Hepatitis B Reactivation: A tiger in sheep’s clothing

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Natural History of Chronic HBV Infection

- Immunotolerance
  - HBV DNA
  - ALT
  - 5-30 years Infection

- Immune Clearance
  - HBeAg+
  - 5-30 years
  - months-years

- Immune Control (Non-Replicative)
  - HBeAg-
  - HBeAb+
  - low/undetectable HBV DNA
  - HBsAg +ve and HBeAg –ve
  - or HBsAg –ve, anti-HBc +ve
  - months-years

Most Oncology Patients
- Normal ALT
- Low/undetectable HBV DNA
- HBsAg +ve and HBeAg –ve
- or HBsAg –ve, anti-HBc +ve
Do you ever really get rid of HBV?

- Immune control – not clearance
- “Resolved HBV” a misnomer – still HBV DNA in liver
Along comes immune suppression

- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution
HBV Reactivation

HBV DNA

ALT

Infection

5-30 years

months-years

HBeAg+
HBeAg-
HBeAb+
HBeAg +

Immunotolerance

Immune Clearance

Immune Suppression

Immune Reconstitution

months-years
Wide clinical spectrum

- **Clinically:**
  - Range from subclinical to severe/fatal hepatitis
  - May occur during or after immunosuppression with immune reconstitution
  - Rise in HBV DNA +/- return of HBeAg
  - May occur in HBsAg –ve, anti-HBc +ve as well (more on this later…)

- ALT increase (may be mild or very dramatic)
- May progress to liver failure/death despite antiviral Tx
Definitions – a problem...

HBV reactivation

- Loss of HBV immune control in a patient with inactive or “resolved” HBV infection – we all agree on this…

- How is this defined?
  - HBV DNA rise – usually reappearance or > 1 log increase
  - Reappearance of HBsAg in HBsAg –ve, anti-HBc +ve → ‘reverse seroconversion’

- Where does the liver fit in?
  - ALT elevation – what threshold? Severity?
  - Liver failure?

I prefer HBV reactivation (DNA/HBsAg only) and HBV-associated hepatitis (reactivation + ALT/liver failure) → VERY variable across studies
Case 1

- 52 yo Asian woman presents with Stage IIIb breast cancer (ER -ve, HER2 -ve)

- PMH: HTN
- Meds: HCTZ

- No hx of liver disease

- Scheduled for surgery + XRT + adjuvant chemotherapy with cyclophosphamide plus doxorubicin followed by paclitaxel

- CBC/lytes/Creat - normal
- ALT - 18
Case 1
Case 1

EPOCH

Hepatology Consulted

HBV DNA [Log IU/mL] / Bilirubin [g/L]
Case 1

Despite lamivudine patient died of liver failure
HBsAg +ve breast cancer patients:

Rate of HBV-associated acute hepatitis = 21% \(^1\)

- With careful monitoring (HBV DNA), up to 41% with HBV reactivation\(^2\)
- HBV DNA may be undetectable by time of ALT peak
- Limited data on other solid tumors

Of those who flare:

78% chemo interruption
14% premature termination of chemotherapy\(^3\)

Hematological Malignancy: The Bigger Risk

100 patients with NHL undergoing CHOP
27 HBsAg +ve

Lok et al Gastroenterology 1991;100:182-8
Risk Factors for Reactivation

- **Malignancy**
  - NHL 40-58% of HBsAg +ve
  - Breast cancer 20-41% of HBsAg +ve

- **Chemotherapy**
  - Prednisone, anthracyclines, rituximab increased risk
  - “Potency of immunosuppression”

- **HBV DNA**
  - If detectable, increased risk
  - Elevated if HBeAg +ve

- **Demographics**
  - Men > women

**Baseline liver tests - not relevant**
Pre-emptive Lamivudine

HBsAg +ve pts with NHL treated with CHOP
Randomized ‘Pre-emptive’ vs ‘On-Demand’ Lamivudine

Lau et al Gastroenterology 2003; 125:1742-9
Case 2

Pt HBsAg +ve with HBV DNA 2.1 log IU/mL at baseline

Uninterrupted chemotherapy with no hepatitis flare – when can we stop?
Value of Pre-Emptive Antivirals

