Hepatitis in patients receiving cancer chemotherapy

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Disclosure slide

- Advisory boards: Gilead and Abbvie
- Honoraria for educational meetings: AstraZeneca, Bayer, BMS, Gilead, Roche, MSD
- Travel and conference support: Bayer, BMS, Gilead, Merk Sharp Dohme, Roche, Schering Plough
- Departmental support: Bayer, BMS, Roche, Gilead, MSD, Jenssen.
- Financial interest – NO CONFLICT OF INTEREST
- There has been no arrangement, financial or other made with a company whose products are discussed in this presentation
HCV and HBV: Two very different viruses

Hepatitis C

- Hepatitis C serology is simple!
  - HCV Ab is a screening test
  - HCV Ab +ve indicates exposure to HCV
  - Hepatitis C PCR confirms current infection
  - Hepatitis C PCR ≥ 6 months defines Chronic hepatitis C infection

Hepatitis B

- Long-term suppression of viral replication
- PEG-IFNα
- Nucleos(t)ide analogues
- Very few patients ‘cured’

Hepatitis C – now a very curable disease

- **Sofosbuvir (SOF)**\(^{1,2}\)
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet

- **Velpatasvir (VEL; GS-5816)**\(^{3-5}\)
  - Picomolar potency against GT 1–6
  - 2\(^{nd}\)-generation inhibitor with improved resistance profile

- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)

Hepatitis C: Cure by Genotype
ASTRAL-1, SOF/VEL


Error bars represent 95% confidence intervals.
Hepatitis B Virus (HBV)

- Hepadnavirus family
- Non-cytopathic
- Capable of reactivation in setting of immunosuppression
- Oncogenic (hepatocellular carcinoma)
Global burden of hepatitis B

- 2 billion (≈ 1/3 world population) exposed to HBV infection
- > 350-400 million have Chronic HBV
- Total global deaths 1 million per year

World Health Organization (WHO), July 2012
Hepatitis B lifecycle

Adapted from Nguyen & Locarnini, Nat Rev 2009
Hepatitis B diagnostic panel

- The diagnostic panel for hepatitis B virus (HBV) contains three tests:

<table>
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<tr>
<td>Hepatitis B core antibody</td>
<td>Anti-HBc</td>
<td>Any infection (past or active)</td>
</tr>
<tr>
<td>covalently closed circular</td>
<td></td>
<td>viral DNA (cccDNA)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>HBsAg</td>
<td>Active infection (acute or chronic)</td>
</tr>
<tr>
<td>Hepatitis B surface antibody</td>
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Hepatitis B reactivation

• HBV replication may spontaneously increase and result in hepatitis flares.
• During immune suppression, viral replication may increase considerably.
• Following restitution of the host’s immune response, T-cell mediated liver injury may occur. (B-cells are also involved in antigen presentation and viral clearance.)
• Hepatitis B reactivation or “flares” following chemotherapy can be fatal.

Hepatitis B reactivation - Definitions

• **New Definition (2013 AASLD):**
  - HBV viral load increase $\geq 100$ ($\geq 2 \text{ Log 10}$) fold above baseline
  Or
  New appearance of HBV VL $\geq 100$ IU/ml (with previously undetectable)
Mechanisms

• Indirect through immunosuppression

• Direct through stimulation of glucocorticoid responsive element in the HBV genome
  • leading to upregulation of HBV gene expression

• Inhibition of TNF may also play a role
Types of HBV reactivation

Baseline HBV Status

- HBsAg⁺/anti-HBc⁺ HBV DNA⁺
- HBsAg⁺/anti-HBc⁺ HBV DNA⁻

Initiation of immunosuppressive therapy

- Rise in HBV DNA level compared with baseline
- Appearance of HBV DNA: HBV DNA⁻ to HBV DNA⁺
Hepatitis B reactivation - Risk

- **Chemotherapy regimes:**
  - Cytoreductive therapy prior to haematopoietic stem cell transplantation
  - Rituximab (CD20 monoclonal antibody) associated with particularly high risk
  - Steroid containing and anthracycline high risk

- **Cancer type:**
  - In general, haematological > non-haematological
  - Lymphoma (≈ 50% reactivation if sAg+ve, with mortality of ≈10%)
  - Breast cancer (41-56%)
  - Other solid tumours (14-21%)

- **Viral Characteristics:**
  - HBsAg +ve, eAg+ve, high HBV viral load
  - In resolved HBV infection (HBcAb +ve) reactivation can still occur

- **Patient characteristics:**
  - Younger age
  - Male gender
Hepatitis B reactivation

• Complications:
  – Early cessation of chemotherapy
  – Reactivation has broad clinical spectrum;
    • Mild asymptomatic hepatitis ranging to
    • Icteric hepatitis associated with 10-40% mortality

• Management:
  – Screen patients for ‘past’ and current HBV infection
  – Assess risk of reactivation or seroreversion
  – Antiviral prophylaxis prior to chemotherapy
  – Continue prophylaxis for minimum 6-12 months after cessation of chemotherapy
Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update

Jessica P. Hwang, Mark R. Samerfield, Devena E. Alston-Johnson, Donna R. Cryer, Jordan J. Feld, Barnett S. Kramer, Anita L. Sabichi, Sandra L. Wang, and Andrew S. Arez

ABSTRACT

Purpose
This updated provisional clinical opinion presents a revised opinion based on American Society of Clinical Oncology panel consensus in the context of an evolving database.

