverse Effects

- Signs and/or symptoms:
  - Jaundice
  - Dark urine
  - Abnormal liver function tests
- Work-up
  - Rule out viral hepatitis
  - Consider CT or ultrasound to rule out liver metastases/obstruction if indicated
  - Consider liver biopsy
- Hepatitis Management
  - Consider hepatology consult
  - Minimize hepatotoxic medications
  - Corticosteroids 1-2 mg/kg/day prednisone equivalent
    - If no response, add mycophenolate mofetil* or azathioprine*

Dermatologic Adverse Effects

- Signs and/or symptoms
  - Pruritus
  - Rash
  - Vitiligo
  - Stevens-Johnson syndrome/Toxic epidermal necrosis
- Work-up
  - Skin biopsy
  - Consider clinical photography
  - Review medications

_____
_____
_____
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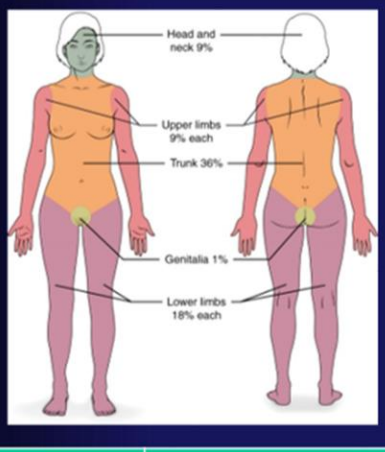
_____

Rash Grading and Rule of 9's



Body Part	Estimated BSA
One entire arm	9%
Entire head	9%
Entire chest	9%
Entire abdomen	9%
Entire back	18%
One entire leg	18%
Groin	1%

NCI CTCAE v4.0	Grade 1	Grade 2	Grade 3
Rash maculo-popular	<10% BSA ± symptoms	10-30% BSA ± symptoms; limiting instrumental ADL	>30% BSA ± symptoms; limiting self -care ADL

By OpenStax College - Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=30131318

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010 -06-14_QuickReference_5x7.pdf (accessed 10/19/2017)

- Dermatologic Side Effect Management
  - Grade 1-2
    - Topical steroids
    - Antihistamines
  - Grade 3-4
    - Topical steroids
    - Antihistamines
    - Dermatology consult
    - Systemic steroids 1-2 mg/kg/day prednisone equivalent
    - Consider hospitalization

Neurologic Adverse Effects

- Syndromes
  - Guillain-Barré Syndrome
  - Myasthenia gravis
  - Peripheral neuropathy

_____
_____
_____
_____
_____

    - Autonomic neuropathy
    - Aseptic meningitis
    - Encephalitis
    - Transverse myelitis
- Neurology consultation
- Work-up & treatment depends on syndrome

Endocrine Adverse Effects

- Adverse events
    - Primary hypothyroidism
    - Hyperthyroidism
    - Primary adrenal insufficiency
    - Hypophysitis: Pituitary inflammation
    - Autoimmune type 1 diabetes mellitus
- Signs and/or Symptoms
    - Fatigue
    - Headache
    - Mental status changes
    - Abdominal pain
    - Unusual bowel habits
    - Hypotension

- Endocrine Adverse Effects: Management
    - Consider referral to endocrinologist
    - Typically can continue checkpoint inhibitor once stable on hormone replacement
    - Check TSH, free T4, ACTH, morning cortisol, glucose
        - Consider LH, FSH, testosterone, prolactin, ACTH stim test
    - Consider MRI with pituitary cuts if concerned for hypophysitis
        - Hypophysitis: Consider short course of high dose steroids along with hormone replacement
    - Replacement hormones
        - Hypothyroidism: Levothyroxine
        - Adrenal insufficiency: Hydrocortisone
        - Recommend medical alert bracelet and provide stress dose steroids PRN
        - Adrenal crisis (severe dehydration, hypotension, shock) → hospitalization indicated (fluids, steroids)
        - Sex hormone deficiency: Testosterone, estrogen
        - Type 1 diabetes: Insulin

Audience Response Question: Which of the following should be monitored during treatment with CTLA-4 and/or PD-1/PD-L1 mAbs?

A. TSH
B. ALT/AST
C. Cortisol
D. All of the above

_____
_____
_____
_____
_____

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- Checkpoint Inhibitors: PD-1/PD-L1 Inhibitors
- Checkpoint Inhibitors: CTLA-4 Inhibitors
- **CD30-Directed Monoclonal Antibodies**
- CD38-Directed Monoclonal Antibodies
- SLAM7-Directed Monoclonal Antibodies
- CD33-Directed Monoclonal Antibodies
- CD22-Directed Monoclonal Antibodies
- CD79b-Directed Monoclonal Antibodies
- CCR4-Directed Monoclonal Antibodies
- IL-6 Receptor-Directed Monoclonal Antibodies

CD30-Directed Monoclonal Antibodies

Brentuximab Vedotin (Adcetris®)

- Chimeric IgG1 monoclonal antibody-drug conjugate targeting CD30
- CD30 is expressed by Reed-Sternberg cells specific to Hodgkin Lymphoma
- CD30 may control apoptosis, cell activation, and proliferation

Mechanism of Action

- Binds to CD30 on the Reed-Sternberg cell
- Cancer cell then internalizes and releases MMAE
- MMAE = microtubule disrupting agent
    - Binds tubulin and disrupts the microtubule network with the cell
    - G2/M cell cycle arrest = apoptosis

Indications

- Treatment of Hodgkin Lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of $\geq$ 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates
- Treatment of systemic anaplastic large cell lymphoma after failure of $\geq$ 1 prior multi-agent chemotherapy regimen
- HL, consolidation therapy after ASCT
- Front-line with chemotherapy (AVD) in patients with stage III/IV HL
- Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone
- Treatment of CD30-expressing mycosis fungoides in adults who have received prior systemic therapy

Dosage and Administration

- Dose =1.8 mg/kg (max 180 mg) IV infusion over 30 minutes q3 weeks (for most indications)
- Continue treatment until disease progression or unacceptable toxicity

- When administering in combination with doxorubicin, vinblastine, and dacarbazine [AVD], begin brentuximab within ~1 hour after completion of AVD
- HL consolidation after auto SCT: up to 16 cycles

Monitoring
- Infusion reactions
  - If occur, premedicate with acetaminophen, antihistamine, and corticosteroid
- Tumor Lysis Syndrome
- Peripheral neuropathy
- Bone marrow suppression: Especially when given with AVD chemotherapy
- Hepatic toxicity
- Pulmonary toxicity: Concurrent use with bleomycin is contraindicated
- Drug interactions
  - MMAE is a substrate and an inhibitor of CYP3A4/5

Monoclonal Antibody Part 2 Lecture Outline by Drug Class
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- IL-6 Receptor-Directed Monoclonal Antibodies

CD38-Directed Monoclonal Antibodies

Daratumumab (Darzalex®)
- IgG1 kappa human monoclonal antibody against CD38 antigen
  - CD38 is a transmembrane glycoprotein expressed on the surface of hematopoietic cells, including plasma cells (i.e. multiple myeloma)
  - Has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity

Mechanism of Action
- Binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking and by immune-mediated tumor cell lysis through CDC, ADCC, and ADCP
- Myeloid derived suppressor cells (MDSCs) and a subset of regulatory T cells (CD38+Tregs) express CD38 and are susceptible to daratumumab mediated cell lysis

Indications

- Multiple myeloma: Newly diagnosed
- Multiple myeloma: Relapsed/refractory
    - In combination and as monotherapy

Dosage and Administration

- Pre-medicate prior to each infusion with corticosteroids, antipyretics and antihistamines
- Post infusion, administer an oral corticosteroid to all patients to reduce risk of delayed infusion reactions
- Varies, but most regimens recommended dosing is 16 mg/kg actual body weight
    - Example:
    - Q1 week = Weeks 1 to 8
    - Q2 weeks = Weeks 9 to 24
    - Q4 weeks = Week 25 onwards until POD
- The initial IV dose (16 mg/kg on week 1) may be divided over 2 consecutive days (8 mg/kg/day on days 1 and 2 of week 1 of therapy) to facilitate administration.

Pre-Infusion Medications

- Administer the following pre-infusion medications 1-3 hours before every infusion:
    - Corticosteroid (long- or intermediate-acting)
        - Monotherapy: Administer methylprednisolone 100 mg (or equivalent) IV. Following the second infusion, consider reducing to 60 mg (or equivalent) PO or IV.
        - In Combination: Administer dexamethasone 20 mg (or equivalent) PO or IV. When dexamethasone is the background regimen-specific corticosteroid, the dexamethasone dose that is part of the background regimen will serve as pre-medication on infusion days. Do not administer background regimen-specific corticosteroids (e.g. prednisone) on infusion days when patients have received dexamethasone (or equivalent) as a pre-medication.
    - Acetaminophen 650 mg to 1,000 mg PO
    - Diphenhydramine 25 mg to 50 mg (or equivalent) PO or IV

Post-Infusion Medications

- Administer the following post-infusion medications:
    - Monotherapy: Administer methylprednisolone 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid) PO for 2 days starting the day after administration.
    - In Combination: Consider administering PO methylprednisolone at a dose of $\leq$ 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid) beginning the day after administration.
    - If a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the daratumumab infusion, additional corticosteroids may not be needed.
    - For patients with a history of COPD, consider prescribing short and long-acting bronchodilators and inhaled corticosteroids.

Following the first 4 infusions, consider discontinuing these additional post-infusion medications, if the patient does not experience a major infusion-related reaction
Warnings and Precautions

- Infusion Reactions
- Interference with Serological Testing
  - Binds to CD38 on RBCs and results in positive indirect Coombs Test
  - Masks detection of antibodies to minor antigens in serum
  - Type and screen :Blood type prior to daratumumab initiation
  - Notify blood banks
  - May persist for up to 6 months
- Bone marrow suppression
- Interference with determination of MM response
  - Drug may be detected on SPEP and immunofixation
  - Impact monitoring of M-protein
- Herpes zoster reactivation
  - Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting and continue for 3 months following treatment
- Do not substitute daratumumab (IV) with daratumumab/hyaluronidase (SUBQ); products have different dosing and are not interchangeable

Monoclonal Antibody Part 2 Lecture Outline

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- CCR4-Directed Monoclonal Antibodies
- IL-6 Receptor-Directed Monoclonal Antibodies

SLAM7-Directed Monoclonal Antibodies

Elotuzumab (Empliciti®)

- Approved in November 2015
- Humanized recombinant monoclonal antibody directed to SLAMF7, a cell surface glycoprotein

Mechanism of Action

- Targets the SLAMF7 protein
  - SLAMF7 is expressed on myeloma cells independent of cytogenetic abnormalities
  - SLAMF7 is also expressed on NK cells, plasma cells, and at lower levels on specific immune cell subsets

- Elotuzumab directly activates NK cells through both the SLAMF7 pathway and Fc receptors
- Targets SLAMF7 on myeloma cells and facilitates the interaction with NK cells to mediate the killing of myeloma cells through ADCC

Indication
- In combination with lenalidomide and dexamethasone for the treatment of patients with MM who received 1-3 prior therapies
- In combination with pomalidomide and dexamethasone for the treatment of MM in patients who received ≥ 2 prior therapies, including lenalidomide and a proteasome inhibitor
- Minimal activity as single agent; must be given in combination with an –IMID agent

Dosage and Administration
- 10 mg/kg IV q1 week for the first 2 cycles followed by q2 weeks thereafter in conjunction with lenalidomide/dex
- 10 mg/kg IV q1 week for the first 2 cycles followed by 20 mg/kg q4 weeks thereafter in conjunction with pomalidomide/dex
- Must premedicate prior to each dose with dexamethasone, acetaminophen, an H1 antagonist, and an H2 antagonist
    - On days that elotuzumab is administered, give dexamethasone 28 mg PO between 3 and 24 hours before plus 8 mg IV between 45 and 90 minutes before elotuzumab
    - On days that elotuzumab is not administered but a dose of dexamethasone is scheduled (Days 8 and 22 of cycle 3 and all subsequent cycles), give 40 mg PO
- Infusion rate
    - 10 mg/kg dose
        - First infusion (Cycle 1, Dose 1): Infuse at 0.5 mL/min for the first 30 minutes. If no infusion reactions occur, may increase rate to 1 mL/min for the next 30 min. If tolerated, may then increase rate to 2 mL/min until infusion completion (max rate: 2 mL/min)
        - Second infusion (Cycle 1, Dose 2): If no infusion reactions during prior infusion, initiate at 3 mL/min for the first 30 minutes. If tolerated, may then increase rate to 4 mL/min until infusion completion (maximum rate: 4 mL/min)
        - Subsequent infusions (Cycle 1, Doses 3 and 4 and all subsequent infusions): If no infusion reactions during prior infusion, initiate and infuse at 5 mL/min until completion (max rate: 5 mL/min)
    - 20 mg/kg dose
        - First infusion (Dose 1): Initiate infusion at 3 mL/min for the first 30 min. Infusion rates which were escalated to 5 mL/min at the 10 mg/kg dose must be decreased to 3 mL/min at the first infusion at 20 mg/kg dose. If no infusion reactions occur at 3 mL/min, may increase the rate to 4 mL/min until infusion completion (max rate: 4 mL/min)
        - Second and subsequent infusions (Dose 2 and all subsequent infusions): If no infusion reactions occurred during the prior infusion, initiate and infuse at 5 mL/min until completion (maximum rate: 5 mL/min)

Warnings and Precautions

- Infusion reactions: Pre-medication is required
- Infection
- Second Primary Malignancies
- Hepatotoxicity
- Interference with determination of complete response: Can interfere with assays used to monitor M-protein. This interference can impact the determination of complete response

Monoclonal Antibody Part 2 Lecture Outline by Drug Class

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- CCR4-Directed Monoclonal Antibodies
- IL-6 Receptor-Directed Monoclonal Antibodies
- CD33-Directed Monoclonal Antibodies

Gemtuzumab Ozogamicin (Mylotarg®)

- Recombinant humanized IgG4 immunoglobulin covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin

Indications

- Treatment of newly diagnosed CD33+ AML in adults and pediatric patients ≥1 month of age
- Treatment of R/R CD33+ AML in adults and pediatric patients ≥ 2 years

Mechanism of Action

- A CD33-directed antibody-drug conjugate (ADC)
  - N-acetyl gamma calicheamicin, is a cytotoxic agent that is covalently attached to the antibody via a linker
- Gemtuzumab ozogamicin binds to CD33-expressing tumor cells, resulting in internalization of the antibody-antigen complex
  - Following internalization, the calicheamicin derivative is released inside the myeloid cell. The calicheamicin derivative binds to DNA resulting in double strand breaks, inducing cell cycle arrest and apoptosis

Warnings and Precautions

- Bone marrow suppression
- Nausea/vomiting
- Hemorrhage: Prolonged thrombocytopenia

- Hepatotoxicity
  - Black box warning for Sinusoidal Obstruction Syndrome (SOS)
- Infusion reaction
- QT prolongation
  - Obtain baseline EKG and monitor electrolytes closely
- Tumor lysis syndrome
- Hyperleukocytosis: Cytoreduction is recommended prior to gemtuzumab ozogamicin administration if hyperleukocytosis (leukocyte count ≥30,000/mm^3) is present

Monoclonal Antibody Part 2 Lecture Outline by Drug Class

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- CD33-Directed Monoclonal Antibodies
- **CD22-Directed Monoclonal Antibodies**
- CD79b-Directed Monoclonal Antibodies
- CCR4-Directed Monoclonal Antibodies
- IL-6 Receptor-Directed Monoclonal Antibodies

CD22-Directed Monoclonal Antibodies

Inotuzumab Ozogamicin (Besponsa®)

- Approved in August 2017
- Recombinant humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody
- Indicated for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Mechanism of Action

- A CD22-directed antibody-drug conjugate (ADC)
- Recognizes CD22 and has N-acetyl-gamma-calicheamicin
  - A cytotoxic agent that is covalently attached to the antibody via a linker
- Binds to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker

Warnings and Precautions
- Bone marrow suppression
- Hemorrhage (prolonged thrombocytopenia)
- Hepatotoxicity
  - Black box warning for VOD/SOS
- Infusion reaction
- Infection
- QT prolongation
  - Obtain baseline EKG and monitor electrolytes closely

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- CD22-Directed Monoclonal Antibodies
- **CD79b-Directed Monoclonal Antibodies**
- CCR4-Directed Monoclonal Antibodies
- IL-6 Receptor-Directed Monoclonal Antibodies

CD79b-Directed Monoclonal Antibodies

Polatuzumab Vedotin (Polivy®)
- A CD79b-directed antibody–drug conjugate indicated in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after $\geq$ 2 prior therapies

Mechanism of Action
- Upon binding CD79b, polatuzumab vedotin is internalized, and the linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE
- MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis

Dose
- Recommended dose = 1.8 mg/kg IV over 90 minutes q21 days for 6 cycles in combination with bendamustine and rituximab
  - Subsequent infusions may be administered over 30 minutes if the previous infusion is tolerated
- Premedicate with an antihistamine and antipyretic

Warnings and Precautions
- Bone marrow suppression
- Hepatotoxicity

- Infection
- Administer Pneumocystis jiroveci pneumonia and herpes virus prophylaxis throughout polatuzumab vedotin treatment
- Infusion-related reactions
- Peripheral neuropathy
- Progressive multifocal leukoencephalopathy
- Tumor lysis syndrome

Monoclonal Antibody Part 2 Lecture Outline by Drug Class

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- CD33-Directed Monoclonal Antibodies
- CD22-Directed Monoclonal Antibodies
- CD79b-Directed Monoclonal Antibodies
- **CCR4-Directed Monoclonal Antibodies**
- IL-6 Receptor-Directed Monoclonal Antibodies

CCR4-Directed Monoclonal Antibodies

Mogamulizumab-kpkc (Poteligeo®)

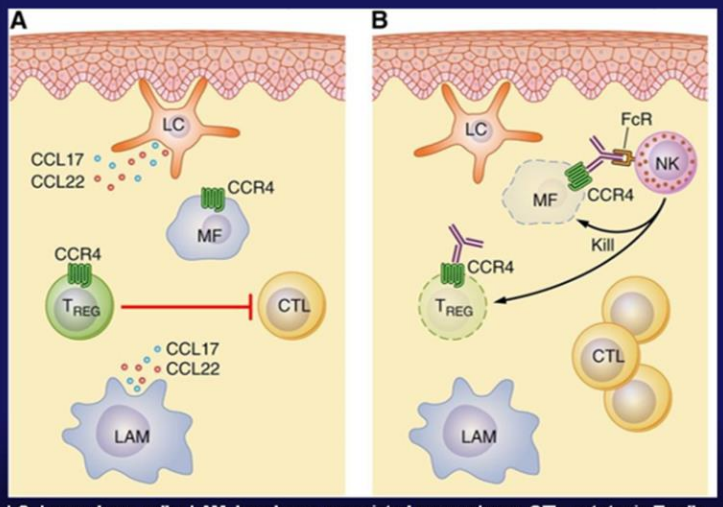
- Approved August 2018
- Humanized IgG1 kappa monoclonal antibody that binds to CCR4
- Indicated for the treatment of adult patients with R/R mycosis fungoides (MF) or Sézary syndrome (SS) after $\geq$ 1 prior systemic therapy

Mechanism of Action

- Anti-CCR4 first-in-class defucosylated, humanized IgG1 kappa monoclonal antibody

Mechanism of Action

- Anti-CCR4 first-in-class defucosylated , humanized IgG1 kappa monoclonal antibody



LC, Langerhans cells; LAM, lymphoma associated macrophage; CTL, cytotoxic T cells

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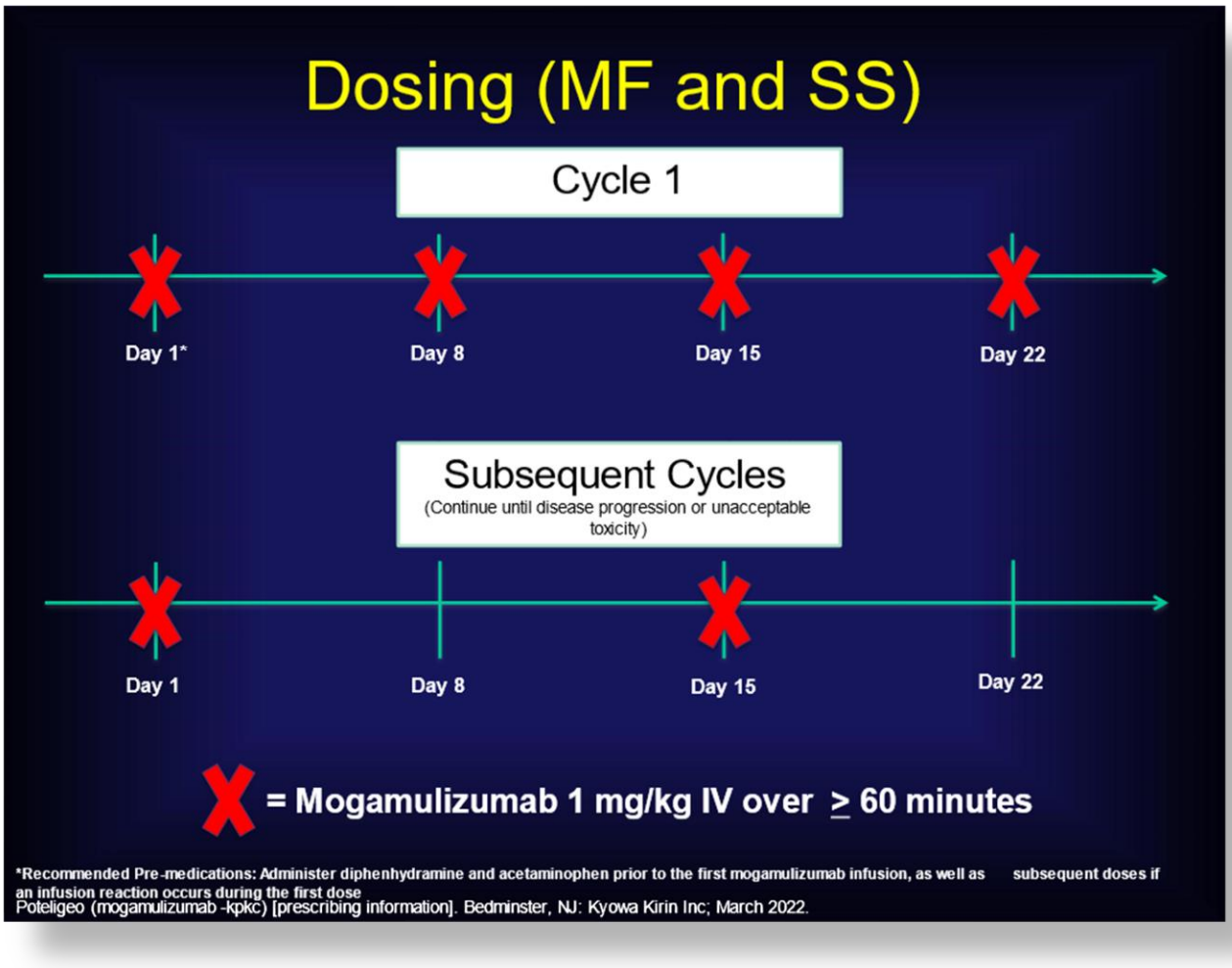
Ryan A. Wilcox Blood 2015;125:1847 -1848



Warnings and Precautions

- Autoimmune toxicity
- Bone marrow suppression
- Dermatologic toxicity
  - Rash is one of the most frequently reported
- Infections
- Infusion reactions
  - Most occur during or shortly after the first infusion, but may also occur with subsequent infusions
  - Premedicate prior to the first infusion with diphenhydramine and acetaminophen
- Increased allogeneic stem cell transplant complications (i.e. GVHD)

Monoclonal Antibody Part 2 Lecture Outline by Drug Class

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- CD22-Directed Monoclonal Antibodies
- CD79b-Directed Monoclonal Antibodies
- CCR4-Directed Monoclonal Antibodies
- **IL-6 Receptor-Directed Monoclonal Antibodies**

IL-6 Receptor-Directed Monoclonal Antibodies

Tocilizumab (Actemra®)

- Interleukin-6 (IL-6) receptor antagonist
  - Endogenous IL-6 is induced by inflammatory stimuli and mediates a variety of immunological responses
  - Inhibition of IL-6 receptors by tocilizumab leads to a reduction in cytokine and acute phase reactant production

Dosing in CAR-T related CRS

- Maximum dose: 800 mg IV over 60 minutes
  - <30 kg: 12 mg/kg
  - ≥30 kg: 8 mg/kg
- If clinical improvement does not occur after the first dose, up to 3 additional doses may be administered (with ≥ 8 hour interval between consecutive doses)
- May be administered as monotherapy or in combination with corticosteroids

Indications

- Cytokine release syndrome (CRS), severe or life-threatening: Treatment of chimeric antigen receptor (CAR) T-cell induced severe or life-threatening CRS in patients ≥2 years of age
- COVID-19, hospitalized patients: Treatment of COVID-19 in adult, hospitalized patients who are receiving systemic glucocorticoids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.
- Giant cell arteritis
- Polyarticular juvenile idiopathic arthritis
- Rheumatoid arthritis
- Systemic juvenile idiopathic arthritis
- Systemic sclerosis (scleroderma)-associated interstitial lung disease

