HBV reactivation in lymphoma patients: Taiwan experience

On behalf of
Taiwan Cooperative Oncology Group (TCOG)

What we have known in the 20\textsuperscript{th} century...

- Cancer chemotherapy can induce HBV reactivation and hepatitis flares in HBV carriers (HBsAg (+) patients)
- Predictive factors:
  - Cancer types
  - Anti-cancer drugs
  - Viral load and underlying liver diseases
A predictive model of HBV reactivation in cancer patients undergoing cytotoxic chemotherapy

- 128 HBsAg (+) cancer patients
- Serial follow-up of liver function (until 8 weeks after completion of chemotherapy)
- HBV DNA quantification: at baseline and when hepatitis occurred
  

<table>
<thead>
<tr>
<th>Cancer types</th>
<th>HBV reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomas</td>
<td>7/12 (58.3%)</td>
</tr>
<tr>
<td>Breast</td>
<td>16/39 (41.0%)</td>
</tr>
<tr>
<td>GI</td>
<td>2/29 (6.9%)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>5/17 (29.4%)</td>
</tr>
<tr>
<td>Lung</td>
<td>3/13 (23.1%)</td>
</tr>
<tr>
<td>Others</td>
<td>3/18 (16.6%)</td>
</tr>
</tbody>
</table>

Predictive factors of HBV reactivation

- Breast cancer or lymphoma
- Steroid use
- Detectable HBV DNA at baseline (by PCR)
- Extent of immunosuppression
  

- Potential ‘underestimation’ of HBV reactivation
- The practice of chemotherapy has changed…
Cancer chemotherapy in the 21st century

• More drugs (cytotoxic agents, molecular targeted agents) and regimens are developed
  – More immuno-suppression in some settings
• More cancers can (and have to) be treated

Advance in cancer therapy in the 21st century: some examples (1)

• Colorectal cancer
  – Cytotoxic agents: 5-FU, irinotecan (CPT-11), oxaliplatin, capecitabine
  – Molecular targeted therapy: bevacizumab (anti-VEGF), cetuximab (anti-EGFR), panitumumab (anti-EGFR), regorafenib

• Advanced/metastatic disease
  – Response rate around 50% for 1st-line chemotherapy
  – Median overall survival ≥ 20 months

• Adjuvant therapy
  – Oxaliplatin-based regimens are current standard

• Neo-adjuvant therapy
Advance in cancer therapy in the 21st century: some examples (2)

- **Non-small cell lung cancer**
  - Cytotoxic agents: platinums, taxanes, gemcitabine, vinorelbine, premetrexed
  - Molecular targeted therapy: erlotinib (anti-EGFR), gefitinib (anti-EGFR), bevacizumab (anti-VEGF), afatinib (anti-EGFR), crizotinib (anti-ALK)

- **Advanced/metastatic disease**
  - Cytotoxic therapy: response rate 30-40% for 1st-line chemotherapy
  - Molecular targeted therapy: EGFR inhibitors are particularly effective in Asian patients
  - Median overall survival $\geq$ 12 months

- **Adjuvant therapy**
  - Recommended for stage II/III patients
  - Chemotherapy, chemo-radiotherapy

---

HBV reactivation in lymphoma patients: What we have known...

- HBV reactivation and hepatitis flares are common in lymphoma patients
  - Yeo et al, *Hepatology* 2006

- Lamivudine significantly reduces the incidence and severity of HBV flares/hepatitis for lymphoma patients who receive chemotherapy
Risk of chemotherapy-induced HBV reactivation in lymphoma patients: before ‘prophylaxis’

<table>
<thead>
<tr>
<th></th>
<th>PACE (steroid-containing)</th>
<th>ACE (steroid-free)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>HBV reactivation</td>
<td>18 (72%)</td>
<td>9 (37.5%)</td>
</tr>
<tr>
<td>HBV reactivation + hepatitis flare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV reactivation + ALT &gt; 10 ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV reactivation + bilirubin &gt; 1.5 ULN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Lamivudine prophylaxis for chemotherapy-induced HBV reactivation

<table>
<thead>
<tr>
<th></th>
<th>Lau et al</th>
<th>Hsu et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>Prophylactic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Cancer types</td>
<td>NHL 24, HD 6</td>
<td></td>
</tr>
<tr>
<td>Duration of prophylactic lamivudine</td>
<td>6 weeks after completion of C/T</td>
<td>2 months after completion of C/T</td>
</tr>
<tr>
<td>When to start therapeutic lamivudine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV reactivation</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>HBV-related hepatitis</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

HBV screening and prophylactic anti-viral therapy for cancer patients

- Resolved HBV infection (HBsAg (-), anti-HBc (+))
  - Around 50-60% anti-HBc (+) in HBV endemic area
  - Anecdotal reports of HBV reactivation

HBV reactivation in lymphoma patients: What we are not sure...

- Impact of rituximab and other immunosuppressive agents
  - More prolonged immune suppression
  - Increased incidence of opportunistic infection
  - Life-threatening HBV reactivation reported
  - Monitoring/treatment strategies undefined

Cost-Effectiveness of Universal Hepatitis B Virus Screening in Patients Beginning Chemotherapy for Solid Tumors
Fiona L. Day, Jonathan Kimmen, and Danny Silchen

Abstract
Purpose
Universal screening for chronic hepatitis B virus (HBV) infection before chemotherapy has been recommended. We evaluated the cost-effectiveness of HBV screening before chemotherapy given for nonhematopoietic solid tumors (STS).

