HEPATOCELLULAR CARCINOMA: UPDATE

Nikolaos T. Pyrsopoulos MD, PhD, MBA
Associate Professor and Chief
Department of Medicine
Division of Gastroenterology and Hepatology
Rutgers NJMS
Medical Director Liver Transplantation
University Hospital

DISCLOSURES

Grant/Research Support - AbbVie, Conatus, Hologic, Intercept, Genfit, Gilead, Mallinckrodt, Merck, Salix, Shire, Vital Therapies
Consultant - AbbVie, Gilead, Merck
Member, Scientific Advisory Board - Vital Therapies

I will be discussing off label/investigational use of tivantinib for hepatocellular carcinoma.

Annual Report to the Nation on the Status of Cancer, 1975-2012

- Latest Annual Report to the Nation
- Period 1975-2012 to provide the best perspective on long-term trends in cancer death rates among all races combined.
- Period 2008-2012 was used for describing the current U.S. burden of cancer,
- Period from 2003-2012 was used for describing trends in cancer incidence and death rates for five major racial and ethnic groups.
- All rates in the report are per 100,000 people in the U.S. population.

Mortality Highlights

- Overall cancer death rates decreased during 2003-2012 by:
- An average of 1.8 percent per year for men
- An average of 1.4 percent per year for women
- An average of 2 percent per year for people ages 0 to 19.
HEPATOCARCINOCENESIS
WHAT WENT WRONG?

Hepatocellular Carcinoma ("HCC")
- the eighth most common cancer in the world
- third leading cause of death from cancer worldwide
- ninth leading cause of cancer deaths in USA
- The epidemiology of HCC is characterized by marked differences between genders, ethnic groups, and geographic regions
  - Almost 80% of cases are due to underlying chronic hepatitis B and C virus infection

Hepatocellular Carcinoma
Global Distribution
Highest incidence of HCC is reported in East Asia and Africa

Causes of Hepatocellular Carcinoma

Incidence Rates for Liver Cancer by Race/Ethnicity
During 2008 to 2012

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Rate per 100,000 People in the U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>14.9</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>13.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.7</td>
</tr>
<tr>
<td>Black</td>
<td>9.9</td>
</tr>
<tr>
<td>White</td>
<td>6.0</td>
</tr>
</tbody>
</table>

LIVER CANCER DEATHS IN THE U.S. ARE INCREASING AT THE HIGHEST RATE OF COMMON CANCERS

Average Annual Percent Change

Per 100,000 People in the U.S.

Source: Annual Report to the Nation on the Status of Cancer: 1975-2014
Two main mechanisms

A: cirrhosis
- the association with hepatic regeneration after chronic liver damage caused by several factors (hepatitis infection, toxins or metabolic impairments)

B: Activated inflammatory cells release free radicals
- reactive oxygen species and nitric oxide reactive species
- DNA damage and lead to gene mutations, fostering neoplastic transformation
- collection of DNA mutations
- impairment of the cellular oncogenesis–oncospert suppression equilibrium
- leading to the development of neoplastic cells

World J Gastrointest Pathophysiol. 2016 Aug 15;7(3):242-55
Patel P, Schultzer S, Pyrsopoulos N

Incident Cases of Severe Consequences of HCV Infection in the US

Why Is Liver Cancer Increasing?
- Liver cancer is increasing because cirrhosis is increasing.
- Cirrhosis is increasing because:
  - There are a lot of baby boomers.
  - They have a high prevalence of hepatitis C.
  - They are getting older.
  - They are getting fatter.

The Future?

HCC Surveillance: Rationale
- HCC detected at onset of symptoms:
  - 5-year survival: 0%-10%.
- Small HCC detected by surveillance:
  - 5-year survival more than 50% for both resection and liver transplantation.

HCC Surveillance: EARLY DETECTION!!!!!!!
- 410 patients were reviewed.
- 77.3% referred from the community.
- 22.7% were followed in our clinic.
  - 75.6% of patients were identified with one nodule at initial diagnosis in the clinic group.
  - 65.6% in the referral group.

Survival by HCC Tumor Stage: VCU/McGuire VA Experience, 1997-2005
- Survival of HCC is strongly related to stage at diagnosis.
- Earlier detection of HCC could improve outcome.

HCC Surveillance: Subpopulation analysis

Hepatitis B
- Non-Asian HBV chronic carriers who are anti-HBe positive without cirrhosis have a low risk of HCC
- Asian Hepatitis B carriers without cirrhosis remain at risk of HCC regardless of replication status
- Caucasian HBV carriers who lose HBsAg, the risk of HCC declines dramatically
- Asian HBV carriers who lose HBsAg, HCC risk persists
- genotype C: higher risk of HCC than genotype B

Hepatocellular carcinoma in patients with chronic hepatitis B

Hepatocellular carcinoma in patients with chronic hepatitis C

The REVEAL Study: Regression Analysis of Serum Level of HBV DNA and Risk of HCC
HCC Surveillance

- Patients with hepatitis C cirrhosis should undergo surveillance
- HALT C study: 5-year risk of non-cirrhotic developing HCC was 4.8%

AFP as a screening Test?