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Warnings and Precautions

- GI perforation
- Hematologic effects
- Hepatic effects
  - Monitor LFTs prior to therapy initiation and during treatment
- Hyperlipidemia
- Hypersensitivity reactions
- Malignancy
- Infections
- Herpes zoster reactivation
- Tuberculosis
  - Both reactivation of latent and new tuberculosis cases (pulmonary or extrapulmonary) have been reported
  - Patients should be tested for latent tuberculosis infection before and during therapy

Oral Adherence

Definition

- Extent to which a patient's behavior coincides with medical advice
- Estimates of adherence are between 15-100%
- Same as compliance?
- Measurement
    - Percentage of prescribed doses taken by the patient over a specified timeframe
        - Dose taking: Taking the amount of medication prescribed for a day
        - Dose timing: Taking the medication within the prescribed period

Significance

- There are more than 40 FDA-approved oral agents for cancer treatment
- Nearly ¼ of the agents being researched now are oral compounds
- 125,000 deaths per year are due to non-adherence
- 10-23% of admissions to hospitals/nursing homes due to non-adherence

Non-Adherence

- Not taking enough of the medication

Over-adherence

- Taking too much of the medication
- The "more is better" approach

Measuring Adherence

- Food for thought: Hippocrates actually measured adherence by noting the effects of various potions and whether the patient took them or not

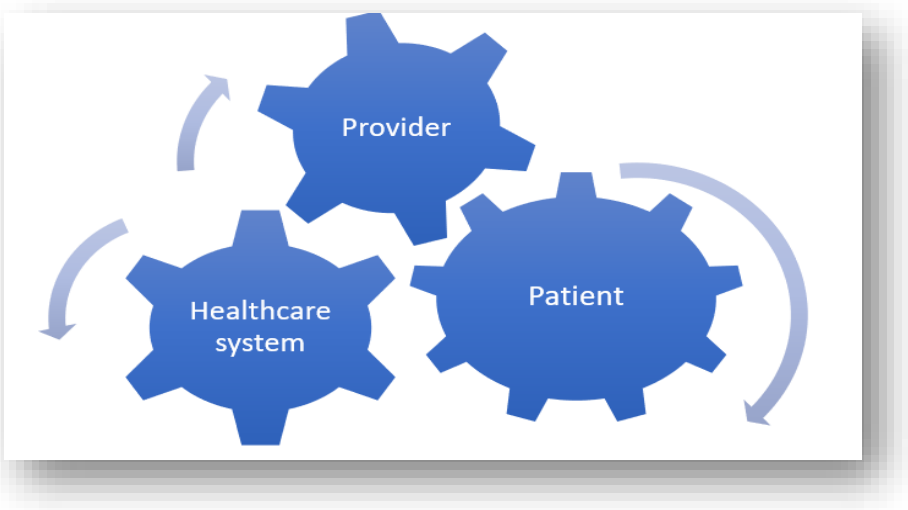
Direct Measures

- Direct observation
    - Most accurate but time consuming and relies on adequate staffing
    - Impractical for routine use: Patients can also hide pills in the buccal cavity
- Measurement of drug levels or biologic markers added to drug formulation
    - Can be altered due to variations in metabolism
    - White coat adherence: Patient is more likely to follow medication schedule when they have a pending appointment or lab values to be drawn

Indirect Measures

- Patient self-report/questionnaire
  - Easy and inexpensive
  - Results easily altered by patient; error-risk increases with longer time between visits
- Pill counts
  - Easy to perform, but can be easily altered by patient
- Prescription refill rate
  - Easy and objective
  - Refilling prescription but not taking the medication
- Clinical response
  - Simple to perform
  - Clinical response may be affected by things other than adherence
- Electronic medication monitor
  - Easily quantified results: Tracks patterns of medication-taking
  - Expensive: Information needs downloaded from medication vials
    - Opening vial but not taking medication
- Physiologic marker measures
  - Useful with other types of medications
  - Easy to perform
  - Other things can affect physiologic response
- Patient diaries
  - Decreases risk of poor memory of taking pills
  - Easily altered by patient
- Caregiver questionnaire
  - Simple can be easily altered

Barriers to Adherence



Impact on Patient Care

- Shift on responsibility
- Benefits of oral therapy
  - Convenient
  - Decreased IV access leads to decrease risk of IV complications
  - Allows patient to be more autonomous
  - Less time spent at clinical/hospital allowing more time for family and work
- Consequences of non-adherence
  - Decreased disease-free survival
  - Inferior treatment outcomes
    - Worsening of disease and/or death
  - Increased physician visits
  - More hospitalizations/longer length of stays
  - Possibility of treatment resistance
  - Over-adherence: Increased adverse effects and drug toxicities

Interventions

- Need to first recognize non-adherence
- Various interventions and strategies
  - Not one has been shown beneficial when used alone
- Should use multiple interventions/strategies to optimize success
- Should be a multi-disciplinary strategy
- Education and communication
- Visual reminders
  - Organizational methods
  - Dispensers
- Proactive management of side effects

- Frequent follow-up
- Motivational interviewing

Education: Patient and Caregiver

- Reason for medication
- Why medication is needed and how it works
- Dosage, frequency, and special instructions for taking the medication
- Is the medication compatible with other medications the patient is taking prescription and nonprescription
- How to handle a missed or late dose
- Common side effects and treatment of those side effects
- When to hold a dose

Organization/Dispensers/Visual Aids

- Calendars
- Pill boxes
- Electronic reminders
    - Timers/alarm clocks
    - Cell phone alerts
    - Telephone reminder services
    - Pagers with text
- Easy-open containers
- Use of medication blister packs
- Labels on bottles with large print

Proactive Side Effect Management

- Education
- Prescriptions for necessary supplemental medications
    - Anti-emetics
    - Laxatives
- Difference between expected side effect and toxicities and complications
- Notification of when to alert physician

Frequent Follow-Ups

- Office visits to ensure understanding of treatment regimen and medication education
- Less complex regimens when feasible
- Telephone and/or email follow-ups by the multidisciplinary care team
    - Nurses
    - Pharmacists
    - Social workers/case managers
    - Frequent follow-up

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Motivational Interviewing

- Patient-centered approach
  - More listening than talking
  - Focuses on encouraging patient to find solution
- Components
  - Empathy
    - Attempt to understand the patient's perspective from an external point of view
  - Reflective listening
    - Paraphrase client's comments as statements rather than questions
    - Open-ended questions
      - "Please tell me about…"
  - Encourage self-motivated statements
    - Point out observations and encourage patients to tell you how they are doing
  - Affirm and summarize
  - Recognize, support, and summarize conversation

Other Implications

- More common in chronic rather than acute disease states
- Often due to similar barriers to adherence
- Non-adherence in other chronic health conditions/disease processes
  - HIV
  - Asthma
  - HTN
  - CHF
  - Hyperlipidemia
  - Diabetes
  - Epilepsy

Patient Scenario #1: Pharmacy

85 y/o female with hx of CHF and COPD – ordered oral chemotherapy 2 weeks ago for breast cancer
Arrives at pharmacy with medication bottle, pharmacy bag with patient ed. sheet, and asking to speak to pharmacist about her chemotherapy pills
Notifies pharmacist that she is doesn't know what the medication is for, when to take it, and is scared because one side effect is "potential death"

The pharmacist notices the pill bottle appears full and upon further examination finds that she has not taken any of the pills
What would you do?

Patient Scenario #2: Social Worker

46 y/o male patient and his wife are seen in the outpatient clinic for a routine appt.
The patient tells the oncologist he has not been taking his chemotherapy pills as prescribed because he is afraid of dying and he feels the pills make him sicker, which affects his QOL
The wife states she was unaware that he was not taking his medicine and was unaware that he is scared to die

The oncologist calls the social worker

What would you do?

Patient Scenario #3: Oncology RN

32 y/o female patient admitted to inpatient unit following lab work that showed increased cancer markers after starting her oral chemo regimen
Patient tells the RN that her pills make her nauseous and dizzy and she doesn't take them unless her husband is going to be home to care for the kids
Patient states she didn't think that missing some of the doses would hurt her treatment because "it's not like it's IV medicine"

What would you do?

Patient Scenario #4: Multidisciplinary

An oncologist office notices that a patient who has just started an oral chemotherapy regimen has missed two appointments since starting the treatment
The office finally speaks with him on the phone and he states he cannot afford the medication because he lost his job and his insurance
The patient states he felt embarrassed to tell anyone at the office, so he figured he would not get treated.

What would you do as a team?

Conclusions

- Despite numerous studies showing rates of non-adherence, adherence to oral therapies is an ongoing issue
- Adherence is a priority for ensuring positive therapeutic outcomes, decreased oncology and non-oncology complications, and decreased costs
- Never assume your patient is being adherent to oral therapies
- Observe for predictors and possible barriers
- Communicate and educate
- Addressing adherence is a multidisciplinary process and should involve the healthcare team as a whole
- Adherence is widespread across chronic disease processes and should be addressed at all levels of care

Plant Alkaloids

Classes: Four classes

- Vinca alkaloids:
- Topoisomerase inhibitors
    - Topoisomerase 1: Asian Happy Tree – Camptotheca Acuminata
    - Topoisomerase 2: Mayapple
- Taxanes: Pacific Yew
- Epothilones

Vinca Alkaloids: derived from periwinkle plant

- Oncovin (vincristine)
- Velban (vinblastine)
- Navelbine (vinorelbine tartrate)

Mechanism of Action

- Bind to microtubular proteins thus arresting mitosis preventing effective functioning of microtubules
- Inhibit Angiogenesis, DNA and protein synthesis
    - Microtubules are dynamic intracellular structures that must breakdown and reassemble for cell division
    - Help transport substances across the cell and provide structure
- Inhibit angiogenesis, DNA, and protein synthesis

Side Effects

- Neurotoxic and can cause both sensory and functional disturbances: Paresthesia's, gait instability, cranial nerve disturbance, and peripheral neuropathy
- Constipation
- Myelosuppression
- Sexual/reproductive issues: Impotence, teratogenic
- Vesicant: Warm compresses intermittently for 24 to 48 hours, hyaluronidase protocol
- Alopecia
- Nausea and vomiting: Mild emetogenic potential

The most neurotoxic Vinca Alkaloid drug is:

A. Velban (vinblastine)
B. Oncovin (vincristine)
C. Navelbine (vinorelbine tartrate)

Oncovin (vincristine)

- Most neurotoxic of class: Stocking/glove, neuropathic pain, autonomic dysfunction, constipation
- Mild myelosuppression
- Dose reduction hepatic dysfunction: Primary excretion through the liver
- Vesicant: Administered by IV infusion
    - History of fatal intrathecal administration: Intrathecal administration causes rapid sensory and motor dysfunction, encephalopathy, coma, and death
- Dose 0.4-1.4 mg/m2: Usually 2 mg maximum
- Mix in 50cc NSS and infuse IV over 15 minutes

Intrathecal Administration Facts

- Between 1968 and 2011 there were120 cases of mistaken intrathecal administration
    - 44 in US and Canada
- All cases involved dispensing in a syringe
- WHO, Joint Commission, ONS Institute for Safe Medication Practices all support IV infusion rather than IV push
- Extravasation risk: Push 0.03% Drip 0.04%

Clinical Applications

- Lymphoma
    - Cytoxan, Adriamycin, Oncovin, Prednisone (CHOP)
    - Cytoxan, Oncovin, Prednisone (CVP)
    - Cytoxan, Etoposide, Oncovin, Prednisone (CEOP)
    - Etoposide, Prednisone, Oncovin, Cytoxan and Adriamycin (EPOCH)
    - Cytoxan, vincricristine, Adriamycin, and Decadron alternating with methotrexate and cytarabine (HyperCVAD)
    - Very often given with Rituxan
- Ewing’s sarcoma
- ALL
- Rhabdosarcoma
- CNS tumors

Tumor Lysis Syndrome (TLS)

- Rapid release of cellular components into the blood after rapid lysis of malignanT-cells
- Occurs with treatment of cancers with high proliferation rates, large tumor burden or highly sensitive to cytotoxic agents
- Increased potassium, phosphorus, uric acid, low calcium, and renal failure

TLS Prevention

- Hydration
- Allopurinol
- Rasburicase: Enzyme that converts uric acid to inactive, soluble metabolite

TLS Treatment

- Correct electrolytes
- Hydration
- Allopurinol
- Rasburicase
- Hemodialysis if needed

Velban (vinblastine)

- Dose: 0.11-6 mg/m2 Q 2-4 weeks and 6 mg/m2 in ABVD regimen
- Nadir: 4-10 days
- Partially metabolized by liver: Dose reduction based on LFTs
- Rare nausea and vomiting

Clinical Applications

- Bladder: Neo-adjuvant, adjuvant, and metastatic uses methotrexate, Velban, Adriamycin, cisplatin (MVAC)
- Testicular: Vinblastine, Ifex, and cisplatin (VeIP)
- Hodgkin's: Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD)
    - Most physicians are now replacing bleomycin with another drug

Navelbine (vinorelbine tartrate)

- Semi-synthetic Vinca alkaloid derived from vinblastine
- Dose: 25 mg/m2 weekly three on and one off
- Nadir 7-10 days
- Dose reduction for liver dysfunction and myelosuppression
- Least neurotoxic of the class

Clinical Applications

- Breast: Usually single agent or with Herceptin if appropriate
    - Used for metastatic disease after failure of Xeloda, Gemzar, and anthracycline
- No longer part of pathway for lung it has been replaced by targeted agents, immunotherapy, and monoclonal antibodies

Topoisomerase Inhibitors

- Topoisomerase I Inhibitors: Camptothecans
  - Hycamtin (topotecan)
  - Camptosar (irinotecan)
- Topoisomerase II Inhibitors: Podophyllotoxins
  - VP-16, VePesid (etoposide)

Mechanism of Action

- Interfere with the actions of the topoisomerase enzymes I and II that control the changes, breaking and repair, in the DNA structure
- Blocking these enzymes leads to single and double stranded breaks that cannot be repaired
- These breaks lead to cell death by inhibiting DNA synthesis

Clinical Applications: Hycamtin (topotecan)

- Small cell: 1.5 mg/m2 daily X5 days every 21days, second line
  - If poorly tolerated may change to 4mg/m2 weekly
- Ovarian: 4 mg/m2 three weeks on and one week off, fourth line
- Sarcomas
- Cervical cancer with cisplatin
- Risk for development of myelodysplastic syndromes
- Myelosuppression in all three cell lines significant
- GI disturbances

Which medication is used to prevent early diarrhea caused by Camptosar (irinotecan)?

A. Atropine
B. Loperamide (Imodium)
C. Octreotide (Sandostatin)

Camptosar (irinotecan)

- Metabolized by Liver
- Dose depends on regimen: 150-200 mg/m2
- Dose limiting side effects: Diarrhea and myelosuppression
- Irritant: Flush with sterile water and apply ice

Clinical Applications: Camptosar (irinotecan)

- Colorectal cancer: 5-FU, leucovorin, and irinotecan (FOLFIRI) 180 mg/m2 or irinotecan and Vectibix 180 mg/m2 or Xeloda and irinotecan (XELIRI) 200 mg/mg
- Pancreatic: 5FU, leucovorin, Irinotecan, and oxaliplatin (FOLFIRINOX) 180 mg/m2
- Esophageal: Irinotecan alone for metastatic disease third line and beyond 180 mg/m2

Irinotecan: Early Diarrhea

- Within first 24 hours after administration
- Cholinergic effect: Diarrhea, lacrimation, diaphoresis, piloerection, bradycardia, flushing
- Atropine: 0.25 mg IV can repeat q 15 minutes to 1 mg total for acute diarrhea
- Should be part of the chemotherapy orders

Irinotecan: Late Diarrhea

- Occurs 24 hours or more after administration
- Caused by changes in intestinal mucosa which prevent the absorption of water
- Imodium (loperamide) 4 mg at first episode then 2 mg q2h until no diarrhea for 12 hours
    - 4 mg at bedtime
- Can lead to dehydration, electrolyte imbalance, and renal failure

Sandostatin (octreotide)

- May require hospitalization for fluid and electrolyte repletion
- Stimulates fluid and electrolyte absorption from the GI tract and decreases transit time
- Start with 100-150 mcg q 8 hours
    - May titrate to 500 mcg q8h if needed

Topoisomerase II Inhibitors: VP-16, VePesid (etoposide)

- Hepatic and renal metabolism and elimination
- Dose: Small cell lung cancer 100 mg/m2 daily for 3 consecutive days every 21 days
- Oral form available but poor bioavailability requires higher dose
- Testicular cancer: Bleomycin, etoposide, and cisplatin (BEP) and etoposide, ifosfamide, and platinum (VIP)
- Stem cell transplant
- Lymphoma: Cytoxan, etoposide, oncovin, and prednisone (CEOP); ifosfamide, carboplatin, etoposide (ICE); Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP)
- Can cause hypotension with rapid infusion
- Anaphylactic reactions
- Nadir: 7-14 days
- Can cause radiation recall
- Risk of secondary malignancy and myelodysplastic syndrome development

Radiation recall causes which of the following:

A. Diarrhea
B. Peripheral Neuropathy
C. Skin irritation

Side Effects continued

- Watch for wheezing, bronchospasm, hypotension and anaphylactic reactions
- Mild GI side effects
- Irritant
- Rare neuropathy
- Rare cardiac complications
- Alopecia

Taxanes: Taxol (paclitaxel), Taxotere (docetaxel), and Abraxane (nab-paclitaxel)

- Inhibit mitosis
- Cell cycle specific
- Hepatic metabolism
- Microtubules must be able to disassemble and reassemble to allow chromosomes to move, align, and separate to make cell replication possible
- Taxanes block the disassembly of microtubules interfering with G2 mitotic phase and inhibiting the replication of cells
- Distortion of mitotic spindles causing chromosome breakage

Taxol (paclitaxel)

- Non-small cell lung cancer (NSCLC)
    - Weekly with radiation 45mg/m2
    - Week on/one off 80mg/m2
    - Every three weeks with carboplatin 200mg/m2
- Ovarian: 175mg/m2 q 3 weeks
    - 135 mg/m2 if given with intraperitoneal therapy
    - Intraperitoneal: 60mg/m2
- Head and neck: Recurrent or metastatic 80mg/m2, weekly
- Metastatic breast: 80mg/m2, 3 weeks on/one off
- Metastatic bladder: 175mg/m2 q 3 weeks
- Angiosarcoma: 80 mg/m2 three weeks on and one off

Paclitaxel Premedication

- Every three weeks: Decadron 20 mg po at 12 and 6 hours prior to therapy
- Weekly: Decadron 20 mg po at 12 and 6 hours prior for week one
- Subsequent weeks Decadron 20mg IV 30 minutes prior to treatment
- Premedicate prior to therapy with Decadron 20 mg IV, anti-emetic, Benadryl, and H2 antagonist

Paclitaxel: Administration

- Hypersensitivity: Drug or diluent or both
- Diluent: Cremophor
- Mix in glass or non-PVC container
- Non-PVC tubing, 0.22 micron in-line filter

Paclitaxel: Hypersensitivity Reaction

- Dyspnea
- Hypotension
- Angioedema
- Tachycardia
- Wheezing
- Chest pain

Paclitaxel: Other side effects

- Alopecia
- Cardiovascular events
- Mild nausea, vomiting and stomatitis
- Myalgias and arthralgias
- Neuropathy
- Bone marrow suppression
- Pneumonitis

Clinical Applications

- Non-small cell lung cancer
- Ovarian
- Bladder
- Breast
- Sarcoma
- Head and neck

Taxotere (docetaxel)

- Requires premedication: Decadron 8 mg bid on day before, day of, and day after therapy for every three weeks dosing
- Weekly premeds: Week one Decadron 4 mg po night before and day of therapy
    - Subsequent weeks: Decadron 10 mg IV 30 minutes prior to chemotherapy
- Reduces risk of hypersensitivity reaction and fluid retention
- Use glass or non-PVC containers and tubing
- Risk of hypersensitivity reaction
- Nadir 7 days with risk of neutropenia, 90% incidence of anemia
- Skin reactions, most common on hands and feet, nail changes, conjunctival irritation, hyperlacrimation
- Alopecia
- Neurotoxicity: Paresthesia's and functional deficits
- Mild GI side effects
- Fluid Retention
    - Cumulative toxicity
    - Begins in lower extremities followed by general weight gain
    - Pleural effusions
    - Decreased risk with steroid premedication
    - May require diuretics
    - Usually resolves completely within weeks of last dose

Abraxane (nab-paclitaxel): Breast cancer, pancreatic cancer, NSCLC

- Bound to albumin
- Can use with patients who have hypersensitivity to other taxanes
- Bound to albumin
- Does not require the same premedication or administration precautions as Taxol
- Less neutropenia than other taxanes
- Peripheral neuropathy

Which taxane drug can be administered by intraperitoneal route for ovarian cancer?

A. Nab-paclitaxel
B. Cabazitaxel
C. Paclitaxel

Which of the following may be a dose limiting side effect of paclitaxel?

A. Diarrhea
B. Myalgias
C. Peripheral Neuropathy

Epithilones

- Similar to taxanes (inhibit the function of microtubules)
- Significant difference in structure from taxanes, less susceptible to taxane drug resistance

Ixabepilone: Clinical applications

- Used in combination with capecitabine for taxane- and anthracycline-resistant, recurrent or metastatic breast cancer
- Monotherapy for patients who do not tolerate capecitabine or who are not candidates for combination therapy
- Third line and beyond

Side Effects

- Neuropathy
- Hematologic toxicity
- May cause myalgias and arthralgias
- Hypersensitivity reaction: Cremophor El Premedication with H1 antagonist (Benadryl) and H2 antagonist (Pepcid)
- No oral steroid premedication needed

Administration and Dosage

- PVC free bags and tubing
- 0.22 micron filter
- Breast: 40mg/m2, q3wks

Principles of Cancer: Drug Therapy

Review of Current Cancer Statistics

Estimated New Cancer Cases in US 2023

Males		Female	
Prostate	29%	Breast	31%
Lung and bronchus	12%	Lung and bronchus	13%
Colon and rectum	8%	Colon and rectum	8%
Urinary bladder	6%	Uterine corpus	7%
Melanoma of the skin	6%	Melanoma of the skin	4%
Kidney and renal pelvis	5%	Thyroid	4%
Non-Hodgkin's lymphoma	4%	Non-Hodgkin's lymphoma	4%
Oral cavity and pharynx	4%	Kidney and renal pelvis	3%
Leukemia	4%	Pancreas	3%
Pancreas	3%	Leukemia	3%

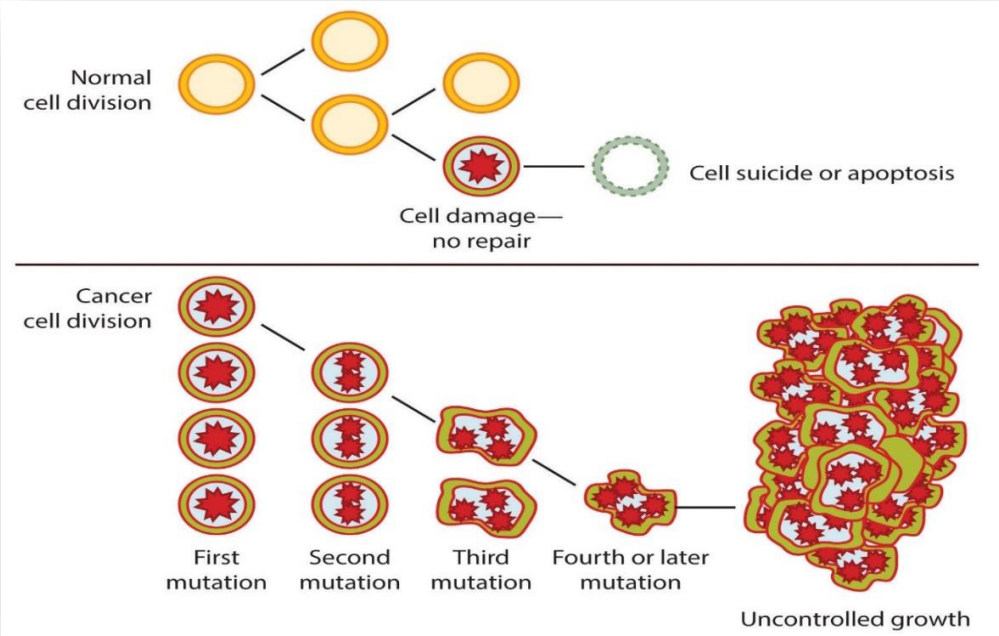
Estimated Cancer Deaths in US 2023

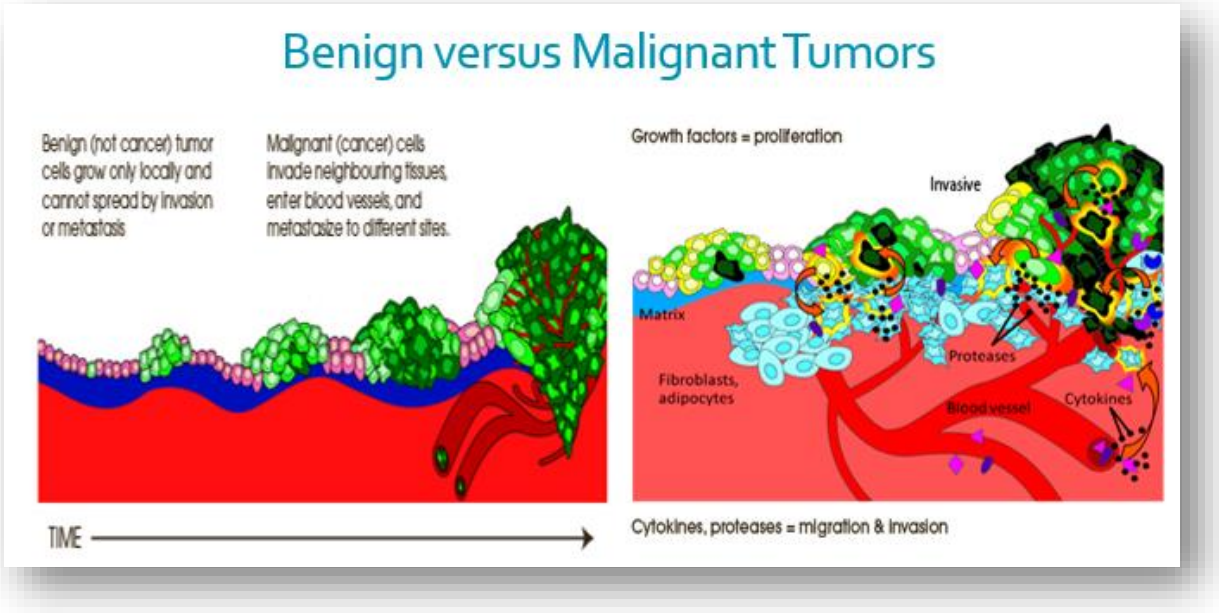
Male: 322,080		Female: 287,740	
Lung and bronchus	21%	Lung and bronchus	21%
Prostate	11%	Breast	15%
Colon and rectum	9%	Colon and rectum	8%
Pancreas	8%	Pancreas	8%
Liver and intrahepatic bile duct	6%	Ovary	5%
Leukemia	4%	Uterine corpus	3%
Esophagus	4%	Liver and intrahepatic bile duct	4%
Urinary bladder	4%	Leukemia	4%
Non-Hodgkin's lymphoma	4%	Non-Hodgkin's lymphoma	3%
Kidney and renal pelvis	3%	Brain and other nervous system	3%
Brain and other nervous system	3%		