Methods
A decision-analytic model was used to compare the cost-effectiveness of universal screening conducted per professional guidelines versus no screening in hypothetical patient cohorts beginning adjuvant chemotherapy for early breast cancer or palliative chemotherapy for advanced non-small-cell lung cancer. Survival times were extrapolated using Markov models. Probabilities were derived from published studies and costs estimated from the perspective of the Australian health care system. One-way and probabilistic sensitivity analyses were performed, including with the application of an alternative HBV screening strategy.
HBV reactivation in HBsAg (-) anti-HBc (+) lymphoma patients: case series

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Cancer types</th>
<th>Chemotherapy regimens</th>
<th>HBV reactivation</th>
<th>HBV-related hepatitis flares</th>
<th>HBV-related death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hui CK (2006)</td>
<td>152</td>
<td>NHL, HD</td>
<td>various</td>
<td>7</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Yeo W (2009)</td>
<td>46</td>
<td>DLBCL</td>
<td>R-CHOP, CHOP</td>
<td>5 (out 21 who received R-CHOP)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Ji (2010)</td>
<td>88</td>
<td>DLBCL</td>
<td>R-CHOP, CHOP</td>
<td>1 (R-CHOP)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Koo (2011)</td>
<td>62</td>
<td>B-cell NHL</td>
<td>R-CHOP, R-COP, others</td>
<td>2</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>
| Niitsu (2010)  | Retracted due to scientific misconduct

Trials of HBV reactivation in lymphoma patients with ‘resolved’ HBV infection

• **Study 1:**

  Prophylactic anti-HBV therapy

  Anti-HBV therapy upon reactivation


• **Study 2:**

  – Prospective observational study to identify the incidence/severity

  • Hsu C et al. *Hepatology* 2013 (e publication ahead of print)
346 non-Hodgkin’s lymphoma patients screened

196 patients excluded. Reasons (no. of patients):
- Histology (12)
- Virology (95) (HBsAg(+), 40; anti-HBC(-), 43; anti-HCV(+), 12)
- Other major systemic diseases (26)
- Previous chemotherapy or radiotherapy (24)
- Age/performace status (7)
- Other concomitant cancer (1)
- Receiving chemotherapy other than rituximab-CHOP (7)
- Patient refusal (21)
- Physician judgment (co-morbid conditions/compliance) (3)

150 patients enrolled

HBV DNA check before every course of rituximab-CHOP chemotherapy and every 4 weeks for 1 year.

HBV reactivation (-) (133 patients)

Follow-up (133 patients)

Follow-up status (no. of patients)*
- Alive and completion of all HBV DNA follow-up (84)
- HBV DNA follow-up ongoing (19)
- Death due to tumor progression/adverse events (21)
- Withdrawal of consent (6)
- Change to other chemotherapy regimen due to medical/personal reasons (3)

HBV reactivation (+) (17 patients)

Follow-up (17 Patients)

Follow-up status (no. of patients)*
- Alive and completion of all HBV DNA follow-up (11)
- HBV DNA follow-up ongoing (1)
- Death due to tumor progression/adverse events (5)

*: as of April 1, 2013

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (No.)</th>
<th>Intervention</th>
<th>C/T</th>
<th>HBV reactivation (patient no./%)</th>
<th>HBV-related hepatitis flare (patient no./%)</th>
<th>HBV-related death (patient no./%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang (2013)(^1)</td>
<td>B-cell (41)</td>
<td>Entecavir prophylaxis</td>
<td>Rituximab-CHOP</td>
<td>HBV DNA increase to &gt; 2000 IU/ml (1/ 2.4)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>B-cell (39)</td>
<td>HBV DNA every month*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsu (2013)(^2)</td>
<td>B-cell (150)</td>
<td>HBV DNA every month*</td>
<td></td>
<td>10-fold increase in HBV DNA (17/ 11.3)</td>
<td>10/ 6.7</td>
<td>0</td>
<td>3-yr OS 72.9%</td>
</tr>
</tbody>
</table>

Unresolved issues

- Optimal preventive strategy?
- High-risk population?
  - Viral factors
    - HBV DNA kinetics/ genotypes
    - Anit-HBs/anti-HBc titers
    - HBsAg sero-conversion
  - Host factors
- Impact of HBV reactivation on survival?
Summary and discussion (1)

• In cancer patients with chronic HBV infection (HBsAg (+))
  – Prophylactic anti-viral therapy is recommended for patients who receive cytotoxic/immunosuppressive therapy (AASLD, EASL guidelines)

• Points to ponder
  – The roles of molecular targeted therapy
  – Cost effectiveness

Summary and discussion (2)

• In lymphoma patients with resolved HBV infection (HBsAg (-) anti-HBc (+))
  – HBV reactivation induced by rituximab-CHOP chemotherapy is not uncommon
  – may not be life-threatening with regular monitoring of HBV DNA and prompt antiviral therapy.

• Points to ponder:
  – Monitoring strategies
  – Indication for ‘prophylactic’ anti-viral therapy
Acknowledgment

• The investigators and the participating centers
• Taiwan Cooperative Oncology Group trial center
• The patients and their families