Could antiviral therapy reduce the incidence of HCC in patients with chronic hepatitis B?

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Main Content

Part 1  Natural progression history of hepatitis B disease and epidemiology and risk factors of HCC

Part 2  Effective long-term treatment of nucleoside (nucleotide) drugs could reduce the development and recurrence risk of HBV-related liver cancer

- Effective long-term antiviral therapy can reduce the incidence of HCC in patients with chronic hepatitis B
- Effective antiviral therapy can reduce the incidence of HCC recurrence in patients with HBV-related HCC

Part 3  Antiviral therapy with nucleoside (nucleotide) drugs could significantly reduce, but can't completely eliminate the risk of HCC
Natural history of hepatitis B disease progression

Acute HBV infection → Chronic HBV infection → Chronic Hepatitis B → Liver cirrhosis → HCC

5-year incidence: 8%~20%
Annual incidence 3%~6%

Liver transplant → Chronic liver failure

350 million patients with chronic hepatitis B infection globally
30% of liver cirrhosis and 53% of HCC are associated with chronic HBV infection
21,000 cases of liver transplant each year

Epidemiology of HBV-related HCC

- HCC is the fifth most common cancer, the third most common cause of death worldwide\(^1,2\)
- Approximately 50% of the global HCC cases is associated with HBV infection.\(^3\) In HBV-epidemic regions (Southeast Asia, Sub-Saharan Africa), as high as 70–80% of HCC cases is associated with HBV infection\(^3,4\)
- Approximately 25% of untreated CHB patients will experience HCC \(^1\)
- There is a higher incidence of HBV-related HCC in cirrhotic patients \(^5\)

5-year cumulative incidence of HCC in patients with chronic HBV infection \(^5\)

<table>
<thead>
<tr>
<th></th>
<th>Inactive carriers</th>
<th>CHB without cirrhosis</th>
<th>CHB with compensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>East Asia</strong></td>
<td>1%</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td>0.1%</td>
<td>1%</td>
<td>10%</td>
</tr>
</tbody>
</table>

## Risk factors for HBV-related HCC

<table>
<thead>
<tr>
<th>Viral factors</th>
<th>Host factors</th>
<th>Environmental factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous HBeAg positive</td>
<td>Elderly</td>
<td>Alcoholic</td>
</tr>
<tr>
<td>Continuous high load of HBV DNA</td>
<td>Male</td>
<td>Aflatoxin</td>
</tr>
<tr>
<td>Mutation of HBV core promoter</td>
<td>Asian</td>
<td>Smoking</td>
</tr>
<tr>
<td>HBV genotype C</td>
<td>Liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Continuous high ALT level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-infection of HDV and HCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of HCC</td>
<td></td>
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</tr>
</tbody>
</table>

- Resistance can lead to an increased risk of HCC
- Antiviral therapy with nucleoside (nucleotide) drugs could significantly reduce, but can’t completely eliminate the risk of HCC (especially in patients with liver cirrhosis)
Part 1  Natural progression history of hepatitis B disease and epidemiology and risk factors of HCC

Part 2  Effective long-term treatment of nucleoside (nucleotide) drugs could reduce the development and recurrence risk of HBV-related liver cancer
  ➢ Effective long-term antiviral therapy can reduce the incidence of HCC in patients with chronic hepatitis B
  ➢ Effective antiviral therapy can reduce the incidence of HCC recurrence in patients with HBV-related HCC

Part 3  Antiviral therapy with nucleoside (nucleotide) drugs could significantly reduce, but can't completely eliminate the risk of HCC
Sustained viral suppression may delay disease progression

The proportion of patients with disease progression

Disease progression: liver decompensation, HCC, or death

Kumada’s study: effects of treatment with nucleoside (nucleotide) drugs (NUC) on incidence of HCC

- A retrospective single-center cohort study in Ogaki Hospital, Japan
- 785 CHB patients (enrolled into HCC monitoring project 1998–2008)
- The primary outcome: HCC incidence
- Follow-up period: until the development of HCC or December, 2011

**Propensity score match**

- **NUC treatment**: 148 patients received treatment (NUC treatment >1 year before NUC detection)
- **Non-NUC treatment†**: 637 patients were followed

- **117 matched patients**


*Propensity score match includes age, gender, HBV DNA, HBeAg status, platelet counting and ALT.
†NUC is not approved in Japan, or refused by patients.
Kumada’s study: NUC treatment reduces the incidence of HCC

Cox proportional hazard model:
HR 0.28 (95% CI 0.13–0.62)
P=0.002

NAs antiviral therapy including ETV could achieve the benefit of HCC risk reduction

Long-term ETV treatment can reduce the incidence rate of HCC in patients with chronic hepatitis B