HBsAg +ve pts with NHL treated with CHOP
Randomized ‘Pre-emptive’ vs ‘On-Demand’ Lamivudine

Pre-emptive group - start LAM 1 day prior to CHOP
On-demand - start LAM if ALT>1.5 x ULN

Pre-emptive antivirals decrease HBV reactivation

Hsu et al Hepatology 2008; 47: 844-53
Antiviral Therapy

- **Which agent**
  - HBV DNA<2000 IU/mL – all fine (including LAM)
  - HBV DNA>2000 IU/mL – Entecavir/Tenofovir
  - Duration of therapy>12 mo – Entecavir/Tenofovir
  - HBV DNA/ALT q 3 months

- **When to start**
  - Ideally before/with chemotherapy
  - Do not delay start of chemotherapy

- **When to stop**
  - Baseline HBV DNA>2000 IU/mL – high risk of withdrawal flare
    - continue therapy as per chronic HBV
  - Baseline HBV DNA<2000 IU/mL – 6-12 mo after end of chemotherapy
  - Monitor for withdrawal flares (monthly HBV DNA/ALT)
Summary

- HBV reactivation is common if HBsAg +ve
- HBsAg +ve patients are usually asymptomatic
- HBsAg testing is cheap and widely available
- Effective treatment exists to prevent HBV reactivation \textit{BUT} must be started early

HBsAg testing prior to chemotherapy fits criteria for population screening
Who should be screened?

AASLD Recommends screening high-risk individuals:

- Immigrants
  - Asia, Africa, Pacific Islands, Middle East, Eastern Europe, South/Central America, Caribbean, Aboriginal
- Children of immigrants
- MSM (men who have sex with men)
- HIV/HCV +ve
- History of IDU, incarceration
- Hemodialysis patients

CDC²,³ & EASL⁴ recommend screening ALL prior to starting chemotherapy²,³

1. Chronic Hepatitis B: Update 2009 Hepatol 2009 1-36
2. Weinbaum et al MMWR 2008 1-20
3. Weinbaum et al Hepatol 2009 S35-44
4. EASL Clinical Practice Guidelines HBV J Hepatol 2009 227-42
What does ASCO say?

- Evidence insufficient to determine net benefits and harms of routine screening for chronic HBV infection.  
- Physicians may consider screening groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapy planned.  
- Antiviral therapy before and during course of chemotherapy may be considered.  

Aartz et al JCO 2010;28:3199-202
ASCO’s Position

1. Evidence for antiviral therapy weak – small studies, questionable effect on mortality
   - Small studies but very strong effect and assessed TIMING, not value of therapy
   - RCT of screening vs not very uncommon

2. Cost of screening + delay in starting chemo
   - HBsAg costs $13
   - No need to delay chemo for results of HBV testing

3. Antiviral therapy – safety + drug interactions
   - Very safe, used for HIV
   - No effect on chemotherapy pharmacokinetics
Which screening strategy is best?

- Screen All
- Screen High-Risk
- Screen None
What about the cost?

Cost effectiveness depends on screening strategy & population

Breast Cancer

<table>
<thead>
<tr>
<th>HBsAg + anti-HBc</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>Screening</td>
</tr>
</tbody>
</table>

- HBsAg testing in **all patients** is cost-effective in patients undergoing adjuvant chemotherapy for solid tumors
- Anti-HBc testing increases cost with no clear benefit

Day et al JCO 2011:29;3270-77
Cost-effectiveness of HBV screening before R-CHOP for lymphoma

Threshold (0.2%)

- United States (0.42%)
- Australia (1.1%)
- Canada (1.26%)
- ...Hong Kong

Incremental cost for 'Screen All' vs. 'Screen None' vs. 0.0

Population HBsAg prevalence (%)

Strategies:

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Cost</th>
<th>1-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen All</td>
<td>$31,646</td>
<td>85.00%</td>
</tr>
<tr>
<td>Screen High-Risk</td>
<td>$31,653</td>
<td>84.96%</td>
</tr>
<tr>
<td>Screen None</td>
<td>$31,704</td>
<td>84.86%</td>
</tr>
</tbody>
</table>

- 'Screen All' dominates other strategies – actually cost-saving!
- Also cost-effective before solid tumor chemotherapy

Zurawska JCO 2012, Wong Submitted
Screening makes sense – is it being done?

