Chemotherapy-induced HBV reactivation in cancer patients

On behalf of
Taiwan Cooperative Oncology Group (TCOG)

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

• HBV reactivation and hepatitis flares are common in lymphoma patients
  • Cheng AL, et al, Hepatology 2003
  • Yeo et al, Hepatology 2006

• Lamivudine significantly reduces the incidence and severity of HBV flares/hepatitis for lymphoma patients who receive chemotherapy
  • Lau et al, Gastroenterology 2003
  • Hsu et al, Hepatology 2008
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>
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<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>
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<td>Head and neck</td>
<td>5/17 (29.4%)</td>
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<td>Lung</td>
<td>3/13 (23.1%)</td>
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<td>Others</td>
<td>3/18 (16.6%)</td>
</tr>
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</table>

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 ≥ 12 months

- **Adjuvant therapy**
  - Recommended for stage II/III patients
  - Chemotherapy, chemo-radiotherapy
Guidelines for HBV screening and prophylactic anti-viral therapy for cancer patients

• EASL guidelines (2012)

HBV positive candidates for chemotherapy and immunosuppressive therapy should be tested for HBV DNA levels and should receive pre-emptive NA administration during therapy (regardless of HBV DNA levels and for 12 months after cessation of therapy).

Laplante M, Sabatini DM. Cell 2012; 149: 274-93
Everolimus related HBV reactivation

- 28 HBsAg (+) subjects
- HBV-related hepatitis flare in 4 subjects
- Improved after antiviral therapy

FDA-approved indication for everolimus in cancer patients

- Renal cell carcinoma (2009)
- Giant cell astrocytoma (2010)
- Pancreatic neuroendocrine tumor (2011)
- Post-menopausal, hormone receptor (+) breast cancer (2012)
Prevention of Acute Exacerbation of Chronic Hepatitis B Infection in Cancer Patients Receiving Chemotherapy in a Hepatitis B Virus Endemic Area

Ping-I Hsu,1 Kwok-Hung Lai,1 Jin-Shiung Cheng,1 Sung-Shuo Kao,1 Yuan-Rung Li,1 Wei-Chih Sun,1 Wen-Chi Chen,1 Kung-Hung Lin,1 Chih-An Shin,1 Po-Hung Chiang,1 Yun-Da Li,1 Wei-Ting Ou,1 Hui-Chun Chen,2 and Hsien-Chung Yu1

<table>
<thead>
<tr>
<th></th>
<th>Educational stage (n=1157)</th>
<th>Screening reminder stage (n=650)</th>
<th>Therapeutic control stage (n=705)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate screening rate (%)</td>
<td>40.2</td>
<td>93.5</td>
<td>99.3</td>
</tr>
<tr>
<td>Prophylactic anti-viral therapy (%)</td>
<td>39.2</td>
<td>41.1</td>
<td>95.8</td>
</tr>
<tr>
<td>Severe HBV reactivation (%)*</td>
<td>1.2</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>HBV related liver decompensation (%)**</td>
<td>1.0</td>
<td>1.2</td>
<td>0</td>
</tr>
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</table>

* ALT > 10 X ULN  
** bilirubin > 2 mg/dL, INR > 1.5, encephalopathy


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< 5% severe reactivation if NO prophylaxis?

HBV reactivation in patients with lymphoma and resolved HBV infection

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

HBV reactivation in HBsAg (-) anti-HBc (+) lymphoma patients: case series

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<tr>
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<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>
<tr>
<td>Niitsu (2010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Retracted due to scientific misconduct
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* 2014; 59: 2092 – 100

<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 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>1/ 2.4</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>B-cell (39)</td>
<td>HBV DNA every month*</td>
<td></td>
<td>HBV DNA increase to &gt; 2000 IU/ml (7/ 17.9)</td>
<td>1/ 2.5</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Hsu (2014)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>
<tr>
<td>Seto (2014)³</td>
<td>B-cell (63)</td>
<td>HBV DNA every month*</td>
<td>Rituximab-containing</td>
<td>HBV DNA negative &gt; positive (19/ 30.1)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Entecavir treatment upon HBV reactivation

The American Gastroenterology Association recommendation for Prevention of HBV reactivation (1)

<table>
<thead>
<tr>
<th>Risk groups (reactivation rate)</th>
<th>Description</th>
<th>Recommendation</th>
<th>Evidence level</th>
</tr>
</thead>
</table>
| High (> 10%)                    | 1. HBsAg (+) or HBsAg (-)/anti-HBc (+) B cell – depleting agents (eg, rituximab, ofatumumab)  
2. HBsAg (+) anthracycline derivatives (eg, doxorubicin, epirubicin)  
3. HBsAg (+) moderate-dose (10–20 mg prednisone daily) or high-dose (>20 mg prednisone daily ) corticosteroids daily for ≥ 4 weeks. | Antiviral prophylaxis for at least 6 months after Tx discontinuation (at least 12 months for B cell–depleting agents). Strong recommendation | Moderate-quality evidence |


