Role of Antivirals in the Prevention of Hepatocellular Carcinoma in Patients with Chronic Hepatitis

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Background

• Approximately 75% of HCC worldwide are attributed to chronic hepatitis B (CHB) and chronic hepatitis C (CHC).
• Most of them occur in cirrhotic liver
• The advent of potent oral antivirals has shown their efficacy to reduce viral load.
• Does antivirals prevent HCC in patients with chronic hepatitis B and C?
Strategies to Prevent HCC

- **HCV**
  - Acute hepatitis
  - Chronic hepatitis
  - Liver cirrhosis
  - HCC

- **HBV**
  - Acute hepatitis
  - Chronic hepatitis
  - Liver cirrhosis
  - HCC

Vaccine, only available for HBV

Antiviral therapy:
- in non-cirrhosis
- in cirrhosis

Lok AS. J Gastroenterol Hepatol 2011; 26:221-7.
Hepatitis B vs. Hepatitis C

**HEPATITIS B**
- DNA virus
- Viral genome replicate in the nuclei
- Primary treatment goal: SUSTAINED HBV SUPPRESSION\(^1\)

**HEPATITIS C**
- RNA virus
- Viral genome replicate in the cytoplasma
- Primary treatment goal: ERADICATION OF HCV\(^2\)

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HCV life cycle

1. Entry into the cell and uncoating;
2. Translation, replication, and packaging into new virion

All occur in the cytoplasm

Eradication is POSSIBLE

Following entry and uncoating, HBV genome enter the nucleus to replicate. **ERADICATION IS IMPOSSIBLE**

Antiviral treatment for HCC prevention

CHRONIC HEPATITIS C
HCC-free survival rate by IFN

IFN-based treatment reduces HCC risk in chronic hepatitis C patients

IBT = Interferon-based treatment

Meta-analysis of antiviral therapy to prevent HCC in CHC

- 8 RCTS and 5 cohort studies;
- antiviral therapy reduced the risk of HCC (RR 0.53, 95% CI 0.34 to 0.81)

Responders vs. non-responders

- Subgroup analysis:
- the effect was more pronounced among responders (RR 0.15, 95% CI 0.05 to 0.45) compared with non-responders (RR 0.57; 95% CI 0.37 to 0.85).

Antiviral treatment for HCC prevention

CHRONIC HEPATITIS B
HCC risk and mortality in CHB is related to the viral load

IFNα reduced cirrhosis in HBeAg-positive patients

IFNα reduced HCC in HBeAg-positive patients

LAM treatment and HCC

- LAM treatment (median: 43 months) reduces HCC incidence by more than 50%.
- 9.7% per year in untreated controls vs. 3.3% per year in LAM-treated patients.
- LAM therapy is associated with a 56% reduction in the incidence of HCC among chronic HBV patients compared with no treatment.

Reduction of HCC with LAM in patients with advanced fibrosis/cirrhosis


Placebo (n=215) Lamivudine (n=436) / 32.4 mo

Excluding 5 cases in yr 1: HR=0.47; p=0.052
# Meta-Analysis of LAM on HCC Incidence in CHB

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lamivudine Events</th>
<th>No treatment Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eun 2010</td>
<td>58</td>
<td>69</td>
<td>69</td>
<td>32.7%</td>
<td></td>
</tr>
<tr>
<td>Liaw 2004</td>
<td>17</td>
<td>16</td>
<td>215</td>
<td>9.4%</td>
<td></td>
</tr>
<tr>
<td>Lok 2003</td>
<td>1</td>
<td>1</td>
<td>200</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Matsumoto 2005</td>
<td>31</td>
<td>239</td>
<td>2138</td>
<td>48.9%</td>
<td></td>
</tr>
<tr>
<td>Papatheodoridis 2005</td>
<td>5</td>
<td>15</td>
<td>195</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Yuen 2007</td>
<td>1</td>
<td>3</td>
<td>124</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.48 [0.38, 0.61]</td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 6.11$ ($P < 0.00001$)

Meta-Analysis of Antiviral Therapy on HCC Risk in CHB

Cumulative carcinogenic rate during ETV treatment A: A patients B: patients stratified with chronic hepatitis (CH) and liver cirrhosis (LC).

cumulative carcinogenic rates were much higher in cirrhotic patients

AASLD 2012. Poster presentation by Ryoko Yamada.
Long-term entecavir (ETV) reduces HCC in HBV infection

### Table 1: Risk factors for hepatitis B virus-related hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Liver factors</th>
<th>Viral factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Advanced fibrosis</td>
<td>High serum HBV DNA</td>
</tr>
<tr>
<td>Male gender</td>
<td>Cirrhosis</td>
<td>Positive HBeAg</td>
</tr>
<tr>
<td>Family history of HCC</td>
<td>Hypoalbuminemia</td>
<td>HBV genotype C</td>
</tr>
<tr>
<td>SNP at human genomic loci, e.g.</td>
<td>Hyperbilirubinemia</td>
<td>HBV subgenotype Ce</td>
</tr>
<tr>
<td>Chromosome 1p36.22</td>
<td>High ALT</td>
<td>Core promoter mutations</td>
</tr>
<tr>
<td>Chromosome 6 of HLA-DP/Q loci</td>
<td>Active necroinflammation</td>
<td>High serum</td>
</tr>
<tr>
<td>Chromosome 8p12</td>
<td>Concomitant liver diseases, e.g.</td>
<td>HBsAg level</td>
</tr>
<tr>
<td>Immunosuppressed condition, e.g.</td>
<td>Hepatitis C virus co-infection</td>
<td></td>
</tr>
<tr>
<td>Human immunodeficiency virus co-infection</td>
<td>Hepatitis delta virus co-infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcoholic liver disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonalcoholic fatty liver disease</td>
<td></td>
</tr>
</tbody>
</table>

Wong GLH, Wong VWS.  
*World J Gastroenterol* 2013; 19(39): 6515-6522
Cirrhosis vs. Non-cirrhosis

• Suppression of viral replication in HBV cirrhosis patients reduces but does not eliminate HCC risk.

• Suppression of viral replication in non-cirrhosis also reduces the risk of HCC, but since the risk of HCC is not as high as in cirrhosis patients, the magnitude of the risk reduction is less.

Conclusion

- Antiviral therapy may prevent HCC by slowing progression of liver disease and possibly even reversing liver damage.
- Standard treatment of chronic hepatitis C may eliminate HCV and reduce the incidence of HCC.
- Risk reduction is more prominent in treatment responders.
- Treatment with potent antiviral therapy for chronic hepatitis B may suppress viral load and possibly prevent HCC.
- Greatest risk reduction occur in cirrhotic compared to non-cirrhotic patients.
Thank you