Hepatocellular Carcinoma: Can We Slow the Rising Incidence?

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Outline

• Epidemiology
• Etiology
• Hepatitis B and HCC
• Hepatitis C and HCC
• Metabolic Syndrome and HCC
Hepatocellular Carcinoma

• Represents 5% of all cancers
  – Estimated annual numbers of cases 500,000

• Rising incidence
  – 2 – 3 times higher in developing countries
    • Southeast Asia and sub-Saharan Africa account for 85% of HCC
  – More common in men

• Survival rates for untreated symptomatic HCC: approximately 1% at 2 years
Figure 1. Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.

The incidence rates shown (numbers of cases per 100,000 persons) pertain to both sexes and all ages. Adapted from the World Health Organization.³
Racial/Ethnic Distribution of HCC in the United States

- **White Non-Hispanic**: 46%
- **Black**: 11%
- **American Indian/Alaska Native**: 1%
- **Asian or Pacific Islander**: 27%
- **Hispanic**: 15%

Etiology of Hepatocellular Carcinoma in the US

- Cryptogenic: 29%
- HCV: 39%
- HCV + Alcohol: 12%
- Alcohol: 10%
- Other: 4%
- HBV: 6%

Hepatitis B
HBV DNA and Natural History

Incidence of HCC\textsuperscript{1}

Incidence of Cirrhosis\textsuperscript{2}

Quantitative Serum Levels of HBV DNA and HBsAg Are Independent Risk Predictors of HCC

- Study examined the effects of HBV DNA and HBsAg levels on the development of hepatocellular carcinoma (HCC) (N=3,411)
- Correlation between HBV DNA and HBsAg (r=0.59)
- HBV DNA and HBsAg levels were significantly associated with HCC risk
  - HCC risk associated with increasing serum HBV DNA and HBsAg levels remained, even in HBeAg(-) participants without cirrhosis

Cumulative incidence of hepatocellular carcinoma by HBV DNA/HBsAg levels at study entry

Chen C, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 1095.
Risk of HCC/cirrhosis increases in patients with family history of HCC

- In Asian families with a history of HCC, there is an increased risk for both HCC and cirrhosis for mothers and siblings but not for fathers of case subjects

<table>
<thead>
<tr>
<th></th>
<th>HCC Odds Ratio</th>
<th>Cirrhosis Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>2.64</td>
<td>2.92</td>
</tr>
<tr>
<td>Father</td>
<td>1.36</td>
<td>0.96</td>
</tr>
<tr>
<td>Brother</td>
<td>3.73</td>
<td>4.69</td>
</tr>
<tr>
<td>Sister</td>
<td>4.55</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Case subjects: HBV carriers with recently diagnosed HCC (n=553)
Control subjects: HBV carriers without HCC (n=4,684)

Recurrence of hepatocellular carcinoma (HCC) in the 115 patients surviving >1 year without recurrence after resection

There is a significantly low recurrence of HCC in the sustained low viraemia group than the other groups (log-rank test, p<0.001)

Impact of Surveillance, HBV Vaccination, and Therapy on HCC
Surveillance for HCC Reduces Mortality: A Randomized Controlled Trial

Survival Probability (%)

Time (Years)

Rate of HCC in Children 6-14 years old

- Taiwan introduced a universal HBV vaccination program in 1984
- Since then, incidence of HCC in children 6-14 years old has fallen by 65-75%

Approved HBV Treatments

• First-line agents:
  – Pegylated interferon alpha 2a (Pegasys) Injectable
  – Entecavir (Baraclude) Oral
  – Tenofovir (Viread) Oral

• Second-line agents:
  – Interferon alpha 2b (Intron) Injectable
  – Lamivudine (Epivir) Oral
  – Adefovir dipivoxil (Hepsera) Oral
  – Telbivudine (Tyzeka) Oral
Lamivudine significantly reduced the incidence of hepatic decompensation and HCC

- Multicenter, DB-RCT in Asian populations, N=651

Hepatitis C
Projected Prevalence of Chronic HCV, Cirrhosis, and Complications

Projected Number of Patients With Decompensated Cirrhosis and Hepatocellular Carcinoma