The American Gastroenterology Association recommendation for Prevention of HBV reactivation (2)

<table>
<thead>
<tr>
<th>Risk groups (reactivation rate)</th>
<th>Description</th>
<th>Recommendation</th>
<th>Evidence level</th>
</tr>
</thead>
</table>
| Moderate (1-10%)                | 1. HBsAg (+) or HBsAg (-)/anti-HBc (+), TNF-α/other cytokine inhibitors, anti-cancer TKI  
2. HBsAg (+), low-dose (< 20 mg prednisone daily ) corticosteroids daily for ≥ 4 weeks  
2. HBsAg (-)/anti-HBc (+) anthracycline derivatives moderate- or high-dose steroids | Antiviral prophylaxis over monitoring Weak recommendation | Moderate-quality evidence |

Patient enrollment: June 2009 to Dec 2011 (n=150)
Last follow-up September 30, 2014
Estimated 3-year overall survival rate:

HBV reactivation (+): 52.3% (95% C.I. 50.2 - 54.4%)
HBV reactivation (-): 78.2% (95% C.I. 72.3 - 84.1%)

**Causes of death**

<table>
<thead>
<tr>
<th></th>
<th>HBV reactivation (+) (n=8)</th>
<th>HBV reactivation (-) (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma progression</td>
<td>5</td>
<td>21</td>
<td>0.64</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>R-CHOP related</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Numbers of R-CHOP cycles (median/range)**

<table>
<thead>
<tr>
<th></th>
<th>HBV reactivation (+)</th>
<th>HBV reactivation (-)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/ 2 - 8</td>
<td>6/ 1 - 8</td>
<td>0.86</td>
<td></td>
</tr>
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</table>

**Dose delay/reduction of R-CHOP chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>HBV reactivation (+)</th>
<th>HBV reactivation (-)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (62.5%)</td>
<td>17 (56.7%)</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>
### Multivariate analysis (Cox proportional hazards model)

<table>
<thead>
<tr>
<th>Variables</th>
<th>PFS</th>
<th></th>
<th>OS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P-value</td>
<td>Hazard Ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Anti-HBe (Positive vs. Negative)</td>
<td>0.61 (0.33 - 1.12)</td>
<td>0.11</td>
<td>0.46 (0.22 - 0.94)</td>
<td>0.033</td>
</tr>
<tr>
<td>Baseline LDH (&gt; ULN vs. ≤ ULN)</td>
<td>2.43 (1.22 - 4.86)</td>
<td>0.01</td>
<td>3.80 (1.59 - 9.06)</td>
<td>0.003</td>
</tr>
<tr>
<td>HBV reactivation (Yes vs. No)</td>
<td>1.68 (0.80 - 3.54)</td>
<td>0.18</td>
<td>2.00 (0.93 - 4.33)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

Yang HC et al. EASL 2015 (abstr#648)

### Receiver-operating characteristic (ROC) analysis of baseline anti-HBc (n=146) and anti-HBs (n=114)

**Anti-HBc**
- Value = 6.41
- AUC = 0.7348

**Anti-HBs**
- Value = 56.48
- AUC = 0.7932

Yang HC et al. EASL 2015 (abstr#648)
<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients</th>
<th>HBV reactivation</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Baseline anti-HBc (IU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6.41</td>
<td>108</td>
<td>5</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥6.41</td>
<td>38</td>
<td>9</td>
<td>6.39 (1.99-20.56)</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline anti-HBs (mIU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;56.48</td>
<td>29</td>
<td>5</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥56.48</td>
<td>85</td>
<td>1</td>
<td>0.06 (&lt;0.01-0.51)</td>
<td>0.011</td>
</tr>
<tr>
<td>Baseline anti-HBc/anti-HBs status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-HBc &lt; 6.41, anti-HBs ≥56.48</td>
<td>22</td>
<td>1</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>anti-HBc &lt; 6.41, anti-HBs &lt; 56.48</td>
<td>64</td>
<td>1</td>
<td>3.00 (0.18-50.10)</td>
<td>0.444</td>
</tr>
<tr>
<td>anti-HBc ≥6.41, anti-HBs &lt; 56.48</td>
<td>7</td>
<td>4</td>
<td>84.00 (7.04-1001.63)</td>
<td>0.001</td>
</tr>
<tr>
<td>anti-HBc ≥6.41, anti-HBs ≥56.48</td>
<td>21</td>
<td>0</td>
<td>&lt;0.01 (&lt;0.01-9999.99)</td>
<td>0.972</td>
</tr>
</tbody>
</table>

Yang HC et al. EASL 2015 (abstr#648)

Progression-free Survival by Baseline (Anti-HBc, Anti-HBsAb)

Overall Survival by Baseline (Anti-HBc, Anti-HBsAb)
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, APASL, AGA guidelines)

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

Summary and discussion (2)

• In lymphoma patients with resolved HBV infection (HBsAg (-) anti-HBc (+))
  – HBV reactivation induced by rituximab-containing chemotherapy is not uncommon

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

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