Reported HBV Screening Practices of 131 US Oncologists

- None: 62%
- High-Risk: 24%
- All: 14%
- Actual Screening Rate: 14%

Few oncologists routinely screen all patients for HBV

Khokhar et al Chemotherapy 2009;55:69-75
Lee et al Current Oncology 2010;17:32-8
How do we increase screening?

Educational intervention followed by prompt with first-time chemotherapy

- Education – no effect
- Prompt increased screening but only to 61%!!
Optimal screening strategy

- Screening high-risk individuals requires recognition of high-risk population.
- Screening all patients is most cost-effective and easiest to implement – definitely true here.
- HBsAg should be tested in all with follow-up HBV DNA in HBsAg +ve patients.
- What about anti-HBc?
Significance of Lone Anti-HBc +ve

- Indicates exposure to HBV
- Usually persists life-long but may lose after years
- No guidelines for management

**Risk for reactivation:**

- Low risk for most standard solid tumor regimens
- Risk increases with:
  - Rituximab or other anti-CD20 therapies
  - Bone Marrow/Stem Cell Transplant
Rituximab: A Particular Problem

- Monoclonal antibody against CD20 - B cell marker
- Reduces B cell numbers and antibody levels
- Increasingly used as part of CHOP-R, EPOCH-R

- Increased risk of HBV reactivation, including HBsAg-negative patients

- **Reverse Seroconversion**: Reappearance of HBsAg in previously HBsAg-negative patient due to loss of immune control
Rituximab in HBsAg-Negative

46 pts Diffuse Large Cell B Lymphoma
HBsAg -ve, anti-HBc +ve
Treated CHOP or CHOP-R

Risk of reactivation with rituximab significant in anti-HBc +ve
Rituximab: Late and Severe

- Reverse seroconversion:
  - Median 98 days \textit{AFTER} last cycle but may occur early as well
  - Median peak ALT - 809 (362-3,499) U/L
  - Median peak Bilirubin – 65 (19-248) \text{µmol/L}

- Other cases reported in literature:
  - 6 to 23 months after rituximab
  - 15 liver failure, 13 liver-related death

Risk Factors for reactivation
1. Men >> women (almost all cases)
2. Anti-HBs negative (or low titer)
3. ? Increased age (>50)

Yeo et al JCO 2009; 27:605-11
Niitsu et al JCO 2010;28:5097-100
Management of anti-HBc +ve patients receiving rituximab?

- No consensus, limited data

- Options
  1. Start antiviral therapy before chemotherapy
  2. Follow HBV DNA closely on therapy → treat if positive
  3. Follow HBsAg closely on therapy → treat if positive

Show me the data!!
Follow HBsAg & HBV DNA

54 yo Asian man stage 4 Diffuse Large Cell B Lymphoma

Patient died of liver failure despite lamivudine

- HBV DNA may rise before HBsAg becomes positive
- Treatment after ALT elevation may be too late

Yamagata et al Leuk Lymph 2007;48:431-3
HBV reactivation VERY common

69 patients anti-HBc +ve receiving rituximab-based chemo
HBV reactivation = HBV DNA > 10 IU/mL – very sensitive

- 19 reactivations
- Median 23 weeks
- 10 after chemo
- 3>1 yr after chemo
- No consequences

Suggest treat anti-HBs –ve with prophylactic antiviral

Seto JCO 2014
What’s wrong with this study?

- In my opinion – nothing!
  - Nicely done
  - Convincing

- Unfortunately – I am not ASCO!!
  - For them – no endpoints reached
  - Not practical to do HBV DNA monthly
  - Is 10 IU/mL clinically significant?
  - Why not just use HBsAg…on this they may have a point
  - Without their support…screening will not happen in most parts of the world
Should we use pre-emptive antiviral therapy?

