NEW OPTIONS TO TREAT ADVANCED HEPATOCellular CARCINOMA

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Learning Objectives

- Evaluate imaging criteria in HCC staging.
- Assess efficacy of biomarkers in early detection of HCC.
- Examine the effect of novel systemic agents on HCC.
- Identify the role of surgery and transplantation in treatment of HCC.
BCLC (Barcelona Clinic Liver Cancer) Staging

- Stage 0
  - PS 0, Child-PuGh A
  - Very early Stage 0: Single < 2cm
  - Early Stage (A): Single or 3 nodules < 3cm, PS 0
  - Portal pressure/bilirubin: Increased, Associated diseases: No, Yes
  - Resection, Liver Transplantation, RFA

- Stage D
  - PS > 2, Child-PuGh C
  - Intermediate Stage (C): Portal invasion, N1, M1, PS 1-2
  - Terminal Stage (D)
  - TACE, Sorafenib

- Stage A-C
  - PS 0-2, Child-PuGh A-B
  - Intermediate Stage (B): Multinodular, PS 0

- Curative treatments
- Palliative treatments

- Symptomatic treatments

Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing “capsule”
- LR-5 – if nonperipheral “washout” OR threshold growth

If unsure about the presence of any major feature: characterize that feature as absent
What is the percentage of HCC and malignancy associated with each LI-RADS category??

The percentage (with 95% confidence intervals) associated with LR-1, LR-2, LR-3, LR-4, LR-5, and LR-M is summarized below:

- **LR-1**: 0% HCC, 18% malignancy
- **LR-2**: 16% HCC, 39% malignancy
- **LR-3**: 37% HCC, 39% malignancy
- **LR-4**: 74% HCC, 81% malignancy
- **LR-5**: 95% HCC, 98% malignancy
- **LR-M**: 37% HCC, 94% malignancy

⚠️ Estimates may be inflated by selection bias for histology-sampled lesions.
Methylated DNA

- Two of four bases can be methylated: cytosine, adenine
- In mammals, DNA methylation exclusively in CpG dinucleotides
  - 75% of CpG methylated in somatic cells - increases frequency of spontaneous mutations (CpG converts to TpG)
  - Exception: CpG islands that are unmethylated (>200 bp, GC content >50%)
  - 25,000 CpG islands in human genome, 50% in gene promoter regions
- In cancer: CpG islands acquire hypermethylation causing transcription silencing of DNA repair gene
Combined methylated DNA and protein markers: an accurate blood-based test for early-stage detection of hepatocellular carcinoma

Aim:
To identify a panel of blood-based biomarkers with high sensitivity for early-stage detection of hepatocellular carcinoma

Methods:
- Multi-center, case-control study
- Patient population: 135 HCC cases; 305 age- and liver disease etiology-matched controls
- Whole blood collected at clinical sites and shipped to central lab for processing; samples blinded upon delivery
- 10 methylated DNA markers (MDMs) and multiple proteins evaluated via logistic regression algorithm to classify samples as positive or negative for HCC

Main Findings:
At 90% specificity, a panel of 4 MDMs (DAB2IP, EMX1, HOXA1, TSPYL5) and 2 proteins (AFP, AFP-L3) detected 71% of early-stage HCC.

Conclusions:
We identified a panel of 6 biomarkers with significantly higher sensitivity for early-stage HCC compared to AFP with or without AFP-L3.

Chalasani N, et al., Abstract 109

<table>
<thead>
<tr>
<th>Biomarker Panel</th>
<th>Early Stage* Sensitivity (95% CI)</th>
<th>All Stage Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exact (4 MDM + 2 Protein)</td>
<td>71% (60-81%)</td>
<td>80% (72-86%)</td>
<td>90% (86-93%)</td>
<td>0.912 (89-94%)</td>
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<tr>
<td>AFP (20 ng/mL)</td>
<td>21% (13-32%)</td>
<td>43% (35-52%)</td>
<td>98% (95-99%)</td>
<td>0.706 (66-76%)</td>
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<tr>
<td>AFP (100 ng/mL)</td>
<td>6.6% (2-15%)</td>
<td>27% (20-36%)</td>
<td>100% (99-100%)</td>
<td>0.637 (58-69%)</td>
</tr>
<tr>
<td>AFP (5 ng/mL) + AFP-L3 (4%)</td>
<td>37% (26-49%)</td>
<td>55% (46-63%)</td>
<td>94% (90–96%)</td>
<td>0.795 (75-84%)</td>
</tr>
</tbody>
</table>

*Early Stage = BCLC Stage 0 and A
Direct-acting antiviral therapy for HCV infection is associated with increased survival in patients with a history of hepatocellular carcinoma

Aim:
Evaluate if direct acting antiviral (DAA) therapy improves survival in patients with a history of complete response to hepatocellular carcinoma (HCC) treatment

Methods:
Multicenter retrospective cohort study examining the association between DAA therapy and all-cause mortality in 797 patients with hepatitis C-related HCC who achieved complete response to HCC treatment

Main Findings:
DAA therapy was associated with significantly reduced mortality (HR 0.54, 95% CI 0.33–0.90); this association was observed in patients who achieved SVR (HR 0.29, 95% CI 0.18–0.47) but not those without SVR (HR 1.13, 95% CI 0.55–2.33).

