Hepatitis B & C in patients receiving cancer chemotherapy

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Disclosure slide

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- Honoraria for educational meetings: AstraZeneca, Bayer, BMS, Gilead, Roche, MSD
- Advisory boards: NO CONFLICT OF INTERESTS
- 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
HBV and HCV – a global problem

• 2 billion people worldwide have been infected by HBV
  – 350 million have chronic HBV infection
  – 600,000 die annually as a result of acute or chronic infection

• 150 million infected with HCV
  – 350,000 die annually from liver disease

World Health Organization (WHO), July 2012
Red: High (HBsAg prevalence ≥8%)
Orange: Intermediate (HBsAg prevalence 2%–7%)
White: Low (HBsAg prevalence <2%)
Hepatitis B prevalence in the general population: HBsAg

- <0.5
- 0.5 - <1
- 1 - <2
- 2 - <4
- 4 - <6
- 6 - <8
- ≥8
- No recent data
- Not included in review

Non-visible countries:
- Liechtenstein
- Luxembourg
- Malta
Hepatitis C prevalence in the general population: anti-HCV

Legend:
- <0.5
- 0.5 - <1
- 1 - <2
- 2 - <4
- 4 - <6
- 6 - <8
- ≥8
- No recent data
- Not included in review

Non-visible countries:
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### Hepatitis B serology

<table>
<thead>
<tr>
<th>Serology</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBsAg</strong></td>
<td>Hallmark of current HBV infection</td>
</tr>
<tr>
<td><strong>HBsAb</strong></td>
<td>Immunity (past infection, vaccination)</td>
</tr>
<tr>
<td><strong>HBcAg</strong></td>
<td>Antigen expressed in infected hepatocytes</td>
</tr>
<tr>
<td><strong>HBcAb total</strong></td>
<td>Indicates exposure to HBV, current or past</td>
</tr>
<tr>
<td><strong>HBcAb IgM</strong></td>
<td>Indicates acute infection, may occur in flares</td>
</tr>
<tr>
<td><strong>HBeAg</strong></td>
<td>Marker of active viral replication, high infectivity</td>
</tr>
<tr>
<td><strong>HBeAb</strong></td>
<td>‘e’ seroconversion &amp; remission if HBV DNA low or negative</td>
</tr>
<tr>
<td><strong>HBV DNA</strong></td>
<td>Active viral replication &amp; increased infectivity</td>
</tr>
</tbody>
</table>
Chronic Hepatitis B infection

Liver

Serum

sAg +ve

cAb

cAg +ve
“Past” Hepatitis B infection

Liver

Serum

ccc DNA

sAb

cAb

www.esmo2012.org
Hepatitis C serology

• Screening test is HCV antibody
  – HCV Ab +ve = past or present infection

• HCV PCR determines if patient currently infected
  – HCV Ab +ve, -ve HCV PCR = Past infection
  – HCV Ab+ve, +ve HCV PCR = current infection
Hepatitis C serology

Liver

Serum

HCV RNA
+ve

CURRENT INFECTION

www.esmo2012.org
Hepatitis C serology

Liver

Serum

HCVAb

PAST INFECTION
(spontaneous clearance or prior treatment)
Hepatitis B reactivation

- Hepatitis B virus is non-cytopathic
- Injury occurs as a result of the host’s immune response
- The natural history of vertical acquired HBV is that of prolonged immunotolerance followed by immune clearance

Hepatitis B reactivation

- During immune suppression, viral replication can increase.
- Restitution of the host’s immune response can cause T-cell mediated liver injury.
- Hepatitis B reactivation following chemotherapy can vary in presentation from asymptomatic ALT elevation to fatal hepatic decompensation.
Mechanism of HBV reactivation

Chronic Hepatitis B - (HBsAg+ve)

Chemotherapy

Viral load

ALT

HBsAg+ve

Jaundice
HBV prior exposure (HBsAg-ve, HBcAb+ve)

HBsAg-ve, HBcAb+ve → SEROREVERSION → HBsAg+ve
Definition of HBV reactivation

• HBV viral load ≥ 10 fold or above $10^8$ IU/ml
• ALT increase ≥ 3 x ULN or > 100 IU/L above baseline

HBV reactivation – why is it important?