Characteristics of Tumors

- What Is cancer?
  - A group of more than 200 diseases caused by genetic alterations and defective cell function
  - Characterized by unregulated growth that
  - Capable of spreading to other parts of the body

Formation of a Tumor





Characteristics of Benign Tumors

- Slow continuous or inappropriate growth
- Retained morphology of parent T-cell
- Differentiated cells may maintain function
- Often encapsulated with fibrous tissue

Characteristics of Malignant Tumors

- Abnormal morphology
- Poorly differentiated
- No contact inhibition
- Unregulated growth pattern
- No programmed apoptosis
- Loss of specific function
- Migration to other areas of the body

Common Cancer Classifications

- Carcinoma: Begins in the skin or in tissues that line or cover internal organs: Adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, transitional cell carcinoma
- Sarcoma: Begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue
- Leukemia: Begins in blood-forming tissue, bone marrow, and produces large numbers of abnormal blood cells to be released in the blood
- Lymphoma: Begins in the cells of the immune system: Lymphatic system
- Myeloma: Begins in the cells of the immune system specifically the antibody-secreting immune cell plasma cell
- Blastoma: Derived from immature "precursor" cells or embryonic tissue,
- Central nervous system cancers: Begins in the tissues of the brain and spinal cord
- Germ Cell Cancers: Derived from pluripotent T-cells, i.e., testicle or ovary

Cancer “Prefixes”

- Adeno – gland
- Chrondo – cartilage
- Erythro – red blood cell
- Hemangio – blood vessels
- Hepato – liver
- Lipo – fat
- Lympho – lymphocyte
- Melano – pigmenT-cell
- Myelo – bone marrow
- Myo – muscle
- Osteo – bone

What is Chemotherapy’s Contribution to Treating Cancer

- Chemotherapy can
    - Decrease tumor volume
    - Alleviate symptoms
    - Prolong life in some metastatic cancers
    - Cure of disease
- Single-agent chemotherapy: Monotherapy
- Multiple-agent chemotherapy: Combination chemotherapy

_____
_____
_____
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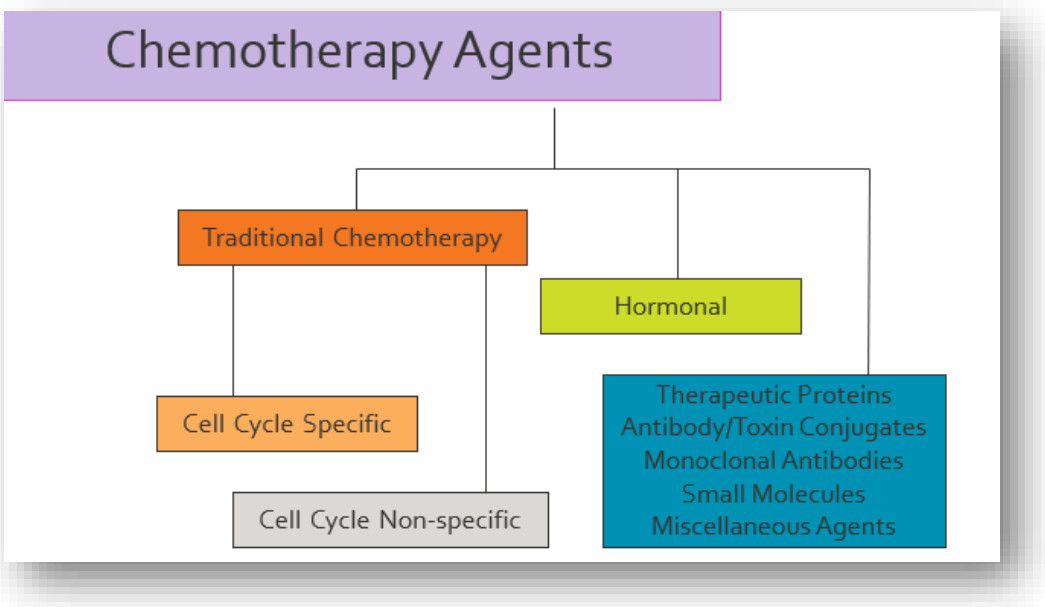
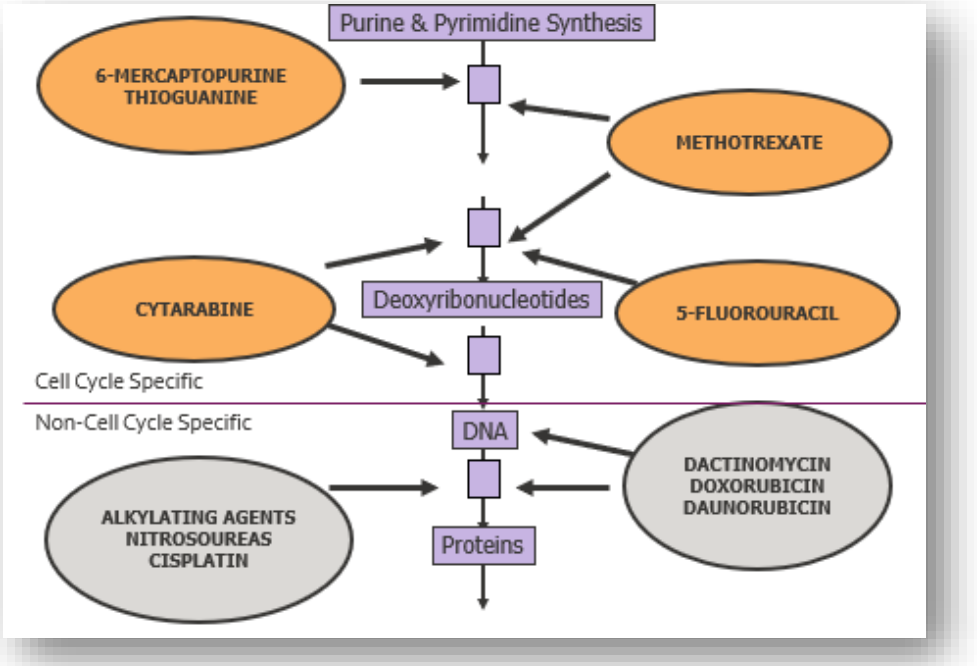
Chemotherapy Classification

- Cytotoxic: Kills the cells
  - Traditional anticancer agents
    - Cell-cycle specific agents
    - Cell-cycle non-specific agents
- Cytostatic: Suppresses growth of cells
  - Newer anticancer agents
    - Small molecules
    - Antibody directed agents
    - Targeted therapies
    - Signal transduction inhibitors
- Systemic chemotherapy
  - Cytotoxic drugs are used to destroy cancer cells or prevent cellular replication by interfering with DNA and RNA, and vital cellular proteins
    - Classified according to the pharmacologic action of effect on the cellular reproduction cycle
    - Goals
      - Cure
      - Control
      - Palliation
      - Reduction of cells
      -

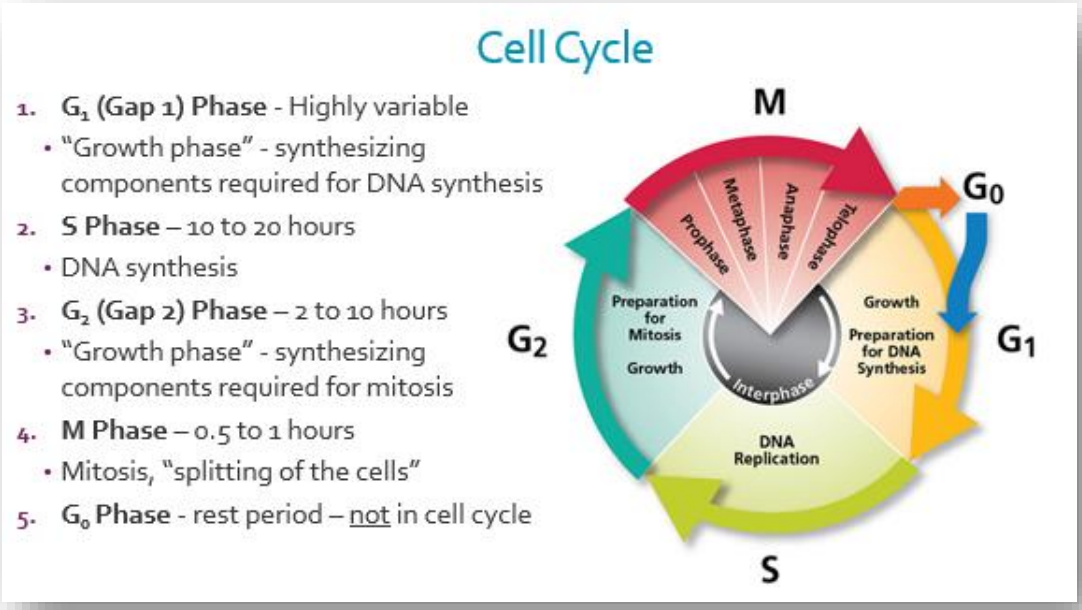
Recognize the Importance of the Cell Cycle and Identify its Relationship to the Efficacy of Chemotherapy



Cell Cycle Specific Treatments vs Non-cell Cycle Specific Treatments



Cell Cycle Phases



Cell Proliferation Rates

None	• Muscle • Bone • Cartilage • Nerve
Slow	• Lung • Endocrine glands • Vascular endothelium • Liver • Kidney
Rapid	• Hair follicle • Bone marrow • Gastrointestinal mucosa • Ovary/Testies

Chemotherapy Agents

Cell Cycle Specific Chemotherapeutic Agents	Non-Cell Cycle Specific Agents

• G_1 Phase dependent agents
  ○ Elspar (asparaginase)
  ▪ Oncaspar (pegasparaginase)
  ○ Erwinaze (asparaginase erwinia chrysanthemi)
  ○ Apsarlas (calasparaginase pegol-mknl)
  ○ Corticosteroids: Prednisone
• S Phase dependent agents
  ○ Purine Antagonists
  ○ Pyrimidine Antagonists
  ○ Folate Antagonists
  ○ Camptothecins
• G2 Phase dependent agents
  ○ Bleomycin
  ○ Podophyllotoxins
  ▪ Etoposide
  ▪ Teniposide
• M Phase specific agents
  ○ Vinca Alkaloids
  ▪ Vincristine
  ▪ Vinblastine
  ▪ Vinorelbine
  ▪ Liposomal Vincristine
	• Alkylating agents
	  ○ Chlorambucil
	  ○ Ifosfamide
	  ○ Cyclophosphamide
	  ○ Melphalan
	  ○ Busulfan
	  ○ Carmustine
	  ○ Lomustine
	• Non-classic alkylating agents
	  ○ Procarbazine
	  ○ Dacarbazine
	  ○ Temozolomide
	  ○ Bendamustine
	  ○ Ixabepilone
	• Anthracycline antibiotics
	  ○ Doxorubicin
	  ○ Liposomal doxorubicin
	  ○ Idarubicin
	  ○ Epirubicin
	  ○ Mitoxantrone
	• Other antitumor antibiotics
	  ○ Dactinomycin
	• Platinum agents
	  ○ Cisplatin
	  ○ Carboplatin
	  ○ Oxaliplatin

- Taxanes
  - Docetaxel
  - Paclitaxel
  - Nab-abraxane
  - Cabazitaxel
- Non-Taxane Agents
  - Eribulin Mesylate

Why is Combination Therapy Superior?

- Tumor cells are frequently resistant or become resistant to a single agent
  - By using multiple agents, the chance of resistance decreases
- Each drug is used at its most efficacious dose (i.e., full dose)
- Each drug works with a different mechanism of action
- Each drug should have a different toxicity pattern

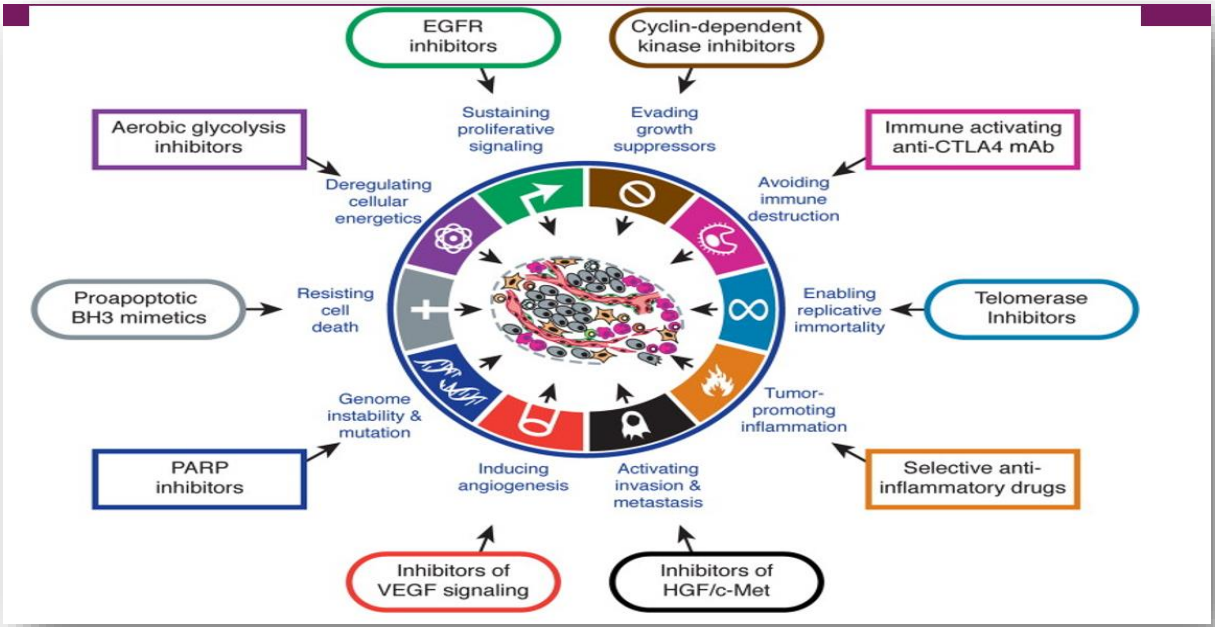
Common Chemotherapy Regimens

- Acute lymphocytic leukemia (ALL)
  - Vincristine, prednisone, doxorubicin, L-asparaginase
- Hodgkin's lymphoma
  - Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD)
- Diffuse large cell (Non-Hodgkin) lymphoma
  - Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
    - 5 to 8 drug regimens
- Testicular carcinoma
  - Bleomycin, cisplatin, and vinblastine or etoposide
- Colorectal carcinoma
  - 5-fluorouracil, leucovorin, oxaliplatin/irinotecan (FOLFOX/FOLFIRI)

Compare and Contrast Traditional Chemotherapy Agents and Targeted Therapies

- Targeted anticancer agents: The genetic link
  - All cancers are caused by genetic alterations at the cellular level.
    - Germline alterations: Inherited during meiosis or during changes in ova/sperm DNA present before birth
    - Acquired and spontaneous alterations: Accumulate within DNA throughout life due to environmental agent exposure responsible for sporadic cancers
  - Certain genetic alterations can be identified and targeted for treatment

Hallmarks of Cancer: The Next Generation



Types of Targeted Therapies

- Monoclonal antibodies
  - Including immune checkpoint inhibitors
- Small molecules: Tyrosine kinase inhibitors (TKI)
  - Therapeutic proteins
  - Alpha-IFN for HCL, CML, others
  - IL-2 (1992) for melanoma, renal cell
  - Peginterferon-alpha-2b for melanoma
- Antibody/toxin conjugates
  - Ontak (IL-2/ricin) for CTCL
  - Mylotarg (CD-33/calicheamycin) for AML
- Recombinant vaccines: No live virus
  - Gardasil for prevention of cervical cancer, precancerous genital lesions and genital warts
  - Cervarix
- Autologous cellular immunotherapy
  - Provenge (sipuleucel-T): Personalized immunotherapy for advanced prostate cancer
  - Recombinant fusion proteins
  - Zaltrap (ziv-aflibercept) Colorectal cancer
- Chimeric Antigen Receptor T-Cell Therapy (CAR-T)
  - Kymriah (tisagenlecleucel): ALL

Monoclonal Antibodies

- Laboratory-produced molecule carefully engineered to attach to specific defects in cancer cells
- Make the cancer cell more visible to the immune system
    - Block growth signals
    - Stop new blood vessels from forming

Immune Checkpoint Inhibitors

- T-cells have built-in checkpoints which prevent them from attacking normal cells
    - PD-1/PDL-1 complex
    - CTLA-4/B7-1/B7-2 complex
- Some tumor cells utilize these surface protein complexes to avoid immune-mediated cell death
- Checkpoint inhibitors attach to surface proteins on tumor cells or T-cells and prevent formation of checkpoint complexes

Immune Checkpoint Inhibitors

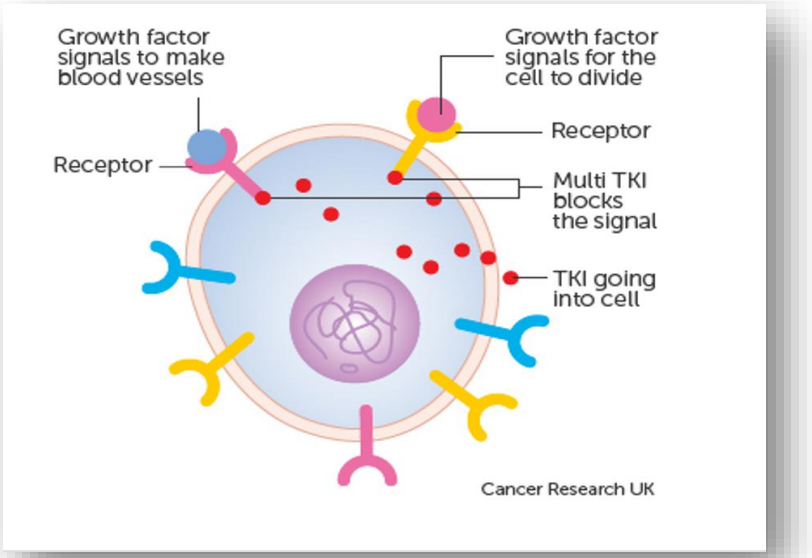
- PD-1 inhibotors
    - Keytruda (pembrolizumab)
    - Opdivo (nivolumab)
    - Libtayo (cemiplimab-rwic)

- PDL-1 inhibitors
    - Tecentriq (atezolizumab)
    - Bevencio (avelumab)
    - Imfinz (durvalumab)
- CTLA-4
    - Yervoy (ipilimumab)

Incorporating Targeted Agents into Traditional Chemotherapy Regimens

- Metastatic colorectal cancer
    - Bevacizumab: First, second and third line
        - 5mg/kg dose with folinic acid, fluorouracil and oxaliplatin (FOLFOX), folinic acid, fluorouracil, and irinotecan (FOLFIRI) or capecitabine, qxaliplatin (CapeOx)
    - Cetuximab: KRAS wild-type only
        - Second line as single agent or with irrinotecan
    - Panitumumab: KRAS wild-type only
- Advanced lung cancer, nonsmall cell lung cancer (NSCLC)
    - Bevacizumab
        - Up to 15mg/kg dose with carboplatin and paclitaxel
    - Cetuximab plus traditional chemotherapy regimen
    - Erlotinib or gefitnib only: EGFR mutation

Small Molecules/TKIs



Challenges of Newer Therapies

- Who should be treated?
  - Quantity and/or presence of receptor sites don't necessarily correlate with response, wild type vs. mutations, or early-stage vs. late-stage disease
- How do you verify activity/response?
  - Testing of biomarkers and determination of stable disease vs. complete response to therapy
- What is the optimal dose
  - Less frequent dose limiting toxicities, what is minimum effective dose?
- How do you manage side effects
  - Skin rashes, diarrhea, hypertension, electrolyte abnormalities, thyroid abnormalities, fluid retention, proteinuria, hepatotoxicity, interstitial lung disease, pancreatitis, visual disturbances, wound healing, bleeding risk, cardiac toxicity, etc.
- Multiple drug-drug interactions
  - Multiple hepatic enzymes involved, increased bleeding risk present, and QT prolongation are possible
- What is a proper dose adjustment: Considerations
  - Should we dose adjust
  - How much of an adjustment is too much…10%, 25%, 50%?
  - Can you split the dosage form, or should you practice this?
- What agents should be used together?
  - Single agent
    - Typically displays little response unless blocks multiple targets
    - Is combination therapy needed to inhibit full signaling cascade?