Number of Cases

0 20,000 40,000 60,000 80,000 100,000 120,000 140,000 160,000

Year


Hepatocellular Carcinoma (HCC)
Decompensated Cirrhosis

Milestones in Therapy of CHC
Average SVR Rates from Clinical Trials

Adapted from US Food and Drug Administration,
Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.
Impact of HCV Therapy on HCC
Cumulative incidence of liver-related mortality in 848 patients with HCV-related histologically-proven cirrhosis stratified according to response to IFN ($P = 0.001$ by log-rank test). Patients died for non-liver-related causes were excluded. SVR, sustained virological response.
Sustained virologic response to interferon is associated with improved survival in hepatitis C patients with hepatocellular carcinoma.

Bruno S, et al 2011 AASLD Meeting, 7-9 November 2011
Incidence of Liver Related Decompensation Following HCC Development According to IFN Virological Response

Log-Rank P=0.0068
Mortality Following HCC Development According to IFN Virological Response

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Non SVR</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since HCC diagnosis</td>
<td>78</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

Log-Rank $P=0.0440$
5-year occurrence

SVR: 9.2% (CI, 0.0%–19.6%)
No SVR: 13.1% (CI, 7.6%–18.6%)

$P = 0.192$ (log likelihood)
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antiviral therapy Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azzaroli 2004</td>
<td>2</td>
<td>9</td>
<td>2.3%</td>
<td>0.09 [0.02, 0.41]</td>
</tr>
<tr>
<td>Benvegnu 1998</td>
<td>4</td>
<td>20</td>
<td>3.8%</td>
<td>0.21 [0.07, 0.57]</td>
</tr>
<tr>
<td>Bruno 1997</td>
<td>6</td>
<td>16</td>
<td>4.4%</td>
<td>0.36 [0.15, 0.88]</td>
</tr>
<tr>
<td>Fattovich 1997</td>
<td>7</td>
<td>16</td>
<td>4.6%</td>
<td>0.31 [0.13, 0.73]</td>
</tr>
<tr>
<td>Gramenzi 2001</td>
<td>6</td>
<td>19</td>
<td>4.6%</td>
<td>0.32 [0.13, 0.74]</td>
</tr>
<tr>
<td>HCC Study Group 1998</td>
<td>21</td>
<td>48</td>
<td>6.9%</td>
<td>0.49 [0.30, 0.79]</td>
</tr>
<tr>
<td>Ikeda 1998</td>
<td>32</td>
<td>271</td>
<td>8.0%</td>
<td>0.61 [0.45, 0.82]</td>
</tr>
<tr>
<td>Imai 1998</td>
<td>8</td>
<td>7</td>
<td>4.6%</td>
<td>0.71 [0.31, 1.67]</td>
</tr>
<tr>
<td>Mazella 1996</td>
<td>5</td>
<td>9</td>
<td>3.6%</td>
<td>0.26 [0.09, 0.77]</td>
</tr>
<tr>
<td>Mura 1999</td>
<td>0</td>
<td>5</td>
<td>0.8%</td>
<td>0.09 [0.01, 1.63]</td>
</tr>
<tr>
<td>Nischiguchi 2001</td>
<td>12</td>
<td>33</td>
<td>6.6%</td>
<td>0.36 [0.22, 0.61]</td>
</tr>
<tr>
<td>Okanue 1999</td>
<td>7</td>
<td>22</td>
<td>5.2%</td>
<td>0.44 [0.21, 0.92]</td>
</tr>
<tr>
<td>Serfaty 1998</td>
<td>2</td>
<td>9</td>
<td>4.4%</td>
<td>0.17 [0.04, 0.73]</td>
</tr>
<tr>
<td>Shioda 1999</td>
<td>22</td>
<td>18</td>
<td>6.3%</td>
<td>0.12 [0.07, 0.21]</td>
</tr>
<tr>
<td>Shiratori 2005</td>
<td>84</td>
<td>35</td>
<td>8.0%</td>
<td>0.66 [0.49, 0.88]</td>
</tr>
<tr>
<td>Sofia 1999</td>
<td>11</td>
<td>4</td>
<td>3.5%</td>
<td>1.58 [0.53, 4.73]</td>
</tr>
<tr>
<td>Testino 2002</td>
<td>15</td>
<td>24</td>
<td>6.5%</td>
<td>0.87 [0.51, 1.49]</td>
</tr>
<tr>
<td>Valla 1999</td>
<td>5</td>
<td>9</td>
<td>3.8%</td>
<td>0.61 [0.22, 1.70]</td>
</tr>
<tr>
<td>Yoshida 1999</td>
<td>33</td>
<td>32</td>
<td>7.2%</td>
<td>0.48 [0.31, 0.74]</td>
</tr>
<tr>
<td>Yu 2006</td>
<td>36</td>
<td>19</td>
<td>6.9%</td>
<td>0.78 [0.48, 1.26]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2691</strong></td>
<td><strong>2009</strong></td>
<td></td>
<td><strong>0.43 [0.33, 0.56]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\text{Chi}^2 = 59.10, \text{df} = 19 (P < .00001)$
Test for overall effect: $Z = 6.27 (P < .00001)$