80 anti-HBc +ve (30 HBV DNA +ve)
ETV pre-trt vs on-demand (HBV DNA > 2000 IU or HBsAg +ve)

HBV reactivation (HBV DNA>2000 IU)
- ETV: 26% (P=0.019)
- CTL: 0%

Reverse Seroconversion (HBsAg +ve)
- Overall 10.3% vs 0%
- ETV: 8% (P=0.032)
- CTL: 0%

• No clinical consequences in either group
• Could argue that on-demand therapy was very effective
• What if they had just monitored with HBsAg?

Huang JCO 2013
Management of anti-HBc +ve patients receiving rituximab?

- No consensus, limited data

- Options
  1. Start antiviral therapy before chemotherapy
     - Anti-HBs –ve and/or HBV DNA +ve
  2. Follow HBV DNA closely on therapy
     - Interval? Monthly? With Chemo?
     - When to intervene unclear – detectable? 2000 IU/mL?
  3. Follow HBsAg closely on therapy
     - Never been tested
     - Likely most cost-effective but possibly some risk
We need to speak the same language

### Table 2. Proposed grading system for HBV reactivation

<table>
<thead>
<tr>
<th>Virological</th>
<th>Hepatic</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V₁</strong></td>
<td><strong>H₀</strong></td>
<td><strong>I₀</strong></td>
</tr>
<tr>
<td>HBV DNA increase by &gt;1 log IU/mL (or from undetectable to detectable)</td>
<td>No hepatitis: ALT remains &lt;2 ULN, no change in bilirubin or INR</td>
<td>No consequence</td>
</tr>
<tr>
<td><strong>V₂</strong></td>
<td><strong>H₁</strong></td>
<td><strong>I₁</strong></td>
</tr>
<tr>
<td>Reverse Seroconversion: Reappearance of HBsAg with or without associated rise in HBV DNA (as in A)</td>
<td>Hepatitis: ALT 2 to 10x ULN with no associated change in bilirubin or INR</td>
<td>No interruption but increased frequency of HBV DNA and ALT monitoring</td>
</tr>
<tr>
<td></td>
<td><strong>H₂</strong></td>
<td><strong>I₂</strong></td>
</tr>
<tr>
<td></td>
<td>Severe hepatitis: ALT&gt;10x ULN and/or elevation of bilirubin (&gt;2 ULN) or INR (&gt;1.3)</td>
<td>Interruption of immunosuppressive therapy with re-initiation of same drug after hepatitis flare resolved</td>
</tr>
<tr>
<td></td>
<td><strong>H₃</strong></td>
<td><strong>I₃</strong></td>
</tr>
<tr>
<td></td>
<td>Fulminant Hepatitis: Criteria for 2 with development of encephalopathy or ascites</td>
<td>Interruption of immunosuppressive regimen with re-initiation of 2nd line, suboptimal, therapy</td>
</tr>
<tr>
<td></td>
<td><strong>H₄</strong></td>
<td><strong>I₄</strong></td>
</tr>
<tr>
<td></td>
<td>Death: Due to liver failure</td>
<td>Discontinuation of immunosuppression</td>
</tr>
</tbody>
</table>
Using the grading system

1. 56 yo woman starts out HBsAg –ve, anti-HBc +ve and gets R-CHOP. Becomes HBsAg +ve and put on therapy with no consequence.
   
   V2 (reverse seroconversion)
   H0 (no hepatitis)
   I0 (no change to immunosuppression)

2. 45 yo man HBsAg +ve, anti-HBc +ve, HBV DNA 200 IU/mL goes to HBV DNA 2.1E6 and develops ALT flare to 732 with jaundice leading to discontinuation of R-CHOP and move to 2nd line therapy.
   
   V1 (rise in HBV DNA > 1 log)
   H2 (ALT > 10x ULN and jaundiced)
   I3 (interruption of therapy, 2nd line treatment)
Management of HBsAg +ve clear
- Screen everyone – this is the major challenge!
- Treat positives for 6 - 12 months beyond IST
- Remember to watch for withdrawal flares

HBsAg –ve, anti-HBc +ve still a challenge
- Solid tumors – low risk, no need to screen
- Rituximab/BMT – higher risk but mgmt unclear
  - Pre-emptive therapy effective
  - Close monitoring effective
- Non-oncology – VERY limited data

Need to agree on definitions so we speak the same language

Need to raise awareness – oncology/other areas
Eventually it will be this easy...

"You've got Hepatitis Bee."