Hormonal Therapies Classes: Breast

- Selective estrogen receptor modulators (SERMs)
  - Nolvadex (tamoxifen)
- Selective estrogen receptor down regulators (SERDs)
  - Faslodex (fulvestrant)
- Aromatase inhibitors (AIs)
  - Arimidex (anastrozole)
  - Aromasin (exemestane)
  - Femara (letrozole)

Hormonal Therapies Classes: Prostate

- Luteinizing hormone-releasing hormone (LHRH) agonists
  - Lupron (leuprolide)
  - Zoladex (goserelin)
  - Trelstar (triptorelin)
- LHRH antagonists
  - Firmagon (degarelix)
- Anti-Androgens
  - Eulexin (flutamide)
  - Casodex (bicalutamide)
  - Nilandron (Nilutamide)
  - Erleada (apalutamide)
  - Nubeqa (darolutamide)

Rationale Design and Utilization of Chemotherapy for Cancer Treatment

- Pathological confirmation of disease
  - A cancer diagnosis is made by determining the anatomical origin of the tumor
    - The primary site is where the cancer first developed
    - The secondary site is where the cancer metastasized
  - A diagnosis is confirmed with advanced imaging and biopsy
    - Imagining can pinpoint location and metastases
    - Biopsies can provide more specific information about the tumor to help determine the best treatment
- Local vs. disseminated disease
  - Localized tumors
    - Surgery and radiation are generally much more effective
    - Chemotherapy has a limited role
  - Disseminated or systemic cancer
    - Chemotherapy becomes the main treatment option
    - Hematological malignancies
      - Widespread at diagnosis, so chemotherapy given with intent to cure
    - Metastatic disease
      - Very rarely curative where intent is to prolong life or for palliating symptoms

- Treatment intent
    - Palliative
        - Goal is to increase quality of life, not create a cure, while providing cancer treatment
        - Provide support for symptoms related to cancer and side effects of treatment as early as possible
        - Social, psychological, and spiritual support
    - Curative
        - Goal is cure disease

Selection of Effective Anticancer Agents

- Is the agent or regimen appropriate for the type of cancer?
    - Regimens are developed based on clinical trials and research
    - There are typically “standard” regimens based on the type of cancer and other factors such as:
        - Cancer stage
        - Patient’s age and overall health
        - Comorbidities
        - Previous treatments
    - If there is no standard treatment or the patient has progressed on the standard, investigation drugs and/or regimens are considered
    - Absorption, distribution, metabolism, and excretion (ADME)
    - Resistance concerns
        - Dose intensification
        - Combination chemotherapy regimens help to prevent development of resistance by interrupting multiple processes in the cell cycle
        - Strategy for overcoming chemotherapy resistance
            - “Standard” doses of effective combination chemotherapy are developed from clinical trials and are sufficient for patients with sensitive tumors
            - High doses are necessary for the subset of patients with tumors that have relative drug resistance
            - Planned doses or schedules of chemotherapy should not be modified in anticipation of toxicity that has not happened or for short-term, non-life-threatening toxicity, e.g., emesis or mild neutropenia
    - Patient performance status
        - Scales are used to measure how cancer affects a patient’s daily living abilities

- Quality of life
  - There are many resources available to patients to help maintain or improve quality of life during and after treatment which include
    - Nutrition
    - Physical exercise
    - Emotional and spiritual support
    - Networking with other cancer patients and survivors
    - Help with appearance
  - Maintaining quality of life helps patients tolerate and complete therapy, which improves treatment outcomes

Supportive Care Drugs

- NSAIDS
- Steroids
- Antiemetics
- Analgesics
- Sedatives
- Antidepressants
- Antibiotics
- Anti-virals
- Antifungals
- Growth factors

Review NCI Common Toxicity Criteria Adverse Events (NCI CTCAE) Classifications

- Classifying and grading toxicity
  - Toxicity is classified into general area: Bone marrow, cardiac muscle, GI system, etc.
  - For toxicity caused by various cancer treatments, the NCI CTCAE version 5.0 is commonly used to describe toxicity

NCI CTCAE version 5.0 Grading

Grade	Severity
Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life threatening or disabling AE
Grade 5 (if appropriate)	Death-related to AE

Recognize the Financial Impact of Cancer Treatment

- Cost of cancer care
  - The economic impact of cancer in the United States is staggering
    - $80.2 billion spent on cancer care in 2015
    - Cancers resulting in greatest expenditures include lymphoma, breast, colorectal, lung, and prostate
    - Lost productivity estimated at $135 billion
    - In 2020, it is projected at least $158 billion will be spent on cancer care
  - Estimates do not include out of pocket expenses
    - Increasing expenditures on targeted and oral chemotherapy agents
    - Number of cancer survivors and cost of cancer care expected to rise

Out of Pocket Expenses

- Copayments
- Cancer/supportive care treatments
- Medical supplies
- Transportation
- Housekeeping
- CAM therapies
- Financial planning
- Child/adult daycare
- Drug costs
- Lodging
- Food
- Nutritional supplements
- Clothing
- Legal

Professional Oncology Organizations

- American Society of Clinical Oncology (ASCO)
- Association of Cancer Online Resources (ACOR)
- American Society of Hematology (ASH)
- National Cancer Institute (NCI)
- National Comprehensive Cancer Network (NCCN)
- Multinational Association of Supportive Care in Cancer (MASCC)
- American Cancer Society (ACS)
- World Health Organization (WHO)
- Hematology/Oncology Pharmacy Association (HOPA)
- Oncology Nursing Society (ONS)

Tyrosine Kinase Inhibitors (TKIs): Part 1

Introduction
BCR-ABL Inhibitors
BTK Inhibitors
FLT3 Inhibitors
IDH Inhibitors
EGFR Inhibitors
FGFR Inhibitors

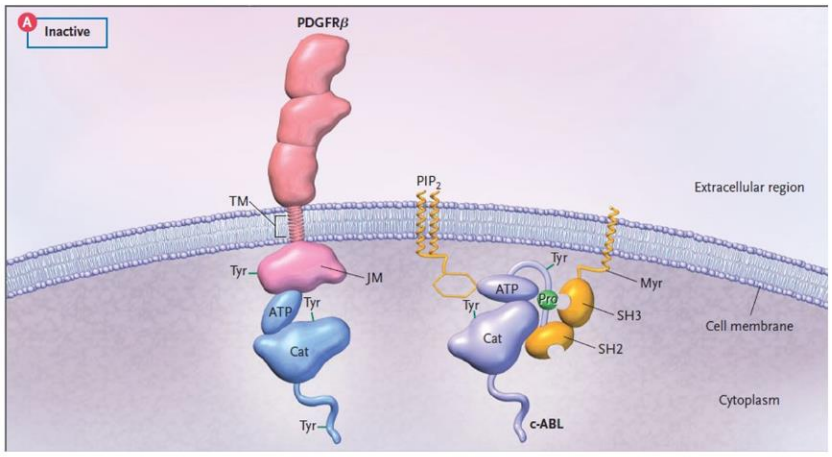
Tyrosine Kinases

- Enzymes that catalyze the transfer of phosphate from ATP to tyrosine residues in polypeptides
- Regulate cellular
  - Proliferation
  - Survival
  - Differentiation
  - Function
  - Motility

Inactive Tyrosine Kinases

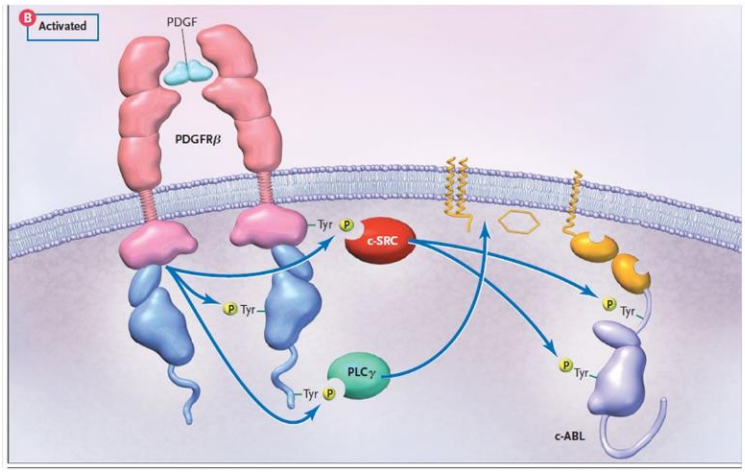
UPMC
LIFE CHANGING MEDICINE

Inactive Tyrosine Kinases



Krause DS, Van Etten RA. N Engl J Med 2005;353:172-187.

Activated Tyrosine Kinases



Krause DS, Van Etten RA. N Engl J Med 2005;353:172187.

Common Features of Most Tyrosine Kinase Inhibitors (TKIs)

- Inhibit more than one tyrosine kinase
  - Most discussed here bind to the ATP site of the targeted tyrosine kinase
- Oral agents; half-lives allow either once or twice daily dosing
  - Expensive even as older agents become generic
  - Most dispensed via mail from specialty pharmacies
- Most are CYP3A4 substrates
  - Consider drug-drug interactions with inducers and inhibitors of CYP3A4
    - Examples of strong inducers: phenytoin, rifampin, carbamazepine
    - Examples of strong inhibitors: voriconazole, clarithromycin
- Warning for embryo-fetal toxicity
  - All agents discussed here

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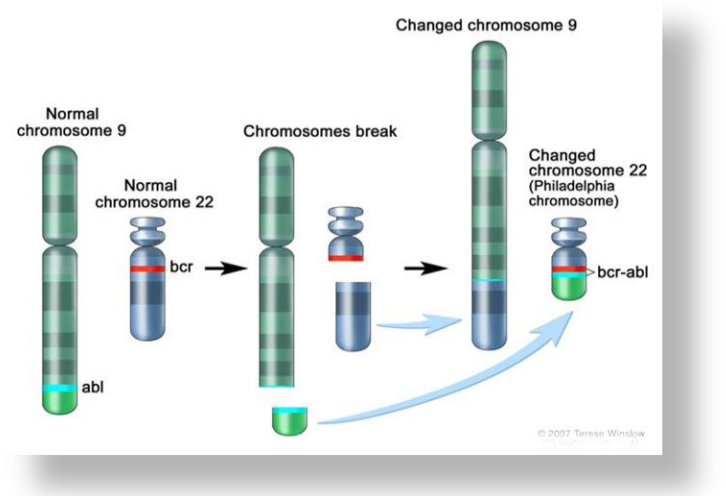
BCR-ABL Inhibitors
BTK Inhibitors
FLT3 Inhibitors
IDH Inhibitors
EGFR Inhibitors
FGFR Inhibitors

BCR-ABL Inhibitors

- Imatinib (Gleevec)
- Dasatinib (Sprycel)
- Nilotinib (Tasigna)
- Bosutinib (Bosulif)
- Ponatinib (Iclusig)
- Asciminib (Scemblix)

BCR-ABL Inhibitors Mechanism of Action

- BCR-ABL is an abnormal tyrosine kinase created by the Philadelphia chromosome
- This class of drugs inhibits the BCR-ABL tyrosine kinase by binding to the ATP site
  - Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein by binding to the ABL myristoyl pocket
- All BCR-ABL TKIs target additional tyrosine kinases



BCR-ABL Inhibitors	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
FDA Approved Indications	-Newly diagnosed Ph+ CML in CP -Relapsed or refractory Ph+ ALL -Kit (CD117)+ unresectable or metastatic malignant GIST - Adjuvant treatment of Kit (CD117)+ GIST - Many others refer to the package insert	-Newly diagnosed Ph+ CML in CP -Any phase Ph+ CML with resistance or intolerance to prior therapy including imatinib -Ph+ ALL with resistance or intolerance to prior therapy	-Newly diagnosed Ph+ CML in CP -CP or AP Ph+ CML with resistance or intolerance to prior therapy that included imatinib *Eligible CP patients may be considered for treatment d/c after 3 years*	-Newly diagnosed Ph+ CML in CP -CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy	-CML CP with resistance or intolerance to 2 prior TKIs -CML AP or BP for whom no other TKIs are indicated -CML any phase with T315I mutation -Ph+ ALL with chemotherapy -Ph+ ALL as monotherapy if no other TKI is indicated or T315I positive	-Ph+ CML CP previously treated with 2 or more TKIs -Ph+ CML in CP with the T315I mutation
Administration	-With a meal and full glass of water -Divide doses of 800 mg into 400 mg BID	-Once daily with or without food in the morning or evening	-Take ~12 hours apart -Do not eat for 2 hours before or 1 hour after administration	- Once daily with food	-Once daily with or without food	-Once or twice daily -Avoid food for at least 2 hours before or 1 hour after
Clinical Considerations	-CYP3A4 interactions	-CYP3A4 interactions -Avoid H2 antagonists and PPIs	--CYP3A4 interactions -Avoid PPIs **-Black Box Warning for QT Prolongation and Sudden Deaths**	-CYP3A4 interactions -Avoid PPIs	-CYP3A4 interactions	-Asciminib effected by strong CYP3A4 inhibitors -Asciminib effects substrates of CYP3A4, CYP2C9, P-gp, OATP1B, BCRP

Imatinib: Select Adverse Reactions Warnings and Precautions

Side Effects	Possible Management
Most common adverse reactions (≥30%)	Edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain
Muscle cramps	OTC pain reliever like ibuprofen; prescription pain medication or calcium and magnesium supplements
Fluid Retention and Edema	Monitor weight regularly and baseline LVEF Diuretics and supportive care, hold if severe weight gain
Hematologic Toxicity (anemia, neutropenia, thrombocytopenia)	Monitor CBC weekly for first month, biweekly for second month then periodically; Consider dose reduction, interruption, or discontinuation
Hepatotoxicity	Monitor LFTs at baseline and monthly or as clinically indicated
GI disorders	Take with a meal + large glass of water; consider dividing dose

Ponatinib **Black Box Warnings**

- **Arterial Occlusive Events (AOEs)**AOEs including fatalities, have occurred in ponatinib-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ponatinib based on severity. Consider benefit-risk to guide a decision to restart ponatinib
- **Venous Thromboembolic Events (VTEs):** VTEs have occurred in ponatinib-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ponatinib based on severity
- **Heart Failure:** Heart failure, including fatalities, occurred in ponatinib-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ponatinib for new or worsening heart failure
- **Hepatotoxicity:** Hepatotoxicity, liver failure and death have occurred in ponatinib-treated patients. Monitor liver function tests. Interrupt or discontinue ponatinib based on severity

Ponatinib: Select Adverse Reactions Warnings and Precautions

Side Effect	Possible Management
Most common adverse reactions ≥20%	Rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunctions and AOEs
Hypertension	Monitor blood pressure and treat as clinically indicated; dose reduce or stop if not medically controlled
Pancreatitis	Monitor lipase every 2 weeks for the first 2 months then monthly; interrupt or discontinue ponatinib accordingly
Neuropathy	Monitor for signs of neuropathy such as paresthesia, discomfort or weakness. Interrupt then resume at the same or reduced dose or discontinue.
Ocular toxicity	Serious events leading to blindness have occurred; conduct baseline & periodic comprehensive eye exams
Hemorrhage	Interrupt for serious or severe hemorrhage; most occurred in patients with grade 4 thrombocytopenia in PACE trial.
Fluid retention	Monitor for fluid retention; interrupt, reduce or discontinue ponatinib
Cardiac arrhythmias	Advise patients of symptoms of slow heart rate (fainting, dizziness) and fast heart rate (palpitations, dizziness or chest pain)

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EGFR Inhibitors
FGFR Inhibitors

BTK Inhibitors

- Ibrutinib (Imbruvica)
- Acalabrutinib (Calquence)
- Zanubrutinib (Brukinsa)
- Pirtobrutinib (Jaypirca)

BTK Inhibitors Mechanism of Action

- Bruton's tyrosine kinase (BTK) is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways
  - BTK's role in signaling through the BCR results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion
  - MAPK, mTOR, NFAT and NF-KB pathways
- Most TKIs inhibit BTK by forming a covalent bond with the cysteine residue in the active site
- BTK inhibition disrupts BCR signaling pathways leading to apoptosis

BTK Inhibitors

- Second generation BTK inhibitors can bind to mutated C481S site
  - This is one mechanism of ibrutinib resistance
- Second generation BTK inhibitors are more potent and selective with reduced off –target side effects

Off target	Ibrutinib	Acalabrutinib	Zanubrutinib
TEC (platelet)	Yes	Minimal	Minimal
ITK (immune function)	Yes	Minimal	Weak
EGFR (dermatologic/ gastrointestinal)	Yes	Minimal	Minimal

- Highly-selective noncovalent (reversible) BTK inhibitor pirtobrutinib FDA approved in 2023
  - 300 times more selective for BTK than 98% of other kinases

BTK Inhibitors	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
FDA Approved Indications *accelerated approval	-CLL/SLL -CLL/SLL with 17p deletion -WM -cGVHD after failure ≥ 1 line of systemic therapy	-CLL/SLL -MCL after ≥1 prior therapy*	-CLL/SLL -MCL after ≥ 1 prior therapy* -WM -R/R MZL after ≥1 anti-CD20 based regimen* -R/R FL in combo with obinutuzumab after ≥2 lines*	-CLL/SLL after ≥ 2 lines of therapy including a BTK and BCL-2 inhibitor* -R/R MCL ≥2 lines of therapy including a BTK inhibitor*
Administration	-Once daily at the same time with a full glass of water	-Take ~12 hours apart with water and with or without food	-Can be taken once daily or twice daily with water and with or without food	-Once daily with water and with or without food
Clinical Considerations	-CYP3A4 interactions -Also available as suspension -Warning for hypertension with risk increasing over time	-CYP3A4 interactions	-CYP3A4 interactions	-CYP3A4 interactions -Caution if used with sensitive CYP2C8, CYP2C19, CYP3A, P-gp or BCRP substrates

BTK Inhibitors Select Warnings and Precautions

- Hemorrhage
- Infections
  - Bacterial, Viral, or Fungal
- Cardiac arrhythmias
  - Highest risk with ibrutinib
- Cytopenias
- Second primary malignancies

BTK Inhibitors Common Adverse Reactions

- Diarrhea
- Musculoskeletal pain
- Bruising
- Upper respiratory tract infection
- Fatigue

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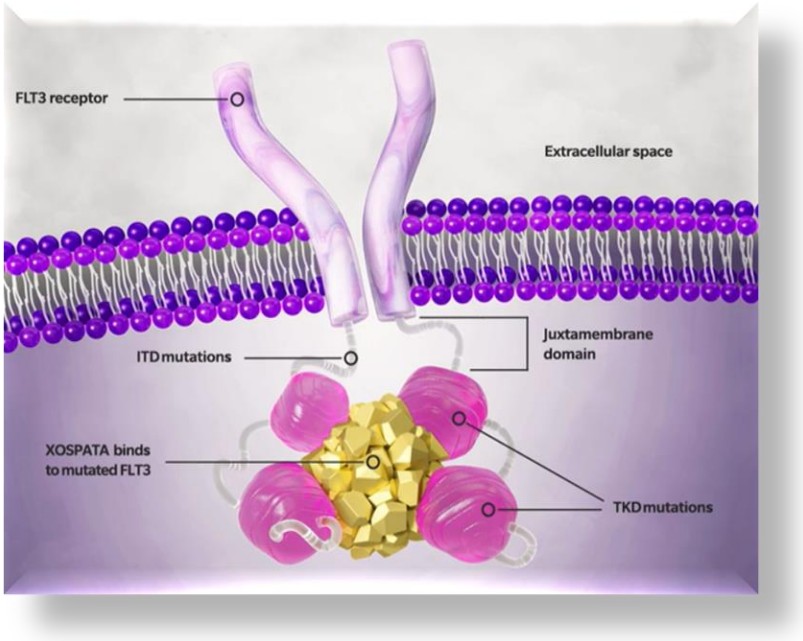
FLT3 Inhibitors

- Midostaurin (Rydapt)
- Gilteritinib (Xospata)
- Quizartinib (Vanflyta)

FLT3 Inhibitors Mechanism of Action

- Inhibition induces apoptosis in leukemic cells expressing FLT3
  - ~30% of newly diagnosed AML patients are FLT3-ITD positive
  - ~7% of newly diagnosed AML patients are FLT3-TKD positive
- Type I inhibit FLT3 ITD and TKD
  - Midostaurin and gilteritinib
- Type II inhibit FLT3 ITD
  - Quizartinib



FLT3 Inhibitors	Midostaurin	Gilteritinib	Quizartinib
FDA Approved Indications *FLT3 as detected by an FDA approved test	-Newly diagnosed AML that is FLT3 mutation positive, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation -See PI for additional indication	-Relapsed or refractory AML with a FLT3 mutation	-Combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for newly diagnosed AML that is FLT3 ITD-positive
Administration	-Twice daily with food approximately 12 hours apart	-Once daily with or without food at about the same time	-Once daily with or without food at approximately the same time
Clinical Considerations	-Requires prophylactic anti-emetics before the dose to reduce risk of n/v -CYP3A4 interactions - Not indicated as monotherapy	-Combined P-gp and strong CYP3A inducers and strong CYP3A inhibitors	-Only for FLT3-ITD -CYP3A interactions
Select Adverse Reactions	-Febrile neutropenia and mucositis in combination with chemotherapy	-ECG monitoring recommended -LFT abnormalities	-Febrile neutropenia and mucositis in combination with chemotherapy

FLT3 inhibitors Select Warnings and Precautions

- **Black box warning for differentiation syndrome: Gilteritinib**
  - Signs and symptoms include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction
  - If suspected initiate dexamethasone and hemodynamic monitoring until improvement
  - Taper steroids after resolution of symptoms for a minimum of 3 days

- **Black box warning for QT prolongation, torsades de pointes, and cardiac arrest: quizartinib**
  - REMS program

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- Perform ECGs at baseline, weekly during induction and consolidation and the first month of maintenance then periodically thereafter or more often if on concomitant drugs known to prolong QT
- Monitor for and correct hypokalemia and hypomagnesemia
- Do not initiate treatment or escalate the dose if QTcF is >450 ms
- Reduce dose when used with strong CYP3A inhibitors

- Pulmonary toxicity: midostaurin
  - Reports of interstitial lung disease and pneumonitis, some fatal

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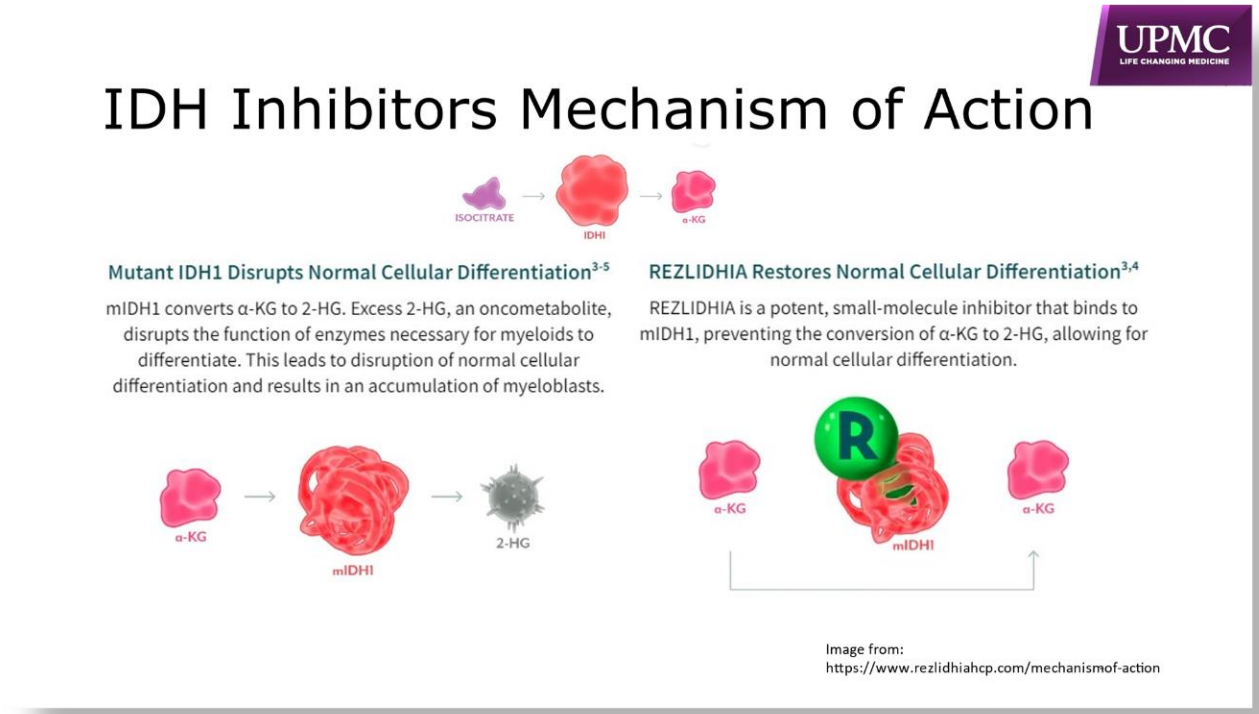
IDH Inhibitors
- Ivosidenib (Tibsovo)
- Olutasidenib (Rezlidhia)
- Enasidenib (Idhifa)



IDH Inhibitors	**Ivosidenib (IDH1)**	**Olutasidenib (IDH1)**	**Enasidenib (IDH2)**
FDA Approved Indications ***All indications require a susceptible IDH mutation as detected by an FDA-approved test**	-Newly diagnosed AML age ≥75 or with comorbidities precluding intense therapy given in combination with azacitidine or monotherapy -R/R AML -R/R MDS -Locally advanced or metastatic cholangiocarcinoma after previous treatment	-R/R AML with a susceptible IDH1 mutation	-R/R AML with an IDH2 mutation
Administration	-Once daily with or without food. -Avoid a high-fat meal	-Twice daily on an empty stomach at least 1 hour before or 2 hours after a meal	-Once daily with or without food
Clinical Considerations	-Continue at least 6 months for patients without disease progression or unacceptable toxicity to allow time for clinical response -CYP3A4 interactions -Avoid QT prolonging drugs	-Continue at least 6 months for patients without disease progression or unacceptable toxicity to allow time for clinical response -CYP3A4 interactions	-Continue at least 6 months for patients without disease progression or unacceptable toxicity to allow time for clinical response -Caution with CYP1A2, CYP2C19 and CYP3A4 substrates as well as with caffeine

IDH Inhibitors

Black Box Warning – Differentiation Syndrome (for all 3 drugs)

- Can be fatal if not treated -associated with rapid proliferation and differentiation of myeloid cells
- Can occur within 1 day of starting to months after starting treatment.
- Symptoms include dyspnea, pulmonary infiltrates, pleural or pericardial effusions, hypotension, fever, weight gain, hepatic, renal or multi-organ dysfunction

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- If suspected initiate corticosteroids and hemodynamic monitoring until symptom resolution. Steroid taper is recommended. If severe withhold the IDH inhibitor (olutasidenib recommended to be held for any severity)

IDH Inhibitors Warnings and Precautions
- QTc prolongation: Ivosidenib
- Hepatotoxicity: Olutasidenib

IDH Inhibitors Select Adverse Reactions
- Fatigue
- Changes in blood counts
- Nausea
- Diarrhea
- Decreased appetite
- Joint pain

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EGFR Inhibitors
- Gefitinib (Iressa)
- Erlotinib (Tarceva)
- Afatinib (Gilotrif)
- Osimertinib (Tagrisso)
- Dacomitinib (Vizimpro)

EGFR Inhibitors Mechanism of Action
- EGFR expressed on normal and cancer cells
- EFGR inhibitors bind to and inhibit EGFR tyrosine kinase
- Exon 19 deletion and exon 21 L858R substitution
- T790M osimertinib
- Results in inhibition of tumor cell survival and proliferation

EGFR Inhibitors	**Gefitinib**	**Erlotinib**	**Afatinib**	**Osimertinib**	**Dacomitinib**
FDA Approved Indications *EGFR mutation as detected by FDA-approved test	-First line metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitution mutation	-Metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitution mutations receiving first-line, maintenance, second or greater line treatment after progression following at least one prior chemotherapy regimen	-First line treatment of metastatic NSCLC with non-resistant EGFR mutations -Metastatic, squamous NSCLC progressing after platinum-based chemotherapy	-First line treatment of metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation alone or with chemotherapy -Adjuvant therapy after tumor resection of NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation -EGFR T790M after progression	-First line treatment of metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations
Administration	-Once daily with or without food	-Once daily on an empty stomach 1 hour before or 2 hours after food	-Once daily on an empty stomach 1 hour before or 2 hours after food	-Once daily with or without food	-Once daily with or without food
Clinical Considerations	-FDA approved a second time in 2015 previously taken off market in 2005	-CYP3A4 & PPI interactions	-Minimal enzymatic metabolism -Caution with co-administration of P-gp inhibitors/inducers	-Continue up to 3 years adjuvantly -Caution with strong CYP3A inducers	-Avoid PPIs

	-CYP3A4 & PPI interactions				

EGFR Inhibitors Select Warnings and Precautions

- Interstitial lung disease and pneumonitis
- Hepatotoxicity
  - gefitinib, erlotinib, afatinib
- Ocular Disorders including keratitis

EGFR Inhibitors Select Adverse Reactions

- Skin Rash
- Consider doxycycline or minocycline or topical clindamycin
- Diarrhea
- Dry skin/pruritis
- Paronychia and nail toxicity
- Stomatitis

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FGFR Inhibitors

- Erdafitinib (Balversa)
- Pemigatinib (Pemazyre)
- Futibatinib (Lytgobi)

FGFR Inhibitors Mechanism of Action

- FGF (fibroblast growth factor) signaling via FGFR plays an important role in tumor proliferation and survival
- Inhibiting FGFR blocks cell signaling and decreases cell viability
- FGFR 1-4 can acquire point mutations, amplifications and fusions in cancer cells

FGFR Inhibitors	**Erdafitinib**	**Pemigatinib**	**Futibatinib**
FDA Approved Indications **1. Must use FDA-approved companion diagnostic tests for FGFR prior to use of these drugs** **2. *accelerated approval**	-Locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 genetic alterations with disease progression on or after ≥ 1 line of prior systemic therapy	-Previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or other rearrangement* -R/R myeloid/lymphoid neoplasms with FGFR1 rearrangement	-Previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements*
Administration	-Once daily with or without food	-Once daily with or without food	-Once daily with or without food
Clinical Considerations	-Interactions with CYP3A4 and CYP2C9 drugs -Start at lower dose and can escalate -Avoid co-administration of serum phosphate level-altering agents before initial dose increase period based on serum phosphate levels (days 14-21) -Limit daily phosphorus	-14 days on followed by 7 days off for cholangiocarcinoma -Continuous dosing for myeloid/lymphoid neoplasms -CYP3A4 drug interactions	-Dual P-gp and CYP3A drug interactions

	intake to 600-800 mg		

FGFR Inhibitors Warnings and Precautions

- Hyperphosphatemia and soft tissue mineralization
  - FGFR1 plays a key role in phosphorus homeostasis
  - Closely monitor phosphorus levels and add binders
- Ocular disorders
  - Retinal pigment epithelial detachment, dry eye/corneal keratitis

FGFR Inhibitors Select Common Adverse Reactions

- Diarrhea
- Stomatitis
- Fatigue
- Alopecia
- Nail toxicity
- Arthralgia

Summary

- Tyrosine kinases function as molecular light switches
- TKIs are oral drugs used for many different cancers
- Monitor patients for side effects and appropriate intervention
- Review patient medication lists for drug-drug interactions
- Always reference the package insert and drug website for the latest information: Ask your pharmacist questions!