Forrest plot for HCC development in patients with HCV cirrhosis: comparison of treated patients with antiviral therapy (IFN or IFN and RBV) and untreated patients.
Sustained Virologic Response Improves Overall Survival in Chronic HCV with Advanced Fibrosis

- 5 large centers from Europe and Canada
- 1990-2003, advanced fibrosis. Treated with interferon based regimens
- 529 patients followed for 20.2 years (median follow up 7.7 years)
- 191 (36.1%) achieved SVR


*Hazard Ratio’s are adjusted for age, gender, center, fibrosis score, diabetes mellitus, heavy alcohol use treatment period.
Metabolic Syndrome and HCC
Comparison of HCC Patients with Cryptogenic Cirrhosis versus other Etiologies

<table>
<thead>
<tr>
<th></th>
<th>Cryptogenic n=30</th>
<th>Other Etiologies n=75</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female(%)</td>
<td>60</td>
<td>28</td>
<td>.001</td>
</tr>
<tr>
<td>Mean age ±SD(yr)</td>
<td>57 ± 16</td>
<td>62 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Non-Hispanic white(%)</td>
<td>90</td>
<td>72</td>
<td>NS</td>
</tr>
<tr>
<td>BMI &gt; 30 (%)</td>
<td>58</td>
<td>25</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes(%)</td>
<td>47</td>
<td>8</td>
<td>.006</td>
</tr>
<tr>
<td>Hypertriglyceridemia(%)</td>
<td>16</td>
<td>2</td>
<td>.001</td>
</tr>
<tr>
<td>Hypercholesterolemia(%)</td>
<td>13</td>
<td>2</td>
<td>.07</td>
</tr>
<tr>
<td>Maximal tumor diameter</td>
<td>7.6 ± 6</td>
<td>4.4 ± 5</td>
<td>.03</td>
</tr>
<tr>
<td>Mean ± SD(cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP &lt; 20 ng/mL (%)</td>
<td>27</td>
<td>30</td>
<td>NS</td>
</tr>
<tr>
<td>Detected by surveillance(%)</td>
<td>23</td>
<td>61</td>
<td>.01</td>
</tr>
</tbody>
</table>

Obesity and Liver Cancer


Death Rate per 100,000

<table>
<thead>
<tr>
<th>BMI</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5-24.9</td>
<td>4.5</td>
<td>9.2</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>4.5</td>
<td>10.5</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>6.3</td>
<td>19.2</td>
</tr>
<tr>
<td>35.0-39.9</td>
<td>7.5</td>
<td>47.8</td>
</tr>
</tbody>
</table>
Diabetes Is Associated with a Two-fold Increase in Risk of HCC

Impact of Diabetes and Overweight on Liver Cancer Occurrence in Cirrhosis

Summary

• Rising Incidence of HCC
• HBV vaccination effectively reduces incidence of HCC
• Hepatitis B viral DNA correlates with HCC-treatment effectively decreases the incidence of HCC
• Rising incidence of HCV related HCC-SVR effectively decreases incidence of HCC
• Metabolic syndrome—a major cause for HCC; education and preventive strategies needed