- A retrospective study in Japan involving 2107 patients with chronic hepatitis B (at least 6 months of HBsAg positive) analyzed the data from the 5-year follow-up period.
- ETV group: 2004-2010. Treatment-naive patients with chronic hepatitis B treated with 0.5mg ETV n=472, after propensity score match n=316
  - Control group: 1973-1999. Chronic hepatitis B patients without NA treatment n=1143, after propensity score match n=316
  - LAM group: 1995-2007 Chronic hepatitis B patients treated by LAM and matched with ETV group n=492, after propensity score match n=182

<table>
<thead>
<tr>
<th></th>
<th>Complete cohort</th>
<th>PS matched cohort*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETV (N=472)</td>
<td>Control (N=1143)</td>
</tr>
<tr>
<td>Age (mean, years)</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>Gender (n)</td>
<td>315</td>
<td>720</td>
</tr>
<tr>
<td>Cirrhosis (n/%)</td>
<td>116 (25)</td>
<td>195 (17)</td>
</tr>
<tr>
<td>HBV genotype (n/%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>A</td>
<td>12 (3)</td>
<td>41 (4)</td>
</tr>
<tr>
<td>B</td>
<td>66 (14)</td>
<td>188 (16)</td>
</tr>
<tr>
<td>C</td>
<td>344 (73)</td>
<td>791 (69)</td>
</tr>
<tr>
<td>D</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other / deletion</td>
<td>50 (11)</td>
<td>122 (10)</td>
</tr>
<tr>
<td>HBeAg(+)</td>
<td>219 (46)</td>
<td>398 (35)</td>
</tr>
<tr>
<td>HBV DNA (log10 copies/mL)</td>
<td>6.7</td>
<td>5.8</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>70</td>
<td>33</td>
</tr>
</tbody>
</table>

*Differences in baseline characteristics is eliminated by propensity score match of age, gender, presence of cirrhosis, HBeAg status, HBV DNA, AST, ALT, γGTP, bilirubin, albumin, and platelet count.

Long-term ETV treatment can reduce the incidence rate of HCC in patients with chronic hepatitis B.

Compared with the control group, ETV treatment can reduce the 5-year risk of HCC by more than 60%.

In cirrhotic patients, cumulative incidence of HCC was significantly lower in ETV group than in LAM and control groups.

Log-rank test: $P < 0.001$

Figure 1. The cumulative incidence rate of HCC

Figure 2. The cumulative incidence rate of HCC in patients with liver cirrhosis
In HCC patients at high risk, the largest decrease of the incidence of HCC has occurred in patients receiving ETV treatment.

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Risk</th>
<th>n</th>
<th>ETV</th>
<th>Control</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang HI 2011²</td>
<td>Low</td>
<td>1272</td>
<td>1.1</td>
<td>2.4</td>
<td>0.313</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>342</td>
<td>8.3</td>
<td>23.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Yuen MF 2009³</td>
<td>Low</td>
<td>1110</td>
<td>0.7</td>
<td>0.5</td>
<td>0.914</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>505</td>
<td>7.2</td>
<td>21.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Wong VWS 2010⁴</td>
<td>Low</td>
<td>1054</td>
<td>0.5</td>
<td>1.5</td>
<td>0.246</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>339</td>
<td>4.3</td>
<td>10.6</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>222</td>
<td>8.0</td>
<td>33.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Real-Life Study in Taiwan: C-TEAM interim report: 
ETV long-term treatment—— a significant reduction of disease progression (HCC) risk in patients with cirrhosis

A multi-center study in Taiwan, 666 patients with cirrhosis receiving ETV monotherapy; 621 patients without treatment as the control group. In ETV group, the mean time of follow-up period was 2.7 years; in control group, the mean time of follow-up period was 9.1 years.

During the 2.7 years of follow-up, 2.4% of patients in ETV group developed HCC; while it was 5.2% in control group (P=0.009)

2.7 years of ETV monotherapy reduced the risk of HCC by 59% in patients with cirrhosis
Main Content

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Natural progression history of hepatitis B disease and epidemiology and risk factors of HCC

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- Effective long-term treatment of nucleoside (nucleotide) drugs could reduce the development and recurrence risk of HBV-related liver cancer
  - Effective long-term antiviral therapy can reduce the incidence of HCC in patients with chronic hepatitis B
  - Effective antiviral therapy can reduce the incidence of HCC recurrence in patients with HBV-related HCC

Part 3
The impact of resistance on incidence of HBV-related HCC
Wu’s study: the impact of nucleoside (nucleotide) drugs on the recurrence of HCC

- A prospective, national cohort study (2003-2010) in Taiwan *
- All newly diagnosed HCC patients who underwent liver resection
- The primary outcome: HCC recurrence > 3 months after resection +/- NUC treatment

Effective hepatic resection for patients with newly diagnosis of HBV related HCC †
N=4569

Non-NUC treatment
N=4051

NUC treatment (duration ≥90 days)
N=518

*Data from the Taiwan’s National Health Insurance (NHI) Research Database (representing >99% of Taiwan total population).
†Those who had accepted antiviral therapy for more than 3 months before surgery were excluded.