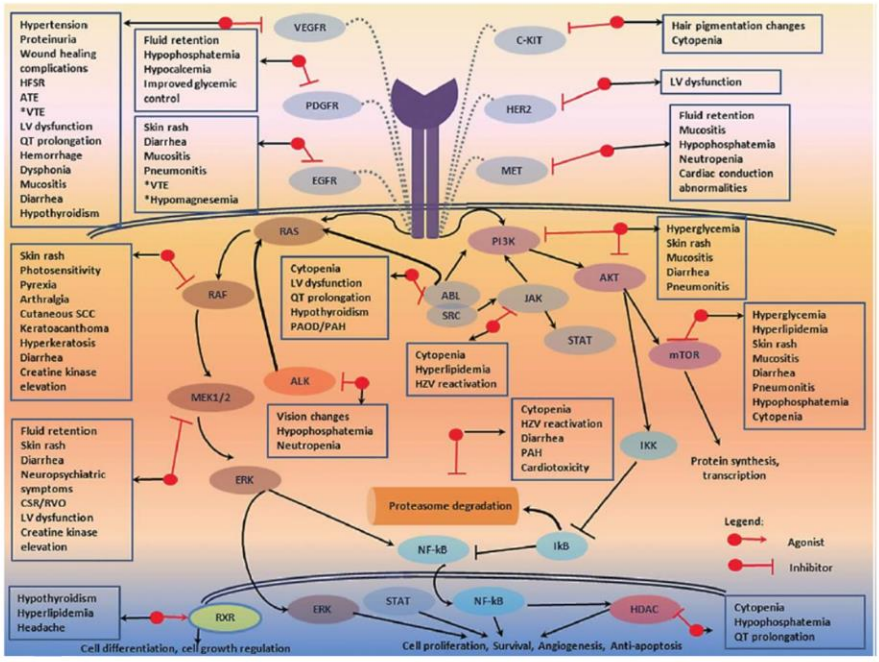
Tyrosine Kinase Inhibitors (TKIs): Part 2

Strong CYP 3A4 inhibitors

- Azole antifungals (ketoconazole, posaconazole, voriconazole)
- Protease inhibitors (ritonavir, darunavir, lopinavir, nelfinavir, etc.)
- Clarithromycin

Strong CYP 3A4 inducers

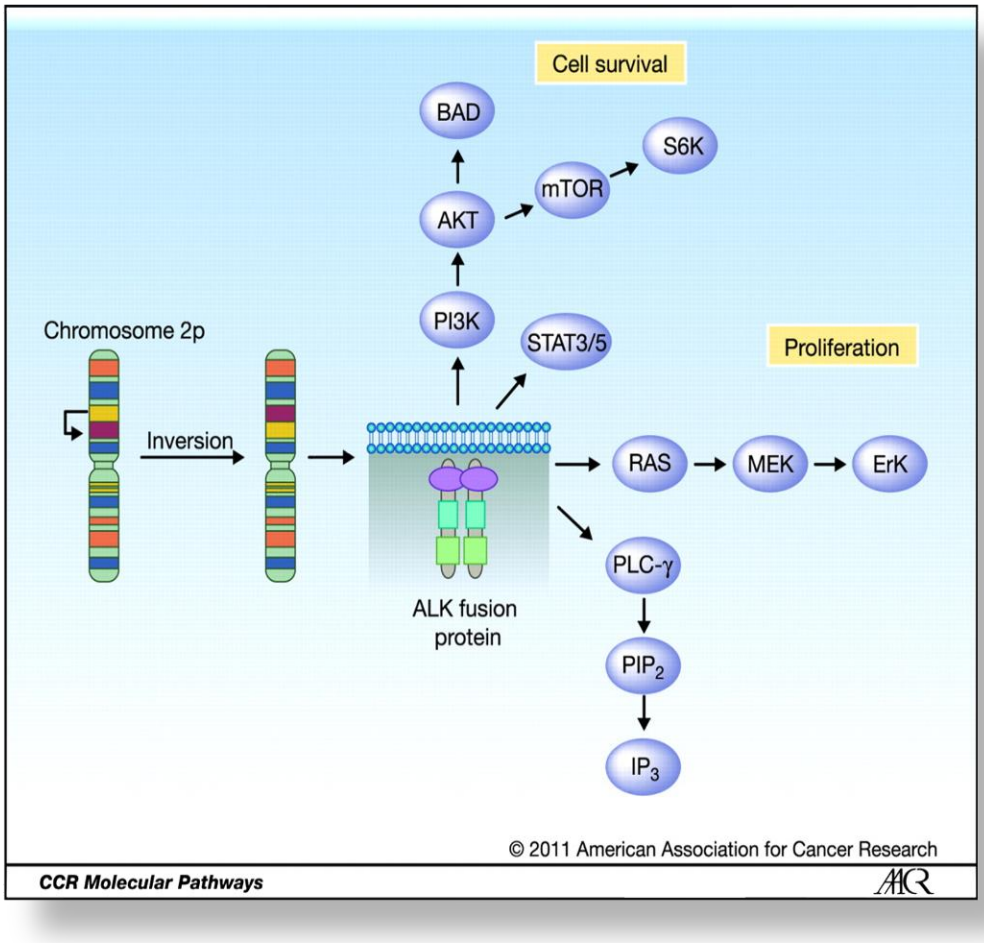
- Barbie's Car Goes Really Phast
- B = Barbiturates
- S = St. John's Wort
- C = Carbamazepine
- G = Griseofulvin
- R = Rifampin
- Ph = Phenytoin



ALK Inhibitors

ALK Mutation

- Arises from an inversion on the short arm of chromosome 2 to EML4
- EML4-ALK fusion oncogene activates signaling cascades (RAS, PI3K) leading to cell survival and proliferation
- Present in 3-7% of NSCLC



ALK Inhibitors

- Crizotinib (Xalkori)
- Ceritinib (Zykadia)
- Alectinib (Alecensa)
- Brigatinib (Alunbrig)
- Lorlatinib (Lorbrena)

ALK Inhibitors	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
FDA Approval	ALK+ or ROS1 mutated mNSCLC	ALK+ mNSCLC	ALK+ mNSCLC	ALK+ mNSLCL	ALK+ mNSCLC
Dose	250mg PO twice daily	750mg PO once daily	600mg PO twice daily	90mg PO daily days 1-7 then 180mg PO daily if tolerated	100mg PO daily
Drug Interactions	CYP3A4 substrate and inhibitor -Avoid strong 3A4 substrates/ inhibitors	-Avoid strong CYP3A4 inhibitors/ inducers -Adjust dose if interaction unavoidable	none	-Avoid use with strong CYP3A4 inhibitors and inducers -Adjust dose if interaction unavoidable	-CYP3A4 inducers, inhibitors, and substrates -↓ to 75mg w/ strong 3A4 inhibitors -**Contraindicated w/ strong 3A4 induces 2/2 serious hepatoxicity**

ALK Inhibitors	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Renal dysfunction	CrCl ≥ 30: no adjustments CrCl <30: ↓ 250mg once daily	CrCl ≥ 30: no adjustments CrCl <30: has not been studied	CrCl ≥ 30: no adjustments CrCl <30: has not been studied	CrCl ≥ 30: no adjustments CrCl 15-<30: reduce dose by ~50% (180mg → 90mg, 90mg → 60mg)	CrCl ≥ 30: no adjustments CrCl <30: has not been studied
Hepatic dysfunction	Mild: none Moderate: 200mg BID Severe: 250mg once daily *Treatment modifications exist if hepatotoxicity is developed during therapy*	Mild: none Moderate: none Severe: ↓ dose by 33% *Treatment modifications exist if hepatotoxicity is developed during therapy*	Mild: none Moderate: none Severe: ↓ 450mg twice daily *Treatment modifications exist if hepatotoxicity is developed during therapy*	Mild: none Moderate: none Severe: Reduce dose by ~40% (180mg → 120mg, 120mg → 90mg, 90mg → 60mg)	Mild: none Moderate: has not been studied Severe: has not been studied *Treatment modifications exist if hepatotoxicity is developed during therapy*

ALK Inhibitors: Adverse Effects
Class Effects: Highest to Lowest

- ILD/pneumonitis
  - Brigatinib
  - Crizotinib
  - Ceritinib
  - Lorlatinib
  - Alectinib

- Hepatotoxicity: Check LFTs and bilirubin at baseline and throughout treatment
  - Alectinib: Typically occurs within the first 2 months
  - Brigatinib: Exception; does not cause hepatotoxicity
- Bradycardia: If asymptomatic, dose modification is not required. If symptomatic, then hold therapy until patient is asymptomatic or HR is >60 bpm. Evaluation for other medication causes (beta blockers, digoxin, etc.). Resume at reduced dose

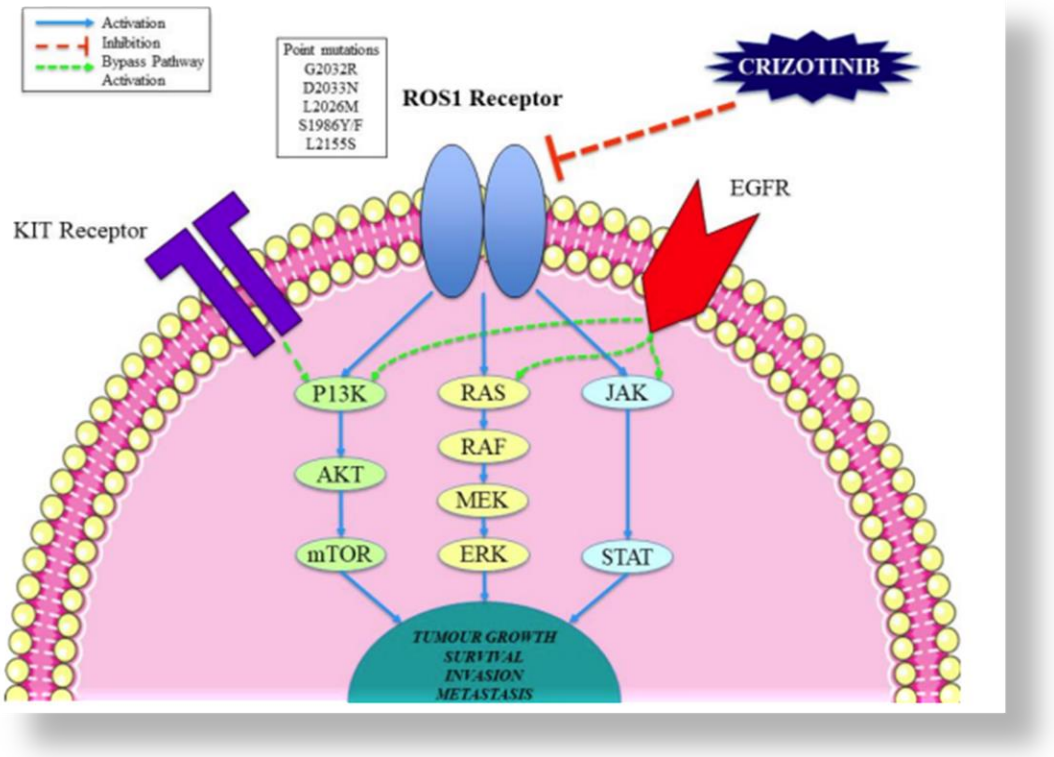
- QTc prolongation: Correct electrolytes prior to therapy initiation. Conduct baseline EKG and periodically throughout treatment. Hold therapy for QTc >500
    - Alectinib and brigatinib are the exceptions and do not cause meaningful QTc prolongation
- Vision disorders: Can manifest as blurred vision, “floaters”, visual impairment, reduced visual acuity, asthenopia and diplopia
    - Patients should have baseline visual exam and repeat with any symptoms
- Myalgias/Musculoskeletal pain- advise patients to report any unexplained muscle pain or weakness
    - Alectinib: Mild symptoms are common (29%). Severe symptoms occurred in ~1% of patients. CPK elevations may occur with median time to Grade 3 elevation of 14 days. Monitor CPK levels every 2 weeks for the first month then as clinical indicated
    - Brigatinib

ALK Inhibitors Drug Specific Adverse Effects

- Alectinib
    - Can cause photosensitivity. Patient should protect skin from sunlight and wear SPF ≥30 sunscreen
- Ceritinib
    - Can cause severe GI toxicity. Nausea, vomiting, diarrhea or abdominal pain occurred in 95% of patients. 14% of patients experienced grade 3 or 4 GI toxicity.
        - Manage with antiemetics and anti-diarrheal agents. IV fluids may be needed to prevent dehydration
    - Hyperglycemia: Monitor glucose closely in those with and without diabetes
    - Pancreatitis
- Brigatinib
    - Hyperglycemia
    - Pancreatitis
    - Hypertension
- Lorlatinib
    - Central Nervous System Effects (54%)
        - Cognitive, mood, and speech effects
        - Hallucinations
        - Seizures

ROS1 Inhibitors

- Gene, located at chromosome 6q22.1, that belongs to the subfamily of tyrosine kinase insulin receptors
- Genomic alterations form oncogenic gene fusions, resulting in ROS1 kinase activity becoming constitutively activated
- ~2% incidence in NSCLC
- ROS1 protein shows substantial homology to ALK, particularly within the ATP binding domains and the kinase domains.



ROS1 Inhibitors

- Crizotinib
- Ceritinib
- Entrectinib
- Repotrectinib

ROS 1 Inhibitors	Entrectinib	Repotrectinib
FDA Approval	-Adult patients with *ROS1*-positive metastatic NSCLC -Adult and pediatric patients older than 1 month of age with solid tumors that: •Have a neurotrophic tyrosine kinase (*NTRK*) gene fusion •Are metastatic or where surgical resection is likely to result in severe morbidity •Have progressed following treatment or have no satisfactory alternative therapy	-Locally advanced or metastatic NSCLC with *ROS1* rearrangement
Dose	600mg PO daily (adults)	160mg PO daily for 14 days, then increase to 160mg PO TWICE daily.
Drug Interactions	Moderate and Strong CYP3A4 Inhibitors: dose reductions exist for concomitant moderate and strong 3A4 inhibitors. Refer to package insert for dose modifications. CYP3A4 inducers: Increase metabolism of entrectinib. Avoid concomitant use	Moderate and Strong CYP3A4 inhibitors: avoid concomitant use CYP3A4 inducers: avoid concomitant sue P-gp inhibitors: Avoid concomitant use Other interactions •Contraceptives: may decrease progrestin or estrogen exposure and reduce hormonal contractive effective. •CYP3A4 substrates with a narrow therapeutic index

ROS 1 Inhibitors	**Entrectinib**	**Repotrectinib**
Renal dysfunction	CrCl ≥ 30 mL/min: none CrCl <30 mL/min: not studied	CrCl ≥ 30 mL/min: none CrCl <30: not studied
Hepatic dysfunction	Moderate (Tbili >1.5 to ≤ 3x ULN): Not studied Severe (Tbili > 3x ULN): Not studied	Mild: none Moderate-Severe: not studied

ROS 1 Inhibitor Toxicities

Side Effect	**Possible Management**
CNS effects	May cause cognitive impairment, mood disorders, dizziness, or sleep disturbances. Withhold until improved symptoms and then consider resuming at same dose or reduced dose
Skeletal fractures	Monitor for signs/symptoms of fractures
Hepatotoxicity	Monitor AST/ALT at baseline and every 2 weeks x 1 month then monthly
Hyperuricemia	Check uric acid at baseline and as indicated

ROS 1 Agent Specific Toxicities

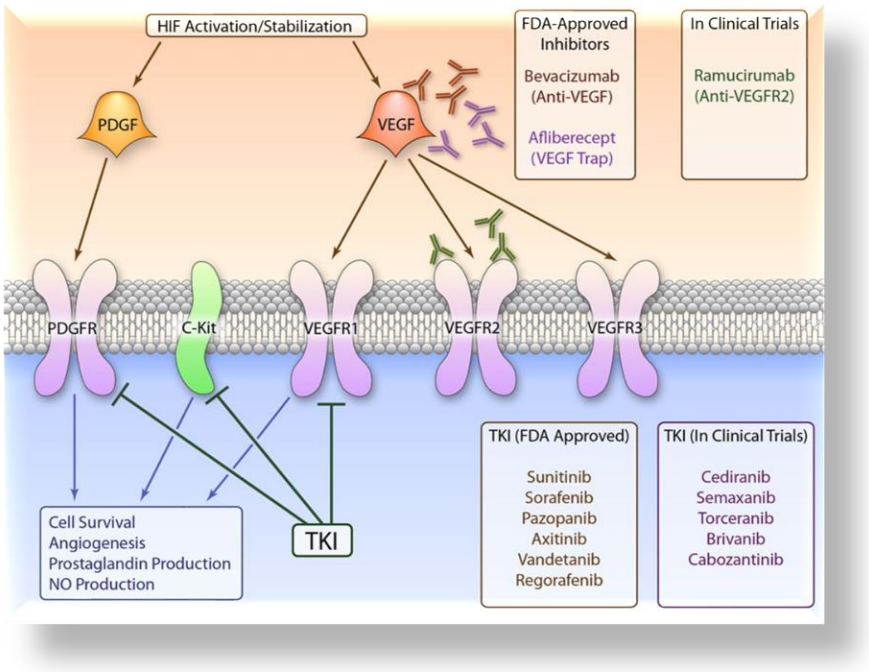
Entrectinib	Possible Management
CHF	Check baseline LVEF prior to initiation of entrectinib and monitor for signs/symptoms of HF. For patients with new onset or worsening HF, withhold entrectinib and institute appropriate medical management and reassess LVEF. Consider resuming entrectinib at a reduced dose if/when LVEF recovers to baseline
Myocarditis	In patients with suspected myocarditis, consider a cardiac MRI or cardiac biopsy
QTc prolongation	Check baseline QTcF and electrolytes at baseline and correct abnormalities. Monitor QTcF periodically during treatment. Based on the severity of QTc prolongation, withhold entrectinib and then resume at the same or reduced dose, or permanently discontinue.
Vision disorders	For patients with new visual changes or changes that interfere with ADLs, withhold entrectinib until improvement or stabilization and consider an ophthalmological evaluation

Repotrectinib	Possible Management
ILD/pneumonitis	Monitor for signs and symptoms of pneumonitis or ILD. Hold repotrectinib with suspected ILD or pneumonitis and permanently discontinue, if confirmed
Peripheral neuropathy	Can occur in up to ~50% of patients, mostly grade 1 or 2. Consider dose reductions based on severity
Myalgias	Check baseline CPK and monitor every 2 weeks during the first month and then as needed. Based on severity, hold repotrectinib and then resume at the same or reduced dose upon improvement

VEGF Inhibitors

VEGF Inhibitors MOA

- Normally is well controlled by pro- and anti-angiogenic factors and is only promoted during events
- Angiogenesis plays a critical step in tumor progression
- New blood vessel growth is required for growth of tumor cells and metastasis formation
- VEGF signaling is the major inducer of angiogenesis
- VEGF inhibitors block angiogenesis



VEGF Inhibitors

- Sorafenib
- Sunitinib
- Pazopanib
- Axitinib
- Regorafenib
- Fruquintinib
- Tivozanib
- Cabozantenib
- Vandetinib

VEGF Inhibitors	Sorafenib	Sunitinib	Pazopanib	Axitinib
FDA Approval	-Unresectable hepatocellular carcinoma -metastatic renal cell carcinoma (mRCC) -Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment	-Adjuvant renal cell carcinoma -mRCC as monotherapy or in combination with nivolumab -GIST tumors after progression/ intolerance to imatinib -locally advanced or metastatic pancreatic neuroendocrine ca (pNET)	-mRCC -Advanced soft tissue sarcoma after prior chemotherapy	-1st line mRCC in combination with either pembrolizumab or avelumab -mRCC after failure on at least one other therapy
Dose	400mg twice daily	RCC/GIST: 50mg daily for 4 weeks on f/b 2 weeks off pNET: 37.5mg daily w/o breaks	800mg daily	5 mg PO BID with or without food ↑ to 7 mg PO BID and then to 10 mg PO BID if tolerated
Drug Interactions	CYP3A4 inducers: Increase metabolism of sorafenib	-consider dose adjustments w/ strong CYP3A4 inhibitors and inducers	Strong CYP3A4 inhibitors: Avoid or reduce to 400mg daily Strong CYP3A4 inducers: Do not use pazopanib if chronic CYP3A4 inducers cannot be avoided	-Strong 3A4 inhibitors: ↓ dose by ~50%

VEGF Inhibitors	Sorafenib	Sunitinib	Pazopanib	Axitinib
Renal dysfunction	CrCl 20-39 mL/min: 200mg PO BID CrCl <20 mL/min: insufficient data Hemodialysis: 200mg PO Daily	n/a	n/a	CrCl >15: n/a
Hepatic dysfunction	Moderate (Tbili >1.5 to ≤ 3x ULN): 200mg PO BID Severe (Tbili > 3x ULN): Not defined- 200mg q3d poor tolerated	Mild-moderate: none Severe: not studied	Moderate (Tbili 1.5 – 3 x ULN): 200mg PO Daily Severe (Tbili >3): do not use	Moderate: Reduce starting dose by 50% Severe: has not been studied

VEGF Inhibitors	Regorafenib	Fruquintinib	Tivozanib
FDA Approval	-metastatic colon cancer previously treated with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy and if KRAS wild type an anti-EGFR therapy -Locally advanced, unresectable or metastatic GIST previously treated with imatinib and sunitinib -Hepatocellular carcinoma (HCC) previously treated with sorafenib	-metastatic colon cancer previously treated with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy and if KRAS wild type an anti-EGFR therapy	-mRCC following two or more prior therapies
Dose	160mg PO daily with a low-fat breakfast days 1-21 of 28 day cycle Alternative: with weekly dose escalation from 80mg to 120mg to 160mg -Improved overall survival (non-statistically significant), tolerability, quality of life Available as 40mg tablets Store in original manufacturer's container Dispose of any unused tablets 28 days after opening	5mg PO once daily, with or without food, days 1-21 of 28 day cycle	1.34 mg PO once daily with or without food days 1-21 of 28 day cycle

VEGF Inhibitors	Regorafenib	Fruquintinib	Tivozanib
Drug interactions	Avoid concomitant strong CYP3A4 inducers or inhibitors	Moderate CYP3A4 inducers: Avoid, if possible. If not possible, continue with standard fruquintinib dosing. Strong CYP3A4 inducers: Avoid use	Avoid concomitant strong CYP3A4 inducers
Renal dysfunction	n/a	n/a	n/a
Hepatic dysfunction	Moderate: no dose adjustments but monitor closely Severe (Tbili > 3x ULN): use is not recommended. Has not been studied	Mild impairment (Tbili <1.5x ULN): no dose adjustments Moderate impairment (Tbili 1.5-3x ULN): not sufficiently studied. Severe (Tbili >3 x ULN): use is not recommended	Moderate (Tbili 1.5 – 3 x ULN): 0.89 mg PO Daily Severe (Tbili >3): use not recommended; dosing not established

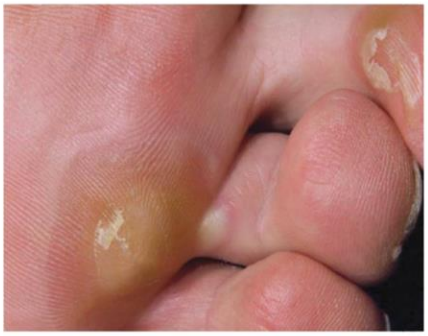
VEGF Inhibitors	**Fruquintinib**
FDA Approval	-metastatic colon cancer previously treated with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy and if KRAS wild type an anti-EGFR therapy
Dose	5mg PO once daily, with or without food, days 1-21 of 28 day cycle
Drug interactions	Moderate CYP3A4 inducers: Avoid, if possible. If not possible, continue with standard fruquintinib dosing. Strong CYP3A4 inducers: Avoid use
Renal dysfunction	n/a
Hepatic dysfunction	Mild impairment (Tbili <1.5x ULN): no dose adjustments Moderate impairment (Tbili 1.5-3x ULN): not sufficiently studied. Severe (Tbili >3 x ULN): use is not recommended.