• Premature cessation of chemotherapy

• Liver-related complications
  – Reactivation has broad clinical spectrum;
    • Mild asymptomatic hepatitis
    • Icteric hepatitis associated with 10-40% mortality

• Treatment after reactivation is less successful than pre-emptive therapy\(^1,^2\)

\(^1\) Lau et al. Gastroenterology 2003; 125: 1742–9
Hepatitis B reactivation - Incidence

• Variable reporting due to lack of uniformity of definition
• Likely to be under reported because of a failure to recognize through lack of viral load data\(^1\)
  – without sequential viral load testing nearly 50% of cases are missed because viral load is already significantly declined by the time hepatitis develops
• Incidence is related to:
  – type of malignancy and chemotherapy used
  – hepatitis B serology (sAg positive >> sAg negative)\(^2\)

\(^1\)Yeo et al. J.Med. Virol 2003;70: 553-61
### TABLE IV. Characteristics of the 78 Patients With HBsAg Positive

<table>
<thead>
<tr>
<th></th>
<th>Patients who had hepatitis B viral reactivation during chemotherapy</th>
<th>Patients who did not develop hepatitis B viral reactivation during chemotherapy</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>15</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td>6 (40%)</td>
<td>9 (14%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Gastrointestinal cancers</td>
<td>2 (13%)</td>
<td>17 (27%)</td>
<td>0.336</td>
</tr>
<tr>
<td>Lung cancers</td>
<td>3 (20%)</td>
<td>5 (8%)</td>
<td>0.177</td>
</tr>
<tr>
<td>Breast cancers</td>
<td>2 (13%)</td>
<td>18 (29%)</td>
<td>0.329</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2 (13%)</td>
<td>14 (22%)</td>
<td>0.723</td>
</tr>
<tr>
<td><strong>HBeAg status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8 (53%)</td>
<td>8 (13%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Negative</td>
<td>7 (47%)</td>
<td>49 (78%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (73%)</td>
<td>27 (43%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Female</td>
<td>4 (27%)</td>
<td>36 (57%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>44.07</td>
<td>51.3</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>20–64</td>
<td>32–74</td>
<td></td>
</tr>
<tr>
<td><strong>Malignant liver infiltration</strong></td>
<td>6 (40%)</td>
<td>16 (25%)</td>
<td>0.339</td>
</tr>
<tr>
<td>Pretreatment (baseline) biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ALT levels (normal &lt; 58 IU/L)</td>
<td>63 (range: 18–234)</td>
<td>42 (range: 18–226)</td>
<td>0.108</td>
</tr>
<tr>
<td>Mean total bilirubin levels (normal &lt; 15 (\mu)mol/L)</td>
<td>7 (range: 2–14)</td>
<td>10 (range: 1–140)</td>
<td>0.512</td>
</tr>
<tr>
<td>Median no. of cycles of chemotherapy prior to peak alanine transaminase</td>
<td>3 (range: 1–5)</td>
<td>3 (range: 1–17)</td>
<td></td>
</tr>
</tbody>
</table>

**Including 19 patients who developed “hepatitis” in the absence of HBV reactivation.**
### TABLE Va. Immunosuppressive Agents Used in the 78 HBsAg Positive Patients

<table>
<thead>
<tr>
<th>Patients who had hepatitis B viral reactivation during chemotherapy</th>
<th>Patients who did not develop hepatitis B viral reactivation during chemotherapy</th>
<th>$P$ value</th>
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</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>15</td>
<td>63</td>
</tr>
<tr>
<td>Steroids</td>
<td>11 (73%)</td>
<td>31 (49%)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>9 (60%)</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>9 (60%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>3 (20%)</td>
<td>25 (40%)</td>
</tr>
<tr>
<td>Folinic acid</td>
<td>2 (13%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>7 (47%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Etopside</td>
<td>4 (27%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Platinum compounds</td>
<td>3 (20%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1 (7%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>2 (13%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Others</td>
<td>2$^a$ (13%)</td>
<td>20$^b$ (32%)</td>
</tr>
</tbody>
</table>

$^a$These included 1 Methotrexate and 1 mitomycin.