Context
Despite the 2010 provisional clinical opinion recommendation, there is still evidence of suboptimal hepatitis B virus (HBV) screening among patients at high risk for HBV infection or HBV reactivation after chemotherapy. This updated provisional clinical opinion introduces a risk-adaptive strategy to identify and treat patients with HBV infection to reduce their risk of HBV reactivation.

Provisional Clinical Opinion
Medical providers should screen by testing patients for HBV infection before starting anti-CD20 therapy or hematopoietic cell transplantation. Providers should also screen patients with risk factors for HBV infection. Screening should include both hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc), because reactivation can occur in patients who are HBsAg positive/anti-HBc positive or HBsAg negative/anti-HBc positive. Either total anti-HBs or anti-HBc immunoglobulin G (not immunoglobulin M) test should be used. Clinicians should start antiviral therapy for HBsAg-positive/anti-HBc-positive patients before or contemporaneously with cancer therapy and monitor HBsAg-negative/anti-HBc-positive patients for reactivation with HBV DNA and ALT levels, promptly starting antivirals if reactivation occurs. Clinicians can initiate antivirals for HBsAg-negative/anti-HBc-positive patients anticipating cancer therapies associated with a high risk of reactivation, or they can monitor HBV DNA and ALT levels and initiate on-demand antivirals. For patients who neither have HBV risk factors nor anticipate cancer therapy associated with a high risk of reactivation, current evidence does not support HBV screening before initiation of cancer therapy. Two panel members provided a minority viewpoint, involving a strategy of universal HBsAg and selective anti-HBc testing.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology
## Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Organisation</th>
<th>HBsAg</th>
<th>HBcAb</th>
<th>HBV DNA</th>
<th>Notes for HBcAb+ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL - 2012</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Monitor HBV DNA, treat with antivirals if +ve</td>
</tr>
<tr>
<td>CDC - 2008</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Also recommends sAb</td>
</tr>
<tr>
<td>ASCO-2015</td>
<td>✓</td>
<td>✓</td>
<td>+/-</td>
<td>Altered position from 2010</td>
</tr>
<tr>
<td>AASLD - 2009</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>If HBV DNA +ve commence antivirals</td>
</tr>
<tr>
<td>WGO- 2008</td>
<td>✓</td>
<td>✓</td>
<td>+/-</td>
<td>Monitor “HBV-markers” in occult HBV</td>
</tr>
<tr>
<td>APASLD - 2009</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>If using Rituximab – give prophylaxis</td>
</tr>
<tr>
<td>BSH-2008</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Use of vaccine in sAb-ve cAb+ve</td>
</tr>
<tr>
<td>GESA - 2010</td>
<td>✓</td>
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European Association for the Study of the Liver (EASL) guidelines 2012

- All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and Anti-HBc prior to initiation of treatment (A1)

- HBsAg-positive candidates should receive pre-emptive NA administration during therapy (regardless of HBV DNA levels) and for 12 months after cessation of therapy (A1)
  - Low VL (<2000 IU/ml) and limited duration - Lamivudine
  - High VL (>2000 IU/ml) and/or prolonged duration – antiviral with high barrier to resistance, eg entecavir or tenofovir (C1)

- Isolated anti-HBc positive patients should have DNA tested
  - DNA positive (occult HBV) treat as HBsAg positive (C1)
  - DNA negative, monitor closely (C1)
Patient receiving cancer chemotherapy or other immunosuppressive therapy

Screen for hepatitis B (HBsAg, HBcAb)

Past exposure (HBsAg -ve, HBcAb +ve)

HBV DNA detectable?

No

Patients receiving intensive immunosuppression or hematopoietic stem cell transplant

No

Monitor LFTs, HBsAg and HBsAb and HBV DNA during chemotherapy

seroreversion

Yes

Occult HBV

Current infection (HBsAg +ve)

No previous exposure (HBsAg -ve, HBcAb -ve)

consider
HBV screening before adjuvant chemotherapy for breast cancer patients would **prevent a significant number of reactivations**, would likely be **moderately cost-effective**, and may **extend the lives of breast cancer patients**.
Summary – Key points

• Hepatitis B
  • Screen patients with appropriate serology
    • HBV sAg and cAb
  • Refer for hepatology advice if serology positive

• Hepatitis C
  • Screen patients with HCV Ab, if +ve test PCR
  • Refer for hepatology advice if PCR +ve
THANK YOU

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