VEGF Inhibitor Toxicities

Side Effect	Possible Management
GI perforations and fistulas	Discontinue therapy
Hemorrhages	Severe, sometimes fatal, hemorrhage including hemoptysis and gastrointestinal hemorrhage may occur. Monitor for signs of bleeding
Venous and arterial thromboembolic events	Discontinue if acute myocardial infarction or other clinically significant arterial thrombotic event occurs
Wound healing	Hold prior to surgery; resume based on clinical judgment. Refer to the specific package insert/recommendations for each agent
Hypertension	Reduced angiogenesis leads to vasoconstriction and hypertension. Hypertension can been seen within days of starting therapy (axitinib). Monitor closely throughout therapy and treat as needed
Cardiac	May cause cardiomyopathy, cardiac ischemia or myocardial infarcts. Check LVEF prior to initiation of therapy and during treatment. Hold or discontinue for reductions in LVEF, ischemia or MI
Proteinuria	Check urinalysis at baseline and during treatment. Can cause nephrotic syndrome and lead to renal dysfunction. May need to hold therapy for proteinuria
Hypothyroidism	Check thyroid function tests prior to initiation and throughout therapy. Treat at necessary

Agent specific adverse effects

Sorafenib
-Hand-foot syndrome
Sunitinib
-QT prolongation
-Adrenal insufficiency
Pazopanib
-QT prolongation
Axitinib
-Hepatotoxicity
-Reversible posterior leukoencephalopathy syndrome (RPLS)
Regorafenib/Fruquintinib
-Hand-foot syndrome
-RPLS

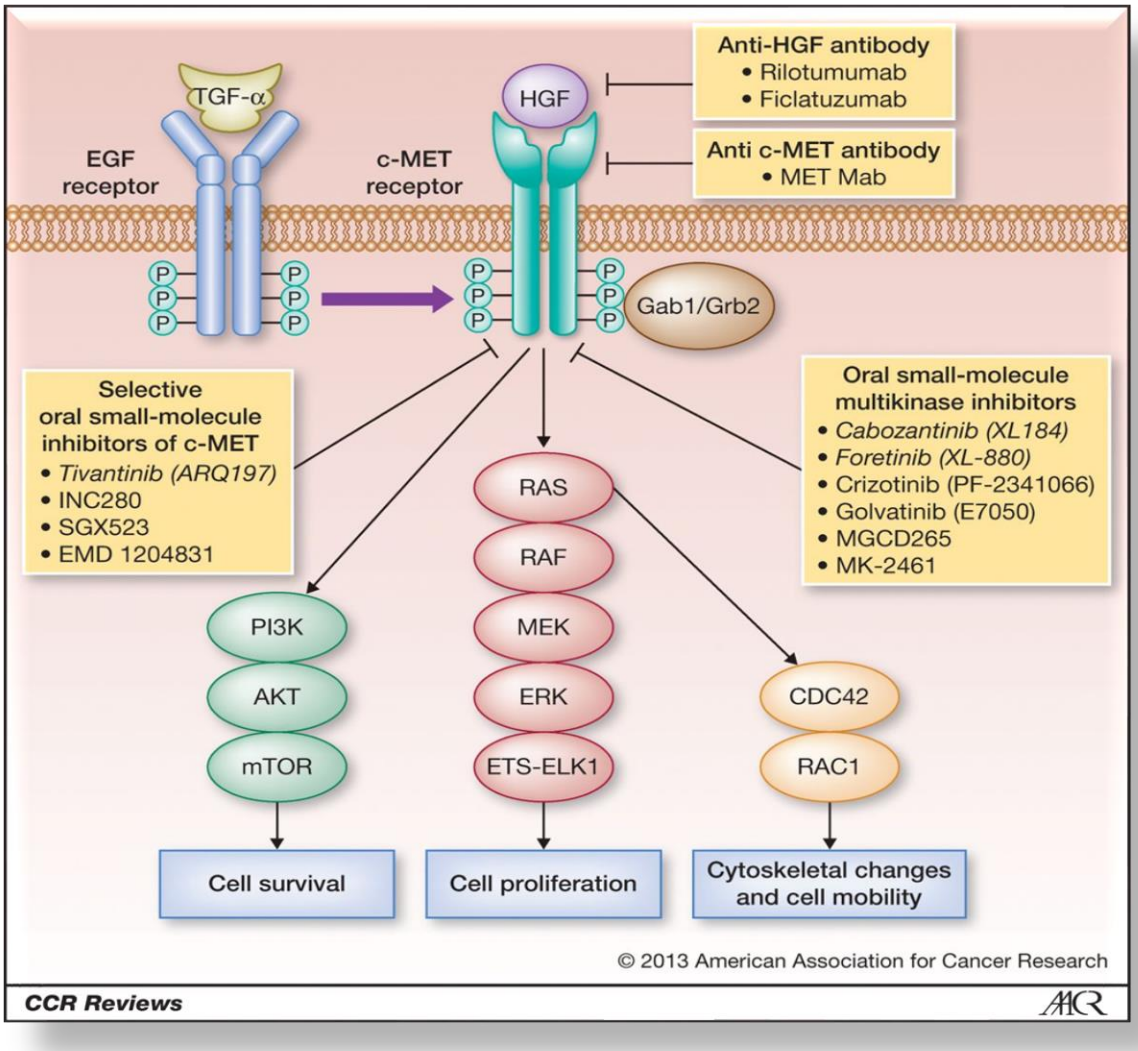


Audience Response Question: Patients treated with TKIs that inhibit VEGF often develop hypertension. When starting a patient on axitinib what should the providers keep in mind?

A. Check baseline blood pressure
B. Monitor blood pressure routinely
C. Add anti-hypertensives if patient develops hypertension
D. BP increases are usually seen in the first month
E. All of the above

MET Inhibitors

- Tepotinib
- Capmatinib
- Cabozantinib



MET Inhibitors	Tepotinib	Capmatinib	Cabozantinib
FDA Approval	Metastatic NSCLC harboring a *MET* exon 14 skipping alteration	Metastatic NSCLC harboring a *MET* exon 14 skipping alteration	-Progressive, metastatic medullary thyroid cancer (MTC) -1st line metastatic renal cell carcinoma (RCC) -Advanced RCC after prior anti-angiogenic therapy or 1st line in combination with nivolumab -Hepatocellular carcinoma (HCC) after prior sorafenib
Dose	450mg PO once daily with food	400mg PO twice daily with or without food	MTC: 140mg PO daily on an empty stomach RCC/HCC monotherapy: 60mg PO daily on an empty stomach RCC w/ nivolumab: 40mg PO daily on an empty stomach
Targets	MET	MET	MET, VEGFR2, FLT3, KIT, AXL, RET

MET Inhibitors	Tepotinib	Capmatinib	Cabozantinib
Drug Interactions	Dual strong CYP3A/P-gp Inhibitors: Avoid concomitant use Strong CYP3A inducers: avoid concomitant use Inhibitor of P-gp	Strong CYP3A inhibitors: monitor closely for toxicity Moderate/Strong CYP3A inducers: Avoid coadministration Inhibitor of CYP1A2, P-gp and BCRP	Strong CYP3A4 inhibitors: MTC: decrease dose by 40mg (i.e. 140mg → 100mg) RCC/HCC: decrease dose by 20mg (i.e. 60mg → 40mg) Strong CYP3A4 inducers: MTC: increase dose by 40mg (i.e. 140mg → 180mg) RCC/HCC: increase dose by 20mg (60mg → 80mg)

MET Inhibitors	Tepotinib	Capmatinib	Cabozantinib
Renal Dysfunction	Mild-Moderate: no dose adjustments required Severe: not studied but minimal renal elimination	Mild-Moderate: no dose adjustments required Severe: no studied but minimal unchanged drug renal elimination	CrCl ≥ 30 ml/min: no dose adjustments CrCl <30 ml/min: hasn't been studied
Hepatic Dysfunction	Mild-Moderate: no dose adjustment required Severe: not studied	No recommendations provided	Mild impairment (Child-Pugh A): MTC: decrease initial dose to 80mg daily RCC/HCC: no dose adjustment necessary Moderate impairment (Child-Pugh B): MTC: decrease initial dose to 80mg daily RCC/HCC: decrease initial dose to 40mg daily Severe impairment (Child-Pugh C): Use is not recommended as it hasn't been studied

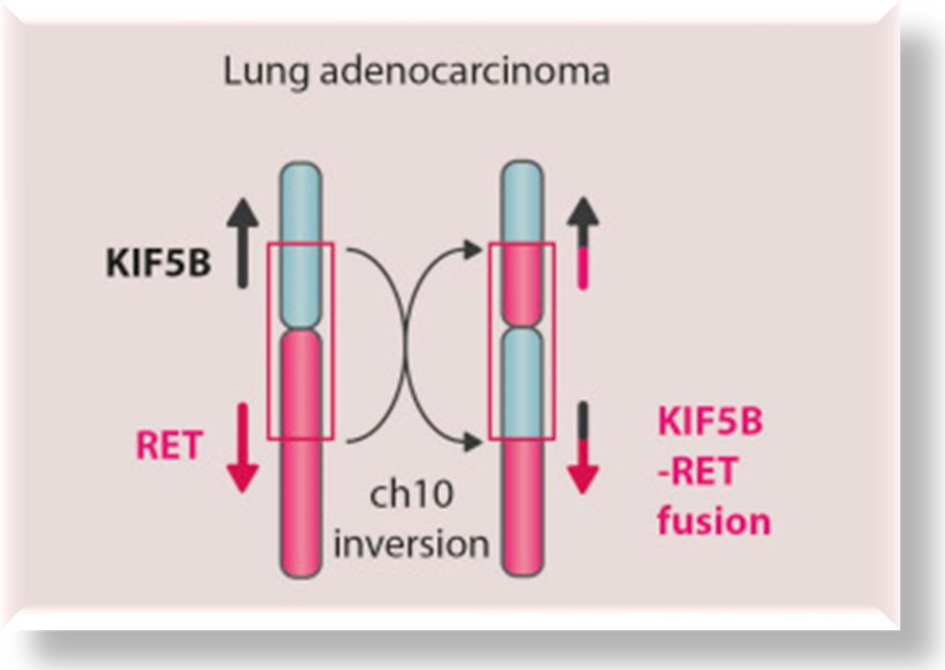
MET Inhibitors: Toxicity

Tepotinib/Capmatinib	Possible Management
Peripheral edema (very common)	Ace wraps, extremity elevation

Cabozantinib	Possible Management
GI perforations and fistulas	Discontinue therapy
Hemorrhages	Severe, sometimes fatal, hemorrhage including hemoptysis and gastrointestinal hemorrhage may occur. Monitor for signs of bleeding
Venous and arterial thromboembolic events	Discontinue if acute myocardial infarction or other clinically significant arterial thrombotic event occurs
Wound healing	Hold 28 days prior to surgery; resume based on clinical judgment
Hypertension	Monitor blood pressure prior to initiation and regularly during treatment; discontinue for hypertensive crisis
Osteonecrosis of the Jaw)	Perform an oral examination prior to and periodically during treatment; withhold 28 days prior to dental surgery if possible
Palmar-Plantar Erythrodysesthesia syndrome (PPES)	Withhold until grade 1 and then at a reduced dose
Proteinuria	Monitor urine protein and discontinue if nephrotic syndrome develops
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Evaluate for RPLS if seizures, headache, visual disturbances, confusion or altered mental status develops

RET Inhibitors

- Selpercatinib
- Pralsetinib
- Lenvatinib
- Vendatinib



RET Inhibitors	Selpercatinib	Pralsetinib
FDA Approval	-metastatic *RET* fusion-positive NSCLC -Advanced or metastatic *RET*-mutant medullary thyroid cancer requiring systemic therapy -Advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine refractory (if radioactive iodine is appropriate) -Adult patients with locally advanced or metastatic solid tumors harboring a *RET* gene fusion that has progressed on or following prior therapy or who have no satisfactory alternative treatment options.	-metastatic *RET* fusion-positive NSCLC -Advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine refractory (if radioactive iodine is appropriate)
Targets	*RET, VEGFR1, VEGFR3, FGFR1, 2, and 3*	*RET,* DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRB, FGFR1
Dose	≥50kg: 160mg PO twice daily <50kg: 120mg PO twice daily	400mg PO once daily on an empty stomach (at least 1 hour before and 2 hours after eating)

RET Inhibitors	Lenvatinib
FDA Approval	-locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC) -Advanced renal cell cancer (RCC) after one prior anti-angiogenic therapy in combination with everolimus -1st line unresectable HCC -In combination with pembrolizumab for advanced endometrial cancer that is not MSI-H or dMMR who have progressed on prior systemic therapy and are not candidates for curative surgery or radiation
Targets	RET, VEGFR1,2 and 3, FGFR, PDGFR-alpha, c-KIT
Dose	DTC: 24 mg PO once daily with or without food RCC: 18 mg PO once daily with or without food in combination with everolimus 5mg PO once daily HCC: dosage is based on actual body weight ≥ 60kg: 12mg PO daily with or without food <60kg: 8mg PO daily with or without food Endometrial: 20mg PO daily with pembrolizumab 200mg IV every 3 weeks

RET Inhibitors	Selpercatinib	Pralsetinib
Drug Interactions	*Acid-Reducing Agents:* Avoid coadministration. If coadministration cannot be avoided, take selpercatinib with food (with PPI) or modify its administration time (with H2 receptor antagonist or locally-acting antacid-2 hours before or 10 hours after H2RA) Moderate/Strong CYP3A4 inhibitors: -Moderate inhibitor: reduce dose by 40mg BID -Strong inhibitor: reduce dose by 80mg BID Moderate/Strong CYP3A4 inducers: Avoid coadministration CYP2C8 and CYP3A substrates: avoid coadministration of selpercatinib with CYP2C8 an dCYP3A substrates with narrow therapeutic ranges. Adjust dose of interacting agent if coadministration cannot be avoided.	Strong/Moderate CYP3A inhibitors and/or P-gp inhibitors: Avoid combination, if possible. If avoidance not possible then refer to the package insert for suggested dose modifications. Strong/Moderate CYP3A inducers: Avoid combination, if possible. If avoidance not possible then increase the pralsetinib dose, according to the packing insert, **starting on Day 7 of coadministration**. After the inducer has been discontinued for at least 14 days, resume pralsetinib at the prior dose

RET Inhibitors	Lenvatinib
Drug interactions	No significant CYP enzyme or efflux pump interactions Lenvatinib can increase the QTc. Avoid concomitant medications that can prolong the QTc.

RET Inhibitors	Selpercatinib	Pralsetinib
Renal Dysfunction	CrCl ≥ 30 ml/min: no dose adjustments CrCl <30 ml/min: hasn't been studied	CrCl ≥ 30 ml/min: no dose adjustments CrCl <30 ml/min: hasn't been studied. Only a small amount is excreted in the urine
Hepatic Dysfunction	Severe impairment (Child-Pugh C): Reduce to 80mg PO twice daily (for both ≥50kg and <50kg, if on full dose)	Mild impairment (Child-Pugh A): No dose adjustment necessary Moderate-severe impairment (Child-Pugh B/C): No dose adjustments provided (has not been studied) however it is primarly metabolized by the liver

RET Inhibitors	Lenvatinib
Renal Dysfunction	CrCl ≥ 30 ml/min: no dose adjustments CrCl <30 ml/min: -DTIC: 14mg once daily -RCC: 10mg once daily -HCC: no adjustments -Endometrial: 10mg once daily
Hepatic Dysfunction	Mild impairment (Child-Pugh A): No dose adjustment necessary Moderate impairment (Child-Pugh B): No dose adjustment necessary Severe impairment (Child-Pugh C): DTIC: 14mg once daily RCC: 10mg once daily HCC: no recommendations provided Endometrial: 10mg once daily

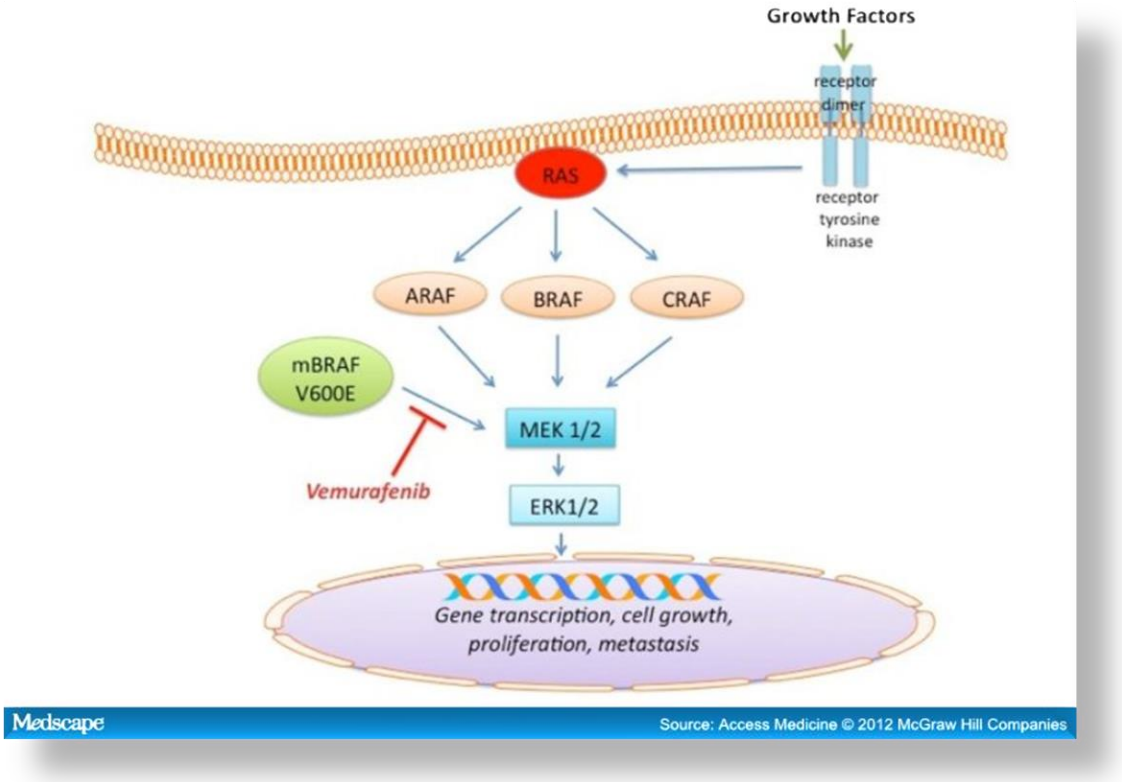
RET Inhibitor Toxicities

Side Effect	Possible Management
Hypertension	Monitor blood pressure prior to initiation, after 1 week, then at least monthly
Hepatotoxicity	Check baseline LFTs and monitor throughout therapy. Withhold, reduced dose, or discontinue depending on severity
Interstitial Lung Disease (ILD)/Pneumonitis	Grade 1 or 2: hold until resolution then resume at a reduced dose Grade 3 or 4: permanently discontinue
GI perforations and fistulas	Discontinue therapy
Hemorrhages	Severe, sometimes fatal, hemorrhage including hemoptysis and gastrointestinal hemorrhage may occur. Monitor for signs of bleeding
Wound healing	Hold prior to surgery; Refer to package insert for each agent for recommended length of time. Resume based on clinical judgment

Side Effect	Possible Management
QTc prolongation	Check EKG at baseline and periodically during treatment. Hold for QTc>500 msec. Resume at a reduced dose once resolved.
Tumor lysis syndrome	Occurred in 1% of patients with MTC. Patients may be at risk if they have rapidly growing tumors, a high tumor burden, or renal dysfunction. Consider close monitoring and appropriate prophylaxis

BRAF Inhibitors
Mechanism of Action

- Inhibits some mutated forms of BRAF serine threonine kinase including $BRAF^{V600E}$
  Some mutations in BRAF including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors needed for proliferation.



BRAF Inhibitors	Vemurafenib	Dabrafenib	Encorafenib
FDA Approvals	-BRAF V600E mutated metastatic melanoma as a single agent or in combination with the MEK inhibitor cobimetinib +/- atezolizumab -Erdheim-Chester Disease with a BRAF V600E mutation	-BRAF V600E mutated metastatic melanoma as a single agent or in combination with trametinib -Adjuvant therapy in BRAF V600E or K mutated, fully resected stage III melanoma, in combination with the MEK inhibitor trametinib -Metastatic NSCLC with BRAF V600E mutation in combination with trametinib -BRAF V600E mutated locally advanced or metastatic anaplastic thyroid cancer (ATC) -Unresectable or metastatic solid tumors with BRAF V600E mutations following prior treatment w/o suitable alternatives -Pediatric patients with BRAF V600E mutant low-grade gliomas	-BRAF V600E or V600K mutated unresectable or metastatic melanoma in combination with the MEK inhibitor binimetinib -BRAF V600E mutated metastatic colorectal cancer, after prior therapy, in combination with cetuximab -Metastatic NSCLC with a BRAF V600E mutation, in combination with binimetinib

BRAF Inhibitors	Vemurafenib	Dabrafenib	Encorafenib
Dose	960mg PO twice daily	150mg PO twice daily	Melanoma/NSCLC: 450mg PO once daily CRC: 300mg PO once daily
Administration	With or w/o food	Empty stomach (1h before or 2h after a meal)	With or w/o food
Renal Dysfunction	No dose adjustments provided (hasn't been studied) though minimal (1%) elimination via urine	None	CrCl ≥ 30 mL/min: none CrCl <30: hasn't been studied
Hepatic Dysfunction	No dose adjustments provided (hasn't been studied)	Mild impairment- none Moderate-severe impairment: No dose adjustments provided, however hepatic metabolism and biliary excretion are primary elimination routes, and exposure may be increased with moderate-severe hepatic impairment.	Mild impairment (Child-Pugh A): none Moderate-severe impairment (Child-Pugh B-C): hasn't been studied *Treatment modifications exist if hepatotoxicity is developed during therapy*

BRAF Inhibitors	Vemurafenib	Dabrafenib	Encorafenib
Drug Interactions	Substrate CYP3A4: Avoid strong 3A4 inhibitors/inducers Inhibitor CYP1A2: Avoid drugs with narrow therapeutic index predominately metabolized by 1A2 (e.g. clozapine, theophylline, etc) or monitor closely Inhibitor of P-gp: Avoid drugs that have a narrow therapeutic index and are a substrate of P-gp (e.g. digoxin). Consider alternative agent or dose reductions.	Substrate CYP3A4 & 2C8: Avoid strong 3A4 or 2C8 inhibitors. If not possible, monitor closely for toxicity. Inducer of CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2B6: may result in decreased efficacy of medications metabolized by these enzymes (e.g. midazolam, warfarin, hormonal contraceptives, etc)	Substrate CYP3A4: Avoid moderate & strong 3A4 inhibitors. If unable to avoid, reduce dose of encorafenib (see next slide for dosing). Strong CYP3A4 inducers may reduce encorafenib drug levels; avoid concomitant use. Encorafenib may make oral contraceptives less effective. Avoid use of oral contraceptives.