NUC combination treatment: combination treatment with nucleoside (nucleotide).

Nucleoside (nucleotide) drugs reduced the recurrence risk of HCC

*In multivariate group, due to the high incidence of liver cirrhosis in the treatment cohort, the difference of absolute recurrence rate is less than that of HR recurrence (0.67; see the next slide)


*In multivariate group, due to the high incidence of liver cirrhosis in the treatment cohort, the difference of absolute recurrence rate is less than that of HR recurrence (0.67; see the next slide)
Treatment with nucleoside (nucleotide) drugs reduced the risk of death

Overall mortality rate

Conclusion:
Patients with HCC who underwent liver resection and received NUC treatment (56% received ETV monotherapy) had significantly reduced recurrence rate of HCC and improved overall survival rate. Considering the baseline viral load, NUC treatment may have greater impact on the risk of HCC recurrence.
Lee's study: effects of ETV treatment on recurrence of HCC

- A prospective, single-center cohort study (2007-2011) in Korea
- Objective: to investigate whether ETV will increase the risk of HCC recurrence

Patients
- HBV-related cirrhosis, Child-Pugh level A
- Newly diagnosed HCC, Phase I
- Who accepted radiofrequency ablation (RFA) treatment

Non-NUC treatment N=58

NUC monotherapy starts between 3 months before and after RFA treatment

ETV N=29

Other NUCs N=19
In patients treated by ETV, HCC recurrence rate is lower than in those without NUC therapy.

Multivariate analysis
The risk of HCC recurrence
ETV vs Non-NUC treatment:

OR 0.454
P=0.015

ETV treatment after RFA could reduce the recurrence risk of HCC in patients with HCC; improve disease-free survival; and provide more potent anti-viral suppression compared with non-NUC treatment.

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Effective long-term treatment of nucleoside (nucleotide) drugs could reduce the development and recurrence risk of HBV-related liver cancer

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Part 3
Antiviral therapy with nucleoside (nucleotide) drugs could significantly reduce, but can't completely eliminate the risk of HCC
Resistance reduces the long-term benefit of antiviral therapy

Resistance may lead to progression of HCC in patients with HBV-related cirrhosis

- A case-control study in Korea: 413 patients with HBV-related cirrhosis treated by lamivudine, 260 patients untreated
- The median follow-up period is 4.7 years. 47.6% of patients treated by lamivudine experienced virologic breakthrough

<table>
<thead>
<tr>
<th>Follow up (years)</th>
<th>Control group</th>
<th>Lamivudine resistance group</th>
<th>Sustained viral suppression group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>P=0.144 (Control group vs Lamivudine resistance group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.005 (Control group vs Sustained viral suppression group)</td>
</tr>
</tbody>
</table>
Kobashi's study: Drug resistance may lead to increased risk of HCC

- A prospective study: 194 patients with CHB and 62 patients with liver cirrhosis were enrolled. Among them, 129 patients received ETV therapy and 127 patients received treatment with LVD.

- Follow-up period lasted for 4.25 years, with a total of 60 patients developing LVD resistance.

\[
P = 0.0352
\]

The incidence rate of HCC (%)

Number of patients at risk

<table>
<thead>
<tr>
<th>Year</th>
<th>LVDs</th>
<th>LVDr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>53</td>
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<tr>
<td>4</td>
<td>57</td>
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<tr>
<td>5</td>
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<td>8</td>
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<tr>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The incidence of HCC after virologic response following salvage therapy in lamivudine resistant patients was analyzed by a meta-analysis: in the 104 patients without virological response, after 13 patients who developed HCC at the start of adefovir treatment being excluded, statistics data (8/91, 8.8% vs 19/320, 5.9%, p = 0.466) did not show any significant difference.

There was no difference in the incidence of HCC regardless the efficacy of salvage therapy.
Despite antiviral therapy, the risk of HCC is still higher in CHB patients than in patients of immune tolerance phase.

Cho et al, Gut 2014, in press
Occurrence of HCC is associated with HBV infection. Hepatic cirrhosis, high HBV DNA levels at baseline, sustained high viral load, high HBsAg levels are independent risk factors of HCC.

For patients with chronic hepatitis B, sustained suppression of HBV replication by nucleoside (nucleotide) drugs can reduce the risk of HCC, especially for patients with hepatic cirrhosis.

For HCC patients after operation, antiviral treatment with nucleoside (nucleotide) drugs can reduce or delay the recurrence of residual tumor in liver tissue, and improve disease-free survival rate.

Antiviral treatment with nucleoside (nucleotide) drugs could significantly reduce, but can't completely eliminate the risk of HCC.
Thank you!