Conclusions:
In a large cohort of North American patients with complete response to HCC treatment, DAA therapy was associated with significantly reduced mortality.

Singal AG, et al., Abstract 199
797 patients with HCV-related HCC:
  • 383 (48.1%) received DAA therapy
  • 414 (51.9%) were untreated

Deaths:
  • 43 deaths occurred during 941 person-years of follow-up among DAA
  • 103 deaths during 527 person-years among DAA-untreated patients
  • crude rate ratio 0.23, 95% CI 0.16–0.33

  • Median time from HCC complete response to death:
    • 25.7 (IQR 19.4–33.9) months- DAA-treated patients
    • 11.5 (IQR 7.1–20.2) months- untreated patients

Multivariable analyses:
  • DAA therapy was associated with significantly reduced mortality (HR 0.39, 95% CI 0.26–0.61)
  • Association driven by SVR, with reduced mortality observed in DAA-treated patients
    who achieved SVR (HR 0.26, 95% CI 0.16–0.42) but not those without SVR (HR 0.78, 95% CI 0.40-1.52).
  • Greater benefit of DAA therapy in patients who remained HCC recurrence-free (HR 0.09, 95% CI 0.02–0.34) compared to those who experienced recurrence (HR 0.62, 95% CI 0.37–1.04) (interaction p-value=0.01).
LXR agonism potentiates sorafenib activity in HCC by inducing metabolic stress

**Objective:**
To identify druggable targets to enhance sorafenib efficiency

**Methods:**
- Use of novel *in vivo* cDNA screen to identify genes required for tumor progression with and without sorafenib
- *In vitro* confirmatory assays including drug screens, RNA sequencing, siRNA

**Main Findings:**
- Sorafenib-resistant tumors do not develop in the presence of LXR.
- LXR agonism and sorafenib combination targets HCC more effectively *in vitro* compared to sorafenib monotherapy.
- Combination therapy alters expression of metabolic genes, and silencing PCK2 (gluconeogenesis) and FASN (fatty acid synthesis) protect against cell death.

**Conclusions:**
Our novel *in vivo* genetic screen led to identification of LXR agonism as an effective dual therapy with sorafenib *in vitro*. Combination therapy effectively targets HCC through metabolic changes, likely involving increased gluconeogenesis and fatty acid synthesis, and decreased glycolysis.

Preziosi ME, et al., Abstract 112
Immune Checkpoint Inhibitors

- **PD-1 inhibitors**
  - Nivolumab
  - Pembrolizumab

- **CTLA-4 inhibitors**
  - Ipilimumab
  - Tremelimumab

- **PD-L1 inhibitors**
  - Atezolizumab
  - Durvalumab
CheckMate 040: nivolumab + ipilimumab in patients with advanced hepatocellular carcinoma (aHCC)

Objective:
To assess the safety and efficacy of nivolumab (NIVO; PD-1 inhibitor) plus ipilimumab (IPI; CTLA-4 inhibitor) in the CheckMate-040 study, the first prospective study of this immunotherapy combination in patients with aHCC treated with sorafenib.

Methods:
Patients treated with SOR were randomized to 3 arms: [A] NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) or [B] NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W, or [C] NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W, until intolerable toxicity or disease progression. Primary endpoints were safety and tolerability, objective response rate (ORR), and duration of response (DOR; investigator assessment using RECIST v1.1).

Main Findings:
- Investigator-assessed ORR: 32%, 27%, and 29% in arms A, B, and C, respectively, concordant with BICR-assessed responses; median DOR: 17.5, 22.2, and 16.6 months, respectively.
- Any-grade immune-mediated hepatic AEs: 20%, 12%, and 6% of patients in arms A, B, and C, respectively
  - The proportion of hepatic events (median time to resolution) that resolved: 90% (6.6 weeks) in arm A, 83% (7.9 weeks) in arm B, and 67% (6.1 weeks) in arm C.
  - Of the 10, 6, and 3 patients who had an immune-mediated hepatic AE, 7, 3, and 2 patients received high-dose glucocorticoids (≥ 40 mg of prednisone per day or equivalent) for a median (range) of 2 weeks (0.4–14.7), 1 week (0.6–1.1), and 3 weeks (2.0–3.0) in arms A, B, and C, respectively.
  - No patients who were rechallenged with NIVO or IPI after experiencing an immune-mediated hepatic AE experienced a recurrence of the event.