BRAF Inhibitors Adverse Effects

Side Effect	Possible Management
Cutaneous squamous cell carcinomas	Perform dermatologic evaluations prior to initiation of therapy and every 2 months while on therapy. Manage with excision and continue treatment without dose adjustments
Severe hypersensitivity reactions	Do not re-challenge; discontinue
Stevens-Johnson syndrome and toxic epidermal necrolysis	Discontinue if severe skin reaction
LFT Abnormalities	Monitor liver enzymes at baseline and monthly during treatment
Ocular toxicities (uveitis)	Perform ophthalmologic exam for any visual disturbance
Arthralgias	Manage symptomatically

Vemurafenib

- Severe photosensitivity: Advise patients to wear sunscreen with SPF ≥30 year round
- QTc prolongation: Monitor EKG and electrolytes at baseline and after dose adjustments. Monitor EKG at day 15, monthly for the first 3 months, then every 3 months
- LFT abnormalities: Monitor liver enzymes at baseline and monthly during treatment

Dabrafenib

- Hemorrhage: Occurred in combination with trametinib; monitor for signs and symptoms of bleeding
- Venous thromboembolism: DVT and PE can occur with the combination of dabrafenib & trametinib; monitor for SOB, leg pain etc.
- Cardiomyopathy: Assess LVEF at baseline, after 1 month then every 2 to 3 months when using the combination

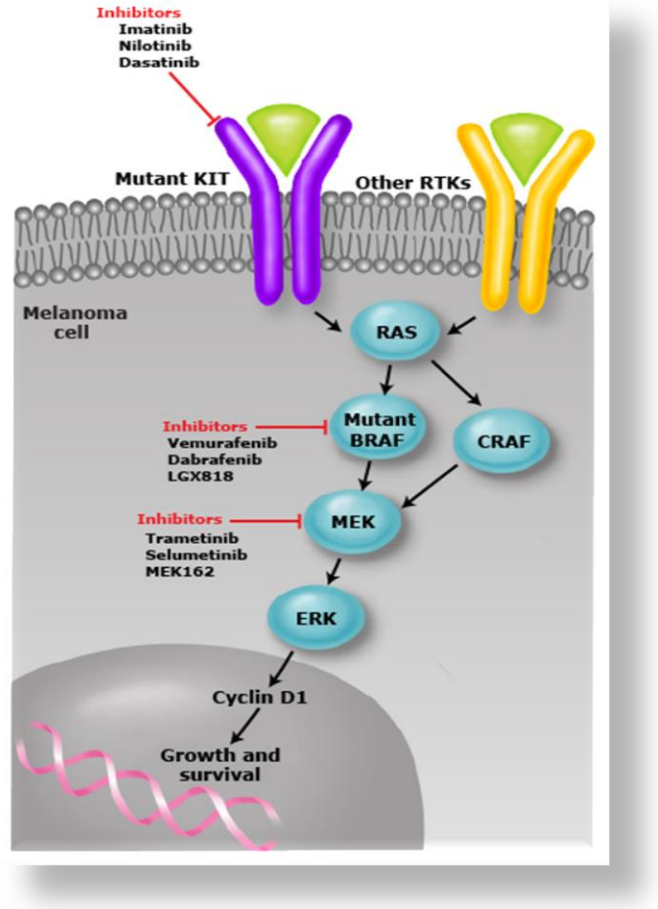
- Serious febrile drug reactions: Withhold if fever ≥101.3°F occurs or if complicated fever (rigors, hypotension, renal failure, dehydration); more common with trametinib combination. For fevers lasting ≥3 days or pyrexia with complications (dehydration, hypotension, renal failure, etc.) then administer corticosteroids (e.g., prednisone 10mg daily) for at least 5 days
- Hyperglycemia: Monitor blood glucose levels in patients with pre-existing diabetes or hyperglycemia
- Glucose 6-phosphate dehydrogenase deficiency: Monitor closely for hemolytic anemia
- Hand foot syndrome
- Hemophagocytosis Lymphohistiocytosis (HLH Syndrome): Immune activation of histiocytes and lymphocytes resulting in organ damage. Hold therapy and initiate HLH treatment

Encorafenib

- Hemorrhage: Monitor for signs and symptoms of bleeding
- QTc prolongation: Monitor EKG and electrolytes at baseline and after dose adjustments. Monitor EKG at day 15, monthly for the first 3 months, then every 3 months. Correct electrolytes (Potassium >4, Magnesium >2) and hold for QTc >500 msec

MEK Inhibitors
Mechanism of Action

- Reversible inhibition of MEK1 and MEK2 (upstream regulators of the ERK pathway)
- BRAF mutations cause constitutive activation of the BRAF pathway which includes MEK1 and MEK2



MEK Inhibitors	Cobimetinib	Trametinib	Binimetinib
FDA Approvals	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation in combination with vemurafenib +/- atezolizumab	-As a single agent in BRAF V600E mutated metastatic melanoma or in combination with the BRAF inhibitor dabrafenib -Adjuvant therapy in BRAF V600E or K mutated, fully resected stage III melanoma, in combination with the BRAF inhibitor dabrafenib -Metastatic NSCLC with BRAF V600E mutation in combination with BRAF inhibitor dabrafenib	-BRAF V600E or V600K mutated unresectable or metastatic melanoma in combination with the BRAF inhibitor encorafenib -Metastatic NSCLC with a BRAF V600E mutation, in combination with binimetinib

MEK Inhibitors	Cobimetinib	Trametinib	Binimetinib
Dose	60 mg PO daily days 1-21 of a 28 day cycle (in combination with vemurafenib)	2mg PO daily (with or w/o dabrafenib)	45mg PO twice daily (in combination w/ encorafenib)
Administration	With or w/o food	Empty stomach (1h before or 2h after a meal)	With or w/o food
Renal Dysfunction	CrCl ≥ 30 mL/min: none CrCl <30: hasn't been studied (minimal urinary excretion)	CrCl ≥ 30 mL/min: none CrCl <30: hasn't been studied (minimal urinary excretion)	No dose adjustments

Hepatic Dysfunction	Mild, Moderate, Severe impairment: No initial dose adjustment is necessary *Treatment modifications exist if hepatotoxicity is developed during therapy*	Mild impairment- none Moderate-severe impairment: No dose adjustments provided. An appropriate dose has not been established.	Mild impairment (Child-Pugh A): none Moderate-severe impairment (Child-Pugh B-C): ↓ to 30mg PO twice daily *Treatment modifications exist if hepatotoxicity is developed during therapy*

MEK Inhibitors	Cobimetinib	Trametinib	Binimetinib
Drug Interactions	Substrate CYP3A4: Avoid moderate/strong CYP3A4 inhibitors. If short term use (≤14 days) is unavoidable in those taking cobimetinib 60mg, reduce cobimetinib to 20mg daily. Avoid moderate/strong CYP3A4 inhibitors on those already on a reduced dose of cobimetinib. Strong CYP3A4 inducers may decrease cobimetinib exposure by more than 80%. Avoid concurrent use.	No clinically relevant drug interactions (keep in mind dabrafenib interactions)	No clinically relevant drug interactions (keep in mind encorafenib interactions)

MEK Inhibitor Adverse Events

Side Effect	Possible Management
New primary malignancies cutaneous and non-cutaneous	Perform dermatologic evaluations prior to initiation of therapy and every 2 months while on therapy. Manage with excision and continue treatment without dose adjustments
Hemorrhage	Rare; monitor for signs and symptoms of bleeding
Cardiomyopathy	Evaluate LVEF at baseline, after 1 month and then every 2-3 months
Severe rash or skin toxicity	Interrupt, reduce or discontinue
Ocular toxicity including serous retinopathy and retinal vein occlusion	Perform eye evaluations at regular intervals and for any visual disturbances

MEK Inhibitor Drug Specific Adverse Effects

Cobimetinib (Cotellic)

- Rhabdomyolysis
  - Obtain baseline CPK and monitor as indicated
- Severe Photosensitivity
  - Avoid sun exposure, wear protective clothing and use UVA/UVB sunscreen and lip balm SPF ≥30
- Hepatotoxicity
  - Monitor LFTs at baseline and monthly or more frequently if indicated

Trametinib (Mekinist)

- Venous Thromboembolism
  - DVT and PE can occur with the combination of dabrafenib & trametinib
- Interstitial Lung Disease
  - Hold for new or progressive unexplained pulmonary symptoms. Discontinue if treatment related ILD or pneumonitis diagnosed
- Serious Febrile Drug Reactions
  - Withhold if fever >104°F occurs or if complicated fever (rigors, hypotension, renal failure, dehydration); more common with dabrafenib
- Serious Skin Toxicity
  - Discontinue for intolerable grade 2 or grade 3 or 4 rash not improving within 3 weeks despite interruption

- Hyperglycemia
  - Monitor blood glucose levels in patients with pre-existing diabetes or hyperglycemia
- HLH Syndrome
  - Hold treatment and initiate HLH directed therapy

Binimetinib (Mektovi)

- Venous Thromboembolism
  - DVT and PE occurred in 6% and 3.1% of patients, respectively. Withhold, reduce dose or permanently discontinue based on severity of symptoms
- Interstitial Lung Disease
  - Hold for new or progressive unexplained pulmonary symptoms. Discontinue if treatment related ILD or pneumonitis diagnosed
- Transaminitis
  - Monitor LFTs as indicated
- Hemorrhage
  - Grade 3/4 hemorrhage in ~3% of patients including GI bleeds, rectal bleed or hematochezia. Fatal intracranial hemorrhage in the setting of new or progressive brain metastasis occurred in 1.6% of patients
- Rhabdomyolysis
  - Obtain baseline CPK as indicated

Audience Response Question

Melanoma patients treated with BRAF inhibitors can develop new squamous cell carcinomas (SCC) of the skin. If this happens in a patient on vemurafenib and cobimetinib which of the following should be done?

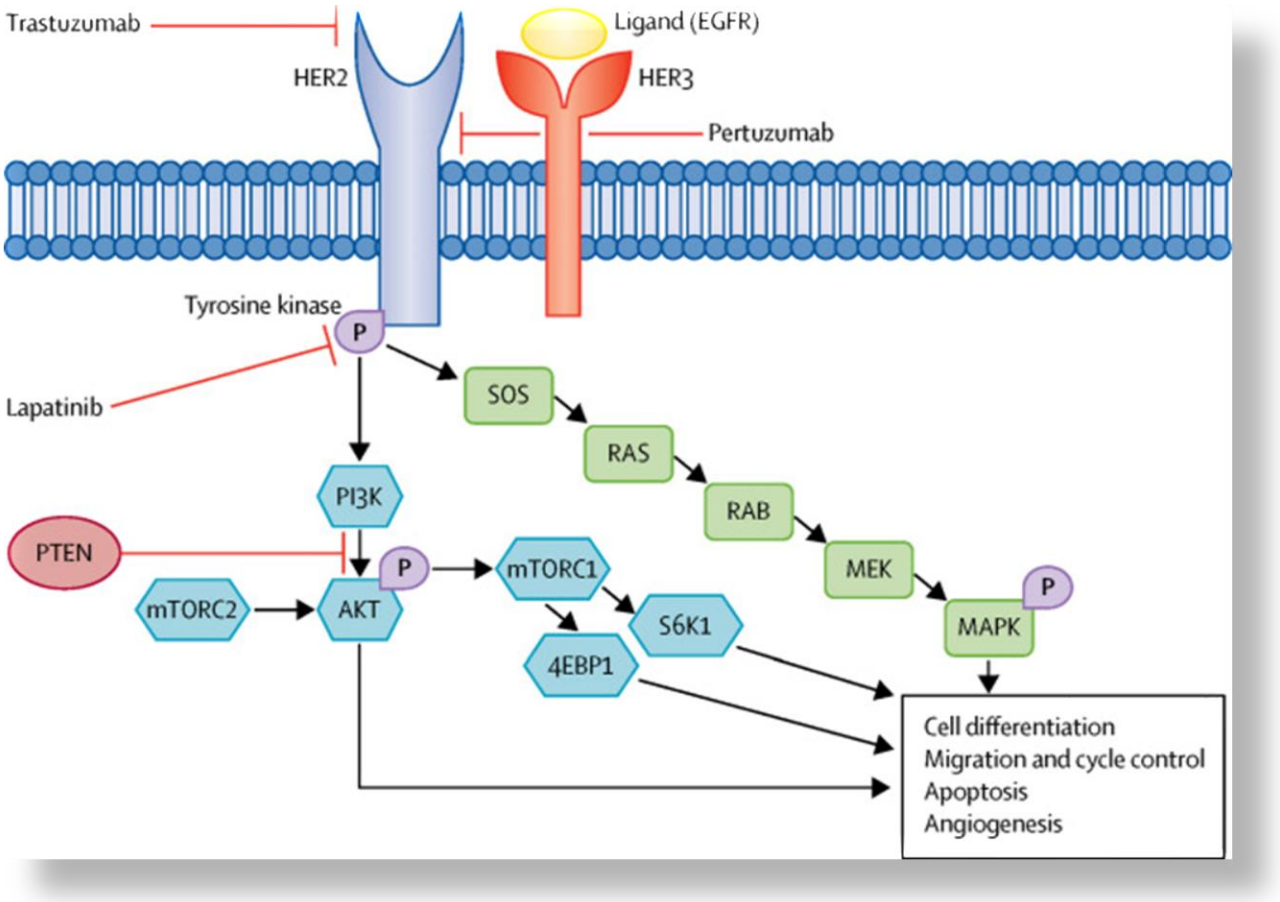
A. No intervention
B. Change therapy to dabrafenib/trametinib
C. Refer to dermatology to excise the SCC
D. Stop the BRAF inhibitor immediately
E. Change therapy to pembrolizumab

HER2 Inhibitors

- Lapatinib
- Neratinib
- Tucatinib

HER2 Inhibitors
Mechanism of Action

- Inhibits the intracellular tyrosine kinase domains of HER2 and HER3
- Inhibit downstream signaling and cell proliferation



HER2 Inhibitors	Lapatinib	Neratinib	Tucatinib
FDA Approval	Metastatic breast cancer overexpressing HER2 and having received prior therapy including an anthracycline, a taxane, and trastuzumab	-Adjuvant therapy for early stage HER2 positive breast cancer after completion of adjuvant trastuzumab -In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting	-In combination with **trastuzumab** and **capecitabine** for HER2 positive metastatic breast cancer, including patients with brain metastases, who have received ≥ prior anti-HER2 based regimens in the metastatic setting
Dose	With capecitabine: 1250mg PO daily on an empty stomach days 1-21 of a 21 day cycle With letrozole: 1500mg PO daily on an empty stomach	Adjuvant therapy: 240mg (6 tablets) once daily, with food, continuously for one year Metastatic therapy: 240mg (6 tablets) PO once daily, with food, continuously **Alternative schedule: 120mg PO daily week 1, 160mg daily week 2, 240mg daily week 3 and onward**	300mg PO twice daily in combination with trastuzumab and capecitabine

HER2 Inhibitors	Lapatinib	Neratinib	Tucatinib
Drug Interactions	Strong CYP3A4 inhibitors: Avoid concomitant use or consider dose reduction to lapatinib 500mg daily Strong CYP3A4 inducers: Avoid concomitant use or consider dose increase up to 4500mg daily or 5500mg daily as tolerated	Strong CYP3A4 inhibitors: avoid concomitant use Moderate CYP3A4 and P-gp dual inhibitors: avoid concomitant use Moderate/strong CYP3A4 inducers: avoid concomitant use P-gp substrates: monitor for adverse effects of drugs with narrow therapeutic indexes (e.g. digoxin, dabigatran) **Gastric Acid Reducing Agents**: avoid PPI's. Take neratinib 2 hours before or 10 hours after H2-receptor antagonists. Separate from antacids by 3 hours.	Strong CYP3A4 inhibitors: avoid concomitant use Moderate/strong CYP2C8 inhibitors (gemfibrozil, trimethoprim, lapatinib): Avoid concomitant use. If not possible then reduce tucatinib to 100mg twice daily CYP3A4 and P-gp substrates with narrow therapeutic ranges: avoid concomitant use if possible. If not, reduce the dose of the substrate according to recommendations for the agent.

HER2 Inhibitors	Lapatinib	Neratinib	Tucatinib
Renal Dysfunction	Not specifically studied but unlikely to be affected.	Not studied but unlikely to be affected	Unlikely to be affected by severe renal dysfunction, however, capecitabine is contraindicated with a CrCl <30 ml/min.
Hepatic Dysfunction	Severe dysfunction: -with capecitabine: reduce to 750mg once daily -with letrozole: reduce to 1000mg once daily	Severe dysfunction: reduce to 80mg once daily	Severe dysfunction: reduce to 200mg twice daily

HER2 Inhibitors	Lapatinib	Neratinib	Tucatinib
Clinical Pearls	Monitor closely for diarrhea and hand-foot syndrome	Diarrhea is a major side effect- ensure patients have loperamide and are counseled on prophylactic therapy. Median time to onset of ≥ Grade 3 diarrhea is 8-11 days	Diarrhea common. Counsel patients to manage with anti-diarrheal agents. Mean time to onset of first diarrhea episode is 12 days Has best data for brain mets

HER2 Inhibitors Drug Specific Adverse Effects

Lapatinib

- Diarrhea
  - Loperamide or other anti-diarrheal agents, replacement of fluids if severe
- Decreased LVEF
  - Monitor LVEF at baseline and periodically; majority of decreases occur within the first 3 months
- Hepatotoxicity
  - Monitor LFTs at baseline and every 4 to 6 weeks during treatment
- Skin reactions (rash or hand-foot syndrome)
- Interstitial Lung Disease (rare)

Neratinib

- Diarrhea
  - Provide loperamide prophylaxis during the 1st 2 cycles (56 days) of treatment.
  - Weeks 1-2: 4mg PO TID
  - Weeks 3-8: 4mg PO BID
  - Weeks 9+: 4mg as needed (not to exceed 16mg/d) titrating to 1-2 bowel movements/d
  - Neratinib dose adjustments exist for diarrhea
- Hepatotoxicity
  - Monitor LFTs at baseline and every month for the 1st 3 months then every 3 months while on treatment
- Stomatitis
  - Encourage oral hygiene
- Cardiotoxicity
  - Minimal change in LVEF seen in trials. Does not carry warnings for cardiotoxicity

Tucatinib

- Diarrhea
  - Antidiarrheals as needed
  - IVF if needed
- Hepatotoxicity
  - Monitor LFTs at baseline and as indicated
- Hanf-Foot Syndrome
  - Avoid long, hot showers
  - Use hypoallergenic moisturizers

Understanding Organ Toxicity: Management and Adverse Events of Chemotherapy

Common Terminology Criteria for Adverse Events (CTCAE)

- Commonly called the common toxicity criteria
- Standardized definitions used to describe the severity of organ toxicity for patients receiving cancer treatments
- The criteria are used for
    - Management of therapy administration
    - Dosing and in clinical trials to provide standardization
    - Consistency in the definition of treatment related toxicity

What Defines an Adverse Event

- Any unfavorable or unintended sign or symptom, illness or disease associated with the treatment, even if it is temporary

Toxicity Grading

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life threatening
- Grade 5: Death

Hematologic Toxicity

- Grading of chemotherapy induced decreases in blood counts, hemoglobulin, lymphocytes, neutrophils and platelets
- Occurs because of effects of treatment on bone marrow
- Areas covered in hematologic toxicities are
    - Anemia
    - Febrile neutropenia
    - Disseminated intravascular coagulation (DIC)
    - Hemolysis
    - Spleen disorder
    - Hemolytic uremic syndrome

Anemia

- Treatment is the most common cause of anemia in cancer patients
- Consequences of anemia
    - Impaired functional status
    - Diminished physiologic reserve
    - Fatigue that can be disabling
- Three main factors contribute to anemia in any patient
    - Red blood cell (RBC) loss
    - Increased RBC destruction
    - Decreased RBC production

Considerations

- Is the anemia a direct effect of the malignancy itself
    - Internal or external bleeding
    - Impaired absorption of nutrients
- Is anemia an effect of the product of malignancy
    - Hemolysis, thrombotic thrombocytopenic purpura, (TTP), disseminated intravascular coagulation (DIC)
- Is anemia an effect of the treatment
    - Chemotherapy
    - Radiation therapy

Nursing Considerations: Assessment

- Patient medical history
- Treatments and medications
- Signs and symptoms
- Diagnostic tests
    - Labs
        - Complete blood count
        - Chemistry panel
- Educate patient on signs and symptoms of anemia
    - Give patient symptoms guidelines that they should alert nurse or physician

Management

- Remove the malignancy
- Transfuse packed red blood cells (PRBC's) as indicated
- Administer recombinant erythropoietin stimulating agents (ESA)

Erythropoietin Stimulating Agents

- Information surrounding the administration of ESAs
  - The presence of anemia has been linked to an adverse prognosis
  - ESA use in patients with cancer has become controversial because of data linking ESA use to an excess of thromboembolic events, inferior survival, and worse cancer outcomes
  - There is general agreement that ESAs are not indicated in anemic cancer patients who are not receiving chemotherapy
  - Whether ESAs should be avoided in patients who are receiving myelosuppressive chemotherapy with the intent of cure remains controversial

Thrombocytopenia

- A decrease in circulating platelets below 100,000/mm^3
- Normal platelet count is 150,000-400,000/mm^3
- Major function of platelets is to prevent blood loss by initiating clot forming mechanisms

Nursing Considerations

- Monitor platelet counts
- Implement thrombocytopenic precautions
- Educate patient and family members on precautions and recognize signs and symptoms of bleeding

Management

- Transfuse as necessary
- Assess patient for signs and symptoms of bleeding

Neutropenia

- An abnormal decrease in the number of neutrophils in the blood
- Neutropenia lasting longer than 7 days and an absolute neutrophil count < 500 increase the patient's risk of infection

Nursing Considerations

- Monitor neutrophil count daily
- Implement neutropenic precautions
- Educate patient and caregiver of signs and symptoms of infection and neutropenic precautions

Cardiac Toxicity

- An alteration in cardiac function related to cancer treatment which includes
    - Heart failure
    - Right ventricle dysfunction
    - Left ventricle dysfunction
    - Hypotension
    - Hypertension
    - Sinus bradycardia
    - QTc interval prolongation

Risk Factors

- Pre-existing cardiac conditions
- Age
- Radiation to chest in the combination with cardio-toxic chemo
- Cumulative drug doses
- Receiving multiple cardio-toxic drugs
- Hematopoietic cell transplantation
- Host susceptibility
- Hepatic or renal dysfunction
- Smoking
- Diabetes

Toxicity

- Differ based on drug, dose, rate of infusion, overall treatment plan, and past treatments
- The most common drug class implicated in cardiac toxicity is the anthracycline class
    - Other common drugs and drug classes that can cause cardiac toxicity are;
        - 5-Fluorouracil (5-FU)
        - Cyclophosphamide and Ifosphamide
        - Taxanes
        - Cisplatin, mitomycin, and busulfan
        - Trastuzumab, lapatinib, sunitinib, sorafenib, rituximab, imatinib, bevacizumab
        - IL-2 and arsenic trioxide

Cardiac Toxicity of Anthracycline

- Class of drug most commonly implicated in cardiotoxity
- The toxicities can be divided into acute and chronic
- The chronic toxicities are mostly linked to a cumulative dose of anthracyclines
- Attempts at altered dose schedules and administration of Totect and Zinecard (dexrazoxane) have not reduced cardiac toxicity

Cardiac Toxicity: Acute vs. Chronic

Acute
- EKG changes
- Arrhythmias
- Heart block
- Ventricular dysfunction
- An increase in plasma brain natriuretic peptide
- Ischemia
- Vasospasms

Chronic
- Cardiomyopathy
- Congestive heart failure
- Low voltage QRS

Anthracyclines Acute Toxicity
- Less common occurring
- Most resolved within one week of occurrence, not life threatening
- Cardiac monitoring is not typically recommended for patients with normal cardiac functions

Management
- Baseline EKG
- Cardiac enzymes
- Correct electrolyte imbalances
- Treat arrhythmia with medication

Anthracycline Chronic Toxicity
- Adults usually present within a year of therapy
- Survival has improved due to more aggressive medical management, including medications such as ACE inhibitors and beta blockers
- In childhood cancer survivors treated with anthracycline many have cardiac dysfunctions

Cardiotoxicity: Doxorubicin Cumulative Dose
- Recommended not to exceed 400-550 mg/m2 in adults

Nursing Considerations
- Thorough history and physical including any pre-existing cardiac conditions
- Monitor cardiac functions throughout treatment and after
- Keep track of cumulative dose of anthracyclines
- Educate patient on importance of informing medical team if any symptoms arise

GI Toxicity/Mucositis: Nausea and Vomiting

- Acute nausea: Occurs within first 24 hours of treatment usually at 1-2 hours
- Delayed nausea: Occurs more than 24 hours after treatment
- Vomiting categorized by number of times vomited in a day and time period between those times
- Anticipatory nausea: Occurs as a conditioned response from previous chemo treatments
    - May occur before during or after treatment
- Breakthrough nausea and vomiting: Nausea and vomiting that occurs within 5 days of prophylactic use of antiemetic's and requires treatment
- Refractory nausea and vomiting: Nausea and vomiting that does not respond to treatment

Medications for Nausea

Major Neurotransmitter Targets	Medication Class	Drugs
Serotonin	5HT3 antagonists	Ondansetron and granisetron
Neurokinin	NK-1 antagonists	Aprepitant
Dopamine	D-2 antagonists	Prochlorperazine
Histamine	H-1 antagonist	Promethazine
Acetylcholine	Muscarinic	Scopolamine
Cannabinoid	Cannabinoid agonist	Dronabinol

Nausea Medications Adverse Events and Nursing Implications

Medication/Drug Classification	Adverse Event	Nursing Implementation
Ondansetron/ Serotonin agnostic	• Headache, fever • Diarrhea, constipation • Transient increase in serum AST/GPT	• Assess for headache and fever, may give Tylenol if indicated • Assess number and consistency of stools • Monitor liver functions
Granisetron/ Serotonin agnostic	• Headache • Constipation	• Assess for headache and severity of headache • Assess for bowel regularity
Palonosetron/Serotonin agnostic	• Headache • Constipation	• Assess for headache and severity • Assess for bowel regularity