- AFP rarely elevated in lesions that are smaller than 2 cm in diameter
- "AFP sensitivity of 66% and a specificity of 82%"
- HALT-C study: HCC developed in 39 subjects, AFP available at the time of diagnosis and 12 months prior to diagnosis
- AFP: not a good screening test for HCC

HCC Screening by Ultrasound

- Performance characteristics of ultrasound as a screening test

<table>
<thead>
<tr>
<th>Performance Characteristic, %</th>
<th>Cohort 1 Years 1-5</th>
<th>Cohort 1 Years 6-8</th>
<th>Cohort 2 Years 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>79</td>
<td>87</td>
<td>80</td>
</tr>
<tr>
<td>Specificity</td>
<td>94</td>
<td>87</td>
<td>91</td>
</tr>
</tbody>
</table>


Surveillance / US Interval

- Doubling time: median = 6 mo (range, 1-19 mo)
- Growth from 1 to 3 cm:
  - 4 mo for most aggressive,
  - 18 mo for moderately aggressive,
  - 5 yr for indolent HCC
- No basis for alternating surveillance modalities
- Lengthening surveillance interval for patients perceived to be a lower risk of HCC neglects the benefits of surveillance

HCC Surveillance

1. Patients at high risk for developing HCC should be entered into surveillance programs
2. The at-risk groups for whom surveillance is recommended are identified
3. Surveillance for HCC should be performed using ultrasonography
4. Patients should be screened at 6 month intervals
5. The surveillance interval does not need to be shortened for patients at higher risk of HCC

AASLD HCC guidelines
HCC can be diagnosed radiologically, without the need for biopsy if the typical imaging features are present. Presence of arterial uptake followed by "washout" is highly specific for HCC that only a single study is necessary. Atypical Findings:
- Sequential imaging decrease the need for biopsy
- Sequential studies increase sensitivity to about 74-80%, the specificity fell to 89-97%, if atypical lesions were biopsied, the specificity was restored to 100%

**Radiological Diagnosis of HCC**

**Clinical Staging**
- No Consensus
- TNM, Okuda, CLIP, and BCLC
- BCLC: Reference staging system links staging with treatment modalities and the estimation of life expectancy

**BCLC Staging System**
- To best assess the prognosis of HCC patients it is recommended that the staging system take into account tumor stage, liver function and physical status.
- The impact of treatment should also be considered when estimating life expectancy.
- Currently, the BCLC system is the only staging system that accomplishes these aims (level II).
Management of HCC
- Liver transplantation
- Resection
- Tumor ablation
  - Radiofrequency thermal ablation
  - Alcohol injection
  - Chemoembolization
- Targeted molecular therapy
- Chemotherapy
  - Regional/systemic

Potentially curative

Liver Transplant for HCC in cirrhosis
- Milan Criteria
  - Single, not > 5cm
  - Up to 3, none > 3cm
  - Absence of Macroscopic Vascular Invasion
  - Absence of Extrahepatic Spread

Curative Treatments for Early Stage HCC
- Liver transplantation
  - Milan criteria
  - 5 yr survival > 70%
  - Recurrence reportedly as high as 40% after transplantation (UNOS 7.5%)


WHERE WE ARE NOW: SORAFENIB
- An oral multikinase inhibitor
- Blocks tumor cell proliferation by targeting the Raf/MEK/ERLK signaling pathway
- Exerts an antiangiogenic effect by targeting the tyrosine kinases of VEGFR-2, VEGFR-3 and PDGFR-beta

SHARP trial included 602 patients with advanced HCC, and was stopped at the interim analysis because of survival advantages favoring sorafenib vs. placebo
31% decrease in the risk of death with a median survival for sorafenib arm of 10.7 months vs. 7.9 months for placebo

Sorafenib

Molecular Targets in HCC

Source: Cancer Center 101, UI/MD Anderson Cancer Center and Research Institute, Inc.
TACE is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread

Sorafenib is recommended as first line option in patients who can not benefit from resection, transplantation, ablation or transarterial chemoembolization, and still have preserved liver function

Tamoxifen, anti-androgens, octreotide or hepatic artery ligation/embolization are not recommended

Regorafenib (RESORCE)

- 573 were enrolled and randomised
- (379 to regorafenib and 194 to placebo), and
- 567 initiated treatment (374 received regorafenib and 193 received placebo).
- Regorafenib improved overall survival with a hazard ratio of 0.63 (p<0.0001);
- median survival was 10.6 months (95%) for regorafenib versus 7.8 months

The Lancet. V 389, No 10064, p 56-66, Jan 2017

Possible Future Studies in HCC

- New targeted molecular agents
- Small molecules in combination
  - With each other
  - With local ablation
  - With conventional chemotherapy

The SHARP Trial: Drug-Related AEs

<table>
<thead>
<tr>
<th>Event</th>
<th>Regorafenib</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>41 (3)</td>
<td>22 (1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>9 (1)</td>
<td>2 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14 (0)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dry skin</td>
<td>8 (0)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>21 (0)</td>
<td>8 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rash or desquamation</td>
<td>16 (1)</td>
<td>7 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other</td>
<td>5 (1)</td>
<td>1 (0)</td>
<td>&lt; 0.001</td>
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Tivantinib

Thank you