Sangro B, et al, Abstract 200

Conclusions:
NIVO + IPI demonstrated durable responses and a manageable safety profile in patients with aHCC treated with SOR.
Laparoscopic versus open hepatectomy for large HCC: a randomized controlled study

Aim:
- Strong evidence from prospective studies for the superiority of either the open or laparoscopic approach is still lacking.
- Aim was to compare feasibility, safety, surgical and oncologic efficiency of laparoscopic versus open hepatectomy (OH) in management of solitary large (>5 cm).

Methods:
150 Child A cirrhotic patients with large HCC met the inclusion criteria and were randomly assigned to either OH group (75 patients) or LH group (75 patients).

Conclusions:
LH is superior to the OH with significantly shorter duration of hospital stay with no compromise to oncological outcomes and similar disease-free survival compared to OH.

Elgendy AM, et al., Abstract 223
Surgical treatment is associated with improved outcome in patients with single less than 2 cm hepatocellular carcinoma

**Aim:**
To investigate the impact of treatment on outcomes of single <2 cm HCCs

**Methods:**
HCC diagnosed between 2004 and 2014 from the NCDB

**Main Findings:**
Liver transplant (HR: 0.27; 95% CI: 0.20-0.37; \(P<0.01\)) or resection (HR: 0.67; 95% CI: 0.48-0.93; \(P=0.02\)) was independently associated with an improved survival compared to ablation. The superiority of surgical treatment remained after propensity score matchings and inversed probability weighting adjusted analysis.

**Conclusions:**
Surgical treatment was associated with longer survival in patients with single <2 cm HCC.

Yang JD, et al., Abstract 224
Six-month waiting rule was associated with lower waitlist mortality/drop-out in LT candidates with HCC

Aim:
To evaluate effects of the 6-month waiting rule on waitlist outcomes in patients with hepatocellular carcinoma (HCC)

Methods:
- Group 1 (pre 6-month rule) comprises transplant candidates with HCC exception scores from Jan. 1, 2013 to Oct. 7, 2015 (n=4814) and Group 2 (post 6-month rule) comprised those from Oct. 8, 2015 to Jun. 30, 2018 (n=3287).
- Conditional waitlist outcomes, defined as outcomes from the time of HCC exception scores were given, were compared between UNOS region groups according to transplant MELD scores (lower: region 3, 10, and 11, mid: 1, 2, 6, 8, and 9, higher: 4, 5, and 7).

Conclusions:
The mandatory 6-month waiting time rule in the HCC exception policy decreased waitlist mortality/dropout and increased transplant probability with increasing regional parity of liver transplant.

Nagai S, Moonka D, et al., Abstract 225
A US multicenter analysis of 2529 HCC patients undergoing liver transplantation: 10-year outcome assessing the role of downstaging to within Milan criteria

**Aim:**
Evaluate the 10-year outcomes of downstaging to within Milan Criteria (MC) prior to liver transplantation (LT)

**Methods:**
- A total of 2529 adult patients undergoing LT for HCC from 2001-2015 from 5 large US centers were reviewed.
- Outcomes of patients downstaged (n=330) to within MC (radiographic) were compared to patients within MC (n=2086) and those transplanted beyond MC (n=110).
- Predictors of downstaging failure and recurrence-free survival were identified.

**Conclusions:**
- We report excellent 10-year post-LT outcomes in patients with HCC successfully downstaged to within MC, thus validating national downstaging policy.
- Tumor characteristics (> 3 nodules; diameter >7 cm) and lack of AFP response prior to LT were factors independently associated with downstaging failure.

Tabrizian P, et al., Abstract 15
Impact of Healthy Lifestyle on incidence of HCC & Cirrhosis related Mortality among US adults (Simon TG et al)

- Prospective cohort study of adults without known liver disease at baseline
- 121,893 adults followed for 2,388,811 person-years
- 121 incident HCC and 350 cirrhosis-related deaths
- Five modifiable risk factors: smoking, alcohol use, BMI, physical activity, healthy diet
- HR for 5 versus 0 risk factors: 3.59 for incident HCC and 4.27 for cirrhosis related mortality
- Overall, single factor with largest population-attributable risk was overweight/obesity (BMI ≥25)