Aprepitant/ NK-1 antagonist	• Constipation or diarrhea • Hiccups • Tiredness	• Assess bowel regularity • Assess level of sedation • Avoid alcohol and CNS depressants • Avoid tasks that require alertness
Prochlorperazine /D-2 antagonist	• Sedation • Blurred vision • Orthostatic hypotension • Dry mouth	• Avoid alcohol and other CNS depressants • Avoid tasks that require alertness • Assess vision and impact on safety • Monitor patient for orthostatic changes • Educate patient to rise slowly from lying or sitting position • Suck on ice chips or hard candy • Frequent intake of fluids
Promethazine/ H-1 antagonist	• Sedation • Hypotension • Dry mouth • Urine retention	• Monitor level of consciousness • Monitor vital signs • Suck on ice chips or hard candy • Drink plenty of fluids • Monitor intake and output
Lorazepam/ Benzodiazepine	• Sedation • Dizziness • Weakness • Anterograde amnesia	• Assess level of conscious • Assess memory

Nursing Considerations

- Assess patient's nausea and vomiting
- Administer medication as per order
- Non-pharmacologic interventions
    - Meditation
    - Warm/cold compress
    - Music

Mucositis

- Mucositis is an inflammatory process that affects the mucous membranes of the oral cavity and gastrointestinal tract
- Estimated to occur in about 40% of patients secondary to chemotherapy and almost 100% of those receiving radiation for head and neck cancer
- Approximately 80% of those undergoing hematopoietic stem cell transplantation will experience some level of oral mucositis

Treatment of Specific Risk Factors

- Age
- Poor oral health and hygiene
- Reduced salivary secretion
- Genetic factors
- Low body mass index
- Decreased renal function
- Tobacco use
- Previous cancer treatment with chemo or radiation
- Poor nutritional status
- Higher levels of oral microflora
- Inflammation

Radiation Therapy

- Increased risks for those patients with primary cancers of the oral cavity, oropharynx, or nasopharynx.
- Radiation treatment with > 5,000 Gray
- Those treated with more than one radiation treatment a day

Chemotherapy

- Antimetabolites such as 5FU, and MTX
- Alkylating agents such as melphalan, and busulfan
- Antitumor agents such as dactinomycin, doxorubicin, and epirubicin
- Taxanes such as docetaxel and paclitaxel

Nursing Considerations

- Manage pain
- Rinse mouth four times a day after meals with bland solutions such as normal saline
- Water based moisturizers to protect lips
- Educate patient on proper oral hygiene
- Educate patient to avoid tobacco, and alcohol

Hepatic Toxicity

- Occurs when drug metabolites cause damage and inflammation to liver cells or blood flow to liver is occluded
- Inhibits liver's ability to metabolize drugs
- Leads to fatty changes, necrosis, and fibrosis

Clinical Manifestations

- Insidious
- Can range from asymptomatic with abnormal lab values to an acute illness resembling viral hepatitis
- Distinguishing between drug induced hepatotoxicity and other causes of liver injury can be difficult
- An abdominal ultrasound could assist in determining cause

Hepatitis
- Jaundice, anorexia, fever, right upper quadrant (RUQ)/epigastric abdominal pain, abdominal distension due to ascites

Portal Hypertension
- Often asymptomatic until a problem develops

Splenomegaly
- Abdominal wall collateral vessels and thrombocytopenia

Liver Failure
- Fatigue/malaise, lethargy, anorexia, N/V, RUQ pain, pruritus, jaundice, abdominal distension, and subtle mental status changes
- As liver failure develops the symptoms usually become more severe, including hepatic encephalopathy, confusion, or eventually comatose

Management: Hepatic Toxicity
- Some agents cause reversible toxicity while others are associated with a progressive course that can lead to fibrosis or cirrhosis
- Toxicity will generally recur upon reintroduction of the offending substance if the reaction was immunologically based
- Patients with pre-existing liver disease should receive treatment for that disorder prior to starting chemotherapy to attempt to minimize the hepatotoxicity of the treatment
- Dose adjustments should occur appropriately based on pretreatment liver function

Management: Liver Failure/Hepatitis
- Managing patients with acute liver failure requires a thorough understanding of the complications that may develop
- Metabolic disturbances, encephalopathy, cerebral edema, seizures, and renal failure
- Correct electrolyte imbalances, decrease ammonia levels, monitor intracranial pressure and preserve renal function

Management: Portal Hypertension
- Manage the underlying cause
- Assess for the presence of esophageal varices, manage bleeding if it is occurring
- Assess for ascites, put patient on sodium restriction, utilize diuretics
- Dose reduce or discontinue medication

Management: Renal and Urinary Tract Toxicity
- Acute kidney injury
- Graded by creatinine level and whether or not dialysis is needed
- Hemorrhagic cystitis
- Proteinuria
    - Graded simply by the amount of protein present in the urine

Risk Factors

- Intravascular volume depletion due to external losses or fluid sequestration
- Concomitant use of other nephrotoxic drugs
- Radiographic ionic contrast media in patients with or without preexisting renal dysfunction
- Urinary tract obstruction secondary to tumor
- Intrinsic renal disease

Management and Treatment

- Prevention/risk reduction with the use of chemo-protectants such as mesna and amifostine
- Aggressive and adequate hydration
- Electrolyte monitoring
- Maintain hemodynamic status
- Urine alkalization
- Forced diuresis
- Monitor labs

Hemorrhagic Cystitis

- Monitor and measure hematuria
- Evaluate for signs and symptoms of urinary obstruction
- Encourage frequent bladder emptying
- Maintain aggressive hydration
- Utilize three-way Foley with irrigation if indicated

Pulmonary Toxicity

- Pulmonary edema and effusions
- Interstitial lung disease (ILD), pulmonary fibrosis, and pneumonitis
- Acute respiratory distress
- Respiratory infections
- Wheezing and bronchospasms

Risk Factors

- Radiation therapy to the chest
- Underlying pulmonary disease
- Multiple drugs that cause pulmonary toxicity
- Hepatic or renal impairment

Pneumonitis

- Inflammation of the lung caused by a chemical or immune mediated response
- Clinical Manifestations
    - Cough, dyspnea, fatigue, fever, pulmonary infiltrates

ILD

- Persistent pneumonitis
- Clinical Manifestations
    - Chronic dyspnea and cough
    - Progressive scarring of lungs leads to fibrosis

Fibrosis

- Loss of elasticity, hardening of lung tissue

Management

- Stop the drug, steroids, manage symptoms, supportive care

Neurological Toxicities

- Dysfunction of cranial nerves
    - Akathisia
    - Amnesia
    - Aphonia
    - Arachnoiditis
    - Ataxia
- Peripheral neuropathy
- Cognitive dysfunction
- Acute encephalopathy
- Ischemia cerebrovascular
- Extrapyramidal disorder
- Autonomic dysfunction
- Agitation
- Anxiety

Neurological: Risk Factors

- Drug dosage
- Radiation to the head
- Intrathecal administration
- Age
- Central Nervous System (CNS) depressants
- History of diabetes or chronic alcohol abuse
- Renal or hepatic dysfunction

Peripheral Neuropathy

- Sensory Clinical Manifestations:
    - Arthralgia, myalgia, paresthesia, sensory loss
- Motor Clinical Manifestations
    - Decrease or loss of deep tendon reflexes, foot drop, muscle weakness and atrophy

Management

- Assess severity and impact on patient's life
- Dose reduce or discontinue the drug
- Consult physical or occupational therapy
- Decrease pain and increase function
- Maintain safety

Ototoxicity

- Related to the cumulative dose effects of cisplatin
- Symptomatic hearing loss occurs in 15-20% of patients
    - Audiometric evidence of impaired hearing appears in 75% of patients
- Early detection of the ototoxicity by audiometry, may minimize the severity of the impairment of sounds recognized for speech

Acute Encephalopathy: Risk Factors

- Significant fluid overload, mean BP greater than 25% of baseline, creatinine greater than 1.8 mg/dL
- Associated with reversible abnormalities in the white matter of the occipital, parietal, and frontal lobes

Clinical Manifestations

- Altered mental status
- Behavioral changes
- Confusion
- Cognitive dysfunction
- Lethargy
- Seizures
- Somnolence
- Hypertension

Diagnosis

- Confirmed by brain MRI and distinct changes in white matter

Treatment

- Stop or dose reduce the offending agent, manage hypertension, seizure prophylaxis

Cognitive Dysfunction

Effects
- Language
- Memory
- Concentration
- Attention
- Multitasking
- Coping
- Performance
- Emotions

Multifactorial Causes
- Cancer
- Changes in hormones
- Side effects
    - Anemia
    - Fatigue
    - Insomnia
    - Neurologic irritation/dysfunction
- Emotions
    - Anxiety
    - Depression
    - Fear

Risk Factors
- Women
- High dose regimens

Treatments
- Assess and manage causative factors
- Orient frequently with calendars and clocks
- Ensure patient safety
- Educate the patient, family members and caregivers

Immunotherapy Goal
- Augment the immune system to create an anti-tumor T-cell response

Mechanism of Action
- Increase activity of T-cells
- Decrease the activity of T-cell suppressors

FDA Approved Novel Immunotherapies

- Bi-Specific T-cell engager antibodies (BiTEs)
- CTLA4 checkpoint inhibitor
- Chimeric antigen receptor (CAR) T-Cells
- Dendritic cell vaccines
- Oncolytic viruses
- PD-1 checkpoint inhibitors
- PD-L1 checkpoint inhibitor
- Peptide vaccines
- T-cell clones
- Tumor infiltrating lymphocytes (TIL)

Toxicity

- Result from stimulation of the immune system by the drug
- Hyper proliferation of lymphocytes and cytokine release
- Can range from mild to severe specific syndromes to severe organ dysfunction

Immune System Toxicities

- Allergic reaction
- Anaphylaxis
- Autoimmune disorder
- Cytokine release syndrome

Adverse Effects

- Related to increased T-cell activity
- More common in CTLA4 checkpoint inhibitors
- Immune response adverse events (irAEs)
    - Cutaneous/mucosal irritation
    - Diarrhea/colitis
    - Hepatotoxicity
    - Pneumonitis
    - Endocrinopathies

Vascular Toxicities

- Flushing
- Hematoma
- Hot flashes
- Hypertension
- Hypotension
- Lymphedema
- Phlebitis
- Capillary leak syndrome

Capillary Leak Syndrome

- A toxicity in which intravascular fluids leak into the tissue space causing generalized edema and can lead to organ failure

Other Adverse Event Reporting Systems

- PRO-CTCAE: Patient reported outcomes consider the patient's perspective on adverse events
    - Not yet in widespread use
- Reports that compared CTCAE and PRO ratings using various PRO measures of adverse events found fair to moderate agreement between the two systems, with large variations in many of the studies
- Radiation Therapy Oncology Group (RTOG): For some toxicities related to radiation therapy
- World Health Organization (WHO) Adverse Drug Reaction Terminology (WHO-ART): International drug monitoring

Homework

Use the following regimen to complete the following case study information. The answers will be reviewed and discussed during the Review session.
Hyper-CVAD/MTX-Ara-C

Course 1:

- Cyclophosphamide 300mg/m2 IV over 3 hours every 12 hours for 6 doses on day 1 (8/1/17), day 2 (8/2/17), and day 3 (8/3/17). Start first dose at 8am.
- Doxorubicin 50mg/m2 IV over 48 hours on day 4 (8/4/17) at 8am.
- Vincristine 2mg IV over 15 minutes on day 4 (8/4/17) at 8am. Repeat on day 11 (8-11-17) at 8am.
- Dexamethasone 40mg/day IV on day 1 (8/1/17), day 2 (8/2/17), day 3 (8/3/17) and day 4 (8/4/17) and day 11 (8/11/17), day 12 (8/12/17), day 13 (8/13/17), and day 14 (8/14/17)
- Administer 30 minutes prior to chemotherapy
- Filgrastim 5mcg/Kg sq daily until ANC > 500. Start day 8 (8/8/17) at 8am.

Course 2**:**

- Methotrexate (MTX) 200mg/m2 over 2 hours IV on day 1 (9/5/17) at 8am
- MTX 800mg/m2 over 22 IV hours on day 1 (9/5/17) at 10am
- Cytarabine 3,000mg/m2 IV over two hours every 12 hours for 4 doses on day 2 (9/6/17), and day 3 (9/7/17): First dose at 8am
- Leucovorin 50mg IV every 6 hours until MTX level <50nM: Start day 2 (9/6/17) at 8pm
- Filgrastim 5mcg/Kg SQ daily until ANC > 500: Start on day 4 (9/8/17) at 8 pm

1. Calculate the doses for all medications using actual body weight
    - BT is 6 ft 3 in tall and weighs 270 pounds
    - SA is 5 ft 1 inch tall and weighs 90 pounds

	BT dose	SA dose
Course 1:		
Cyclophosphamide 300mg/m2		
Doxorubicin 50mg/m2		
Vincristine 2mg		
Filgrastim 5mcg/Kg		
Course 2:		
Methotrexate Bolus 200mg/m2		
Methotrexate Infusion 800mg/m2		
Cytarabine 3,000mg/m2		
Filgrastim 5mcg/Kg		

_____
_____
_____
_____
_____

2. For each chemotherapeutic agent in the regimen list:
    - 2 pretreatment physical assessments
    - 2 labs, diagnostic studies
    - 1 indication dose reduce or hold the dose
    - 2 components of patient/ family education for each agent

	2 Physical Assessments	Labs and/or Diagnostic Studies	Variables to Reduce or Hold Dose	2 Patient/ Family Education Aspects
Course 1				
Cyclophosphamide				
Doxorubicin				
Vincristine				

_____
_____
_____
_____
_____

	Physical Assessments	Labs and/or Diagnostic Studies	Variables to Reduce or Hold Dose	Patient/ Family Education
Course 2				
Methotrexate				
Cytarabine				
Leucovorin				

3. List 2 co-morbid conditions may impact the patient's ability to receive full doses of each of these agents or at least require closer monitoring?

   A.

   B.

_____
_____
_____
_____
_____

4. On the attached calendars write in the schedule, including start times, for all agents.

Course 1

August 2017						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

_____
_____
_____
_____
_____

Course 2

September 2017						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

_____
_____
_____
_____
_____

Case Study One

JK is a 62 y/o female who noted a nodule in her breast 4 weeks ago. Work-up revealed breast cancer with the sentinel lymph node dissection positive for malignant T-cells. The plan is to begin chemotherapy at this time. She is now presenting to you for her first dose of chemo. You obtain the following information:

Weight: 122 kg Height: 5'5" BP: 160 / 98 P: 68 RR: 20 T: 37.4 C

Lab Test	JK's Lab Values	Reference Range
CBC		
WBC	5. 5 x 103/cu mm	(4.3 - 10.8 x 103/cu mm)

Differential:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils:
  ○ Bands
  ○ Segmented
• Platelets
• Hgb
• Hct
	
	40 %
	
	2%
	55%
	250 K
	12 gm/dl
	35%
		
		0 %
		0 %
		(20 - 40%)
		3 %
		
		(0%)
		(40 - 60%)
		(200 -400K)
		(13 - 18 gm/dl)
		(37 - 48%)

Chemistry		
Na+	140 mEq/L	(135 - 145)
K+	3.5 mEq/L	(3.5 - 5.0)
Cl-	100 mEq/L	(95 - 106)
Phos	3.8 mg/dl	(3.0 - 4.5)
Glucose	106 mg/dl	(70 - 110)
BUN	10 mg/dl	(8 - 25)
Cr	0.8 mg/dl	(0.6 - 1.5)
Mg	1.7 mEq/L	(1.5 - 2.0)

Calculate JK's ANC

$$ANC = \frac{(\%\ \text{neutrophils} + \%\ \text{bands})}{100} \times WBC$$

Show your work:

The physician orders paclitaxel (Taxol) 135mg/m2 and carboplatin (Paraplatin) with an AUC 4. The physician calculates JK's drug doses at:

- paclitaxel (Taxol): 330 mg
- carboplatin (Paraplatin): 660 mg

The physician hands you JK's orders to check. You must calculate JK's drug doses for paclitaxel and carboplatin. Calculate JK's BSA:

Formulas

Weight Conversion Formula	Pounds = Kg x 2.2	Kilograms = lbs ÷ 2.2
Height Conversion Formula	Inches = cm ÷ 2.54	Centimeters = in x 2.54
BSA (m2) =	$\frac{\text{height (in) x weight (lbs)}}{3131}$	$\frac{\text{height (cm) x weight (Kg)}}{3600}$

Calculate JK's paclitaxel dose:

Drug dose = ordered dose x BSA

Show your work:

You determine that your dose is not the same as the dose the physician ordered. You must follow the 10% rule to determine if the written dose (dose calculated by the physician) is safe to administer. Calculate the 10% rule:

Formulas

Method 1	Method 2
	10% = your dose x 0.1
Upper Limit = your dose x 1.10	Upper Limit = your dose + 10%
Lower Limit = your dose x 0.90	Lower limit = your dose – 10%
	10% = your dose x 0.1

Show your work

The safe administration range is _____ mg - _____ mg.

Is the physician's dose safe to administer (circle your answer) Yes No

Calculate JK's carboplatin dose:

Female CrCl = $\left(\frac{(140 - \text{age}) \times \text{Weight in Kilograms}}{72 \times \text{Serum Creatinine}} \right) \times 0.85$

Calvert Formula: Dose in mg = AUC x (CrCl + 25)

Show your work

What would JK's carboplatin dose be if she were a male? _____

_____
_____
_____
_____
_____

Case Study Two

MR is a 74 y/o male who presented with persistent mild cough, concerning for recurrent sinus malignancy. Work-up revealed a new malignancy: T4N1 non-small cell lung cancer. The plan is to begin definitive chemoradiotherapy. He is now presenting to you for his first dose of chemo. You obtain the following information:

- Weight: 77 kg
- Height: 5'9"
- BP: 149 / 65 P: 71 RR: 18 T: 97.8 F

Lab Test	MR's Lab Values	Reference Range
CBC		
WBC	6.3 x 10^3 /cu mm	(3.8 - 10.6 x 10^3 /cu mm)
Differential:		
Basophils	0 %	(0 -1%)
Eosinophils	3.8 %	(0 - 6%)
Lymphocytes	14 %	(13 - 44%)
Monocytes	9.5 %	(4 - 13%)
Neutrophils:		
Bands	0%	(0%)
Segmented	71.3%	(40 - 60%)
Platelets	302 K	(156 -369K)
Hgb	8.3 gm/dl	(13 - 17 gm/dl)
Hct	25.1 %	(38 - 48%)

Chemistry		
Na+	139 mEq/L	(136 - 146)
K+	3.5 mEq/L	(3.5 - 5.0)
Cl-	109 mEq/L	(98 - 107)
Phos	3.2 mg/dl	(2.5 - 4.6)
Glucose	145 mg/dl	(70 - 99)
BUN	15 mg/dl	(8 - 26)
Cr	0.9 mg/dl	(0.5 - 1.4)
Mg	2.0 mEq/L	(1.6 - 2.3)

Calculate MR's ANC:

ANC = (% neutrophils + % bands) x WBC

100

Show your work:

Is patient neutropenic? (circle answer) Yes No

If yes, who and how neutropenic is the patient?

_____

_____

_____

_____

_____

_____

Let’s do another:

Lab Test	Lab Values	Reference Range
CBC		
WBC	0.9 x 10^3 /cu mm	(3.8 - 10.6 x 10^3 /cu mm)
Differential:		
Basophils	0 %	(0 - 1%)
Eosinophils	0 %	(0 - 6%)
Lymphocytes	2 %	(13 - 44%)
Monocytes	10 %	(4 - 13%)
Neutrophils:		
Bands	2%	(0%)
Segmented	84%	(40 - 60%)
Platelets	10 K	(156 -369K)
Hgb	7.8 gm/dl	(13 - 17 gm/dl)
Hct	22 %	(38 - 48%)

Calculate ANC:

ANC = (% neutrophils + % bands) x WBC

100

Show your work:

_____
_____
_____
_____
_____

Is patient neutropenic? (Circle answer) Yes No

If yes, who and how neutropenic is the patient?

_____

The physician orders weekly nab-paclitaxel (Abraxane) 40mg/m2 and carboplatin (Paraplatin) with an AUC 2 for the patient to receive with CRT. The physician calculates MR's drug doses at:

- nab-paclitaxel (Abraxane): 75 mg
- carboplatin (Paraplatin): 207 mg

The physician hand you MR's orders to check. You must calculate MR's drug doses for nab-paclitaxel and carboplatin.

Calculate MR's BSA:

Pounds = Kg x 2.2 Kilograms = lbs ÷ 2.2

Inches = cm ÷ 2.54 centimeters = in x 2.54

$$\text{BSA (m2)} = \frac{\text{(inches) x weight (lbs)}}{3131} \quad \frac{\text{height (cm) x weight (Kg)}}{3600}$$

Show your work:

Calculate MR's nab-paclitaxel dose:

Drug dose = ordered dose x BSA

Show your work:

_____
_____
_____
_____
_____

You determine that your dose is not the same as the dose the physician ordered. You must follow the 10% rule to determine if the written dose (dose calculated by the physician) is safe to administer.

Calculate the 10% rule:

Method 1:

Upper Limit = your dose x 1.10

Lower Limit = your dose x 0.90

Method 2:

10% = your dose x 0.1

Upper Limit = your dose + 10%

Lower limit = your dose – 10%

Show your work:

The safe administration range is _____ mg - _____ mg.

Is the physician's dose safe to administer (circle your answer) Yes No

_____
_____
_____
_____
_____

Calculate MR's carboplatin dose:

$$\text{Male CrCl} = \frac{(140 - \text{age}) \times \text{Weight in Kilograms}}{72 \times \text{Serum Creatinine}}$$

Calvert Formula

Dose in mg = AUC x (CrCl + 25)

Show your work:

What would MR's carboplatin dose be if he were a female? _____

Appendix A

Antineoplastic Therapy Formulas

Metric to English Conversions

1 kg = 2.2 lbs

1 inch = 2.54 centimeters

BSA

$$\text{BSA } (m^2) = \text{metric units} \quad \sqrt{\frac{\text{height (cm)} \times \text{weight (Kg)}}{3600}}$$

$$\text{BSA } (m^2) = \text{English units} \quad \sqrt{\frac{\text{(inches)} \times \text{weight (lbs)}}{3131}}$$

ANC

$$\text{ANC} = \frac{(\%\ \text{neutrophils} + \%\ \text{bands})}{100} \times \text{total WBC}$$

Creatinine Clearance Formula

$$\frac{(140 - \text{age}) \times \text{Weight in Kilograms}}{72 \times \text{Serum Creatinine}} = \text{CrCl males}$$

$$\left(\frac{(140 - \text{age}) \times \text{Weight in Kilograms}}{72 \times \text{Serum Creatinine}}\right) \times 0.85 = \text{CrCl females}$$

Calvert Formula

Dose in mg = AUC x (CrCl + 25)

Appendix B

Oncology Drug Handling Precautions

National Institute for Occupational Safety and Health (NIOSH)

- Through the Centers for Disease Control and Prevention (CDC)
- Hazardous drug exposures in healthcare
    - Important in Oncology due to risk of exposure to hazardous drugs
    - Antineoplastic agents

Oncology Drug Handling Precautions

- UPMC employees can access the list of oncology drug handling precautions through the Infonet

Access Infonet

- Infonet→Clinical Tools→Standards of Care→Pharmacy→Hazardous Drug Risk Assessments>Hazardous Drug Chart OR:
- https://infonet.upmc.com/Pages/default.aspx
- Search
    - In the search bar type in; NIOSH list, drug excretion list, antineoplastic excretion, oncology drug handling precautions list and click search
    - Document selection
    - Click on the document titled Oncology Drug Handling Precautions List
    - Drug handling list

Medication Name	Dosage Form[1]	Patient Care Areas		Pharmacy	
		Administration Precautions	Excretion Precautions[2] (PPE and Duration)	Medication Pre-pack	Compounding/Manipulation (Sterile and Non-sterile)
Omacetaxine	Subcutaneous	High	A/HDP	-	High + RESP
Ospemifene	Tablet (intact)	Low	A/HDP	High + RESP	-
	Tablet (crushed)	High + RESP	A/HDP	High + RESP	High + RESP
Oxaliplatin	Injection (CSTD)	High	A/HDP	-	High + RESP
OXcarbazepine	Tablet, Immediate Release (intact)	Low	A/HDP	High + RESP	
	Tablet, Immediate Release (crushed)	High + RESP	A/HDP	High + RESP	High + RESP
	Tablet, Extended Release (intact)	Low	A/HDP	High + RESP	-
	Oral Suspension	High	A/HDP	High + RESP	High + RESP
Oxytocin	Intramuscular	Low	SP	-	High
	Injection	Low	SP		High

	Low: single gloves		Long excretion precautions (7 days after last dose)
	High: full PPE (2 pairs of gloves, gown, face shield if splash risk)		Short excretion precautions (72 hours after last dose)
	High + RESP: Full PPE + N95/PAPR or appropriate ventilation	A/HDP	Antineoplastic/Hazardous Drug Precautions: gloves and gown; face shield if splashing is anticipated
CSTD	Closed system transfer device	SP	Standard Precautions: single gloves
*	Charcoal adsorbent vapor precautions for spill/PAPR for compounding	^^	Excretion via sweat, additional precautions necessary

Updated 7.2024

Updated 7.2024