$^b$These included 10 methotrexate, 2 fludarabine, 4 cytarabine, 1 asparaginase, 2 bleomycin, and 1 melphalan.
Hepatitis B reactivation - Risk

• **Patient characteristics:**
  – Younger age
  – Male gender

• **Chemotherapy regimens:**
  – 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
Hepatitis B Virus Reactivation in Lymphoma Patients With Prior Resolved Hepatitis B Undergoing Anticancer Therapy With or Without Rituximab

HBV seroreversion with rituximab

- Prospective study 2003 to 2006 in Hong Kong\textsuperscript{1}
- 104 lymphoma cases treated CHOP or R-CHOP
  - 80/104 HBsAg -ve
  - 46/80 HBcAb +ve (resolved infection)
- In 25 treated with CHOP
  - None had reactivation
- In 21 treated with R-CHOP
  - 5 developed reactivation
  - 1 died of hepatic failure

\textsuperscript{1}Yeo et al. Journal of clinical oncology. 2009;27 (4) 605-611
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-2010</td>
<td>✓</td>
<td>+/-</td>
<td></td>
<td>Consider In hematopoietic cell transplant and rituximab</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>
<td>✓</td>
<td>✓</td>
<td>If HBV DNA +ve commence antivirals</td>
</tr>
</tbody>
</table>
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
    - Yes
      - Patients receiving intensive immunosuppression or hematopoietic stem cell transplant
        - No
        - Yes
          - Consider
            - Monitor LFTs, HBsAg and HBsAb and HBV DNA during chemotherapy
            - Seroreversion
  - Yes
    - Occult HBV
      - Yes
        - Evidence of hepatic inflammation/ fibrosis
          - ALT elevated + HBV DNA >20000 IU/ml
          - Significant fibrosis with detectable HBV DNA
            - Yes
              - Commence antiviral treatment (as per local protocol)
            - No
              - Commence lamivudine* 1 week prior to chemotherapy and continue for at least 6 months after chemotherapy or until immune system reconstituted
                - Monitor LFTs and HBV DNA for 1 year
                - * other potent inhibitors of HBV replication with lower resistance rates such as entecavir and tenofovir can be considered

- Current infection (HBsAg +ve)
  - Assess for treatment or prophylaxis
    - Clinical assessment + LFTs + HBeAg + HBV DNA +/- Liver histology
  - No
    - Start chemotherapy

- No previous exposure (HBsAg -ve, HBcAb -ve)
  - Start chemotherapy
Hepatitis C and Cancers

• Exacerbation of HCV occurs less frequently than HBV reactivation and significance more contentious
• HCV flares can occur, especially in those receiving Rituximab.
• In 207 consecutive patients with NHL, biochemical flares (ALT > 5x ULN) occurred in;
  – 26.3% (5/19) of HCV infected (all received Rituximab)
  – 2.1% (4/188) of non-HCV infected

Hepatitis C “reactivation”

- No clear definition
- Unlike Hepatitis B viral suppression with NAs, current HCV treatments are IFN-based and poorly tolerated and require planning
- Literature limited to a few case series & reports
- Position is likely to change with development of better tolerated anti-HCV therapies and more immunosuppressive chemotherapies
Fig. 1. (a–f) Virological, immunological and biochemical changes during and after Rituximab-based chemotherapy in patients #1–6. R-CHOP: Rituximab–Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; R-FC: Rituximab–Fludarabine + Cyclophosphamide.
HCV reactivation recommendation

• Check HCV status (HCV Ab ± HCV PCR prior to treatment)
• If positive HCV RNA, check VL and assess fibrosis (non-invasive)
• Monitor LFT and VL during therapy (monthly)
• If Bilirubin increase or evidence of decompensation (in cirrhotic patients) consider cessation of chemotherapy
Summary – Key points

• HBV-
  – Screen patients with sAg and cAb
  – Refer for hepatology advice

• HCV-
  – Screen patients with HCV Ab, if +ve do PCR
  – Refer for hepatology advice
Thank You