Hepatitis B Reactivation

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Outline

• Case
• Definition
• Scenarios
• Data
• Gaps in knowledge
Case

- 45 year old female born in Romania and then immigrated to the United States 10 years ago was diagnosed with Non-Hodgkin Lymphoma (NHL)

- Presented to Hematology department
  - Baseline comprehensive blood tests showed normal liver enzymes

- She denied any history of liver disease or family history of liver disease

- Patient was initiated with CHOP + Rituximab (R-CHOP) and received 5 cycles
Case

- 9 weeks after last cycle of chemotherapy, patient presented with increasing fatigue and her husband noticed that her eyes were turning yellow

- Labs at office visit
  - ALT 630 IU/L
  - AST 558 IU/L
  - Total Bilirubin 4.5 mg/dl
  - Direct Bilirubin 3.0 mg/dl
  - INR 1.5
  - HBsAg positive
  - Anti-HBc positive
  - HBV DNA PCR 2 million IU/ml
  - Platelets: 180K

- Exam:
  - AAO X 3, No asterixis
  - Vitals stable
  - ABD: Mildly tender liver edge palpable, no splenomegaly or ascites
Clinical diagnosis

- Acute liver failure in the setting of NHL and R-CHOP
  - Clues to the most likely diagnosis
    - **Patient:**
      - Born in Romania (endemic area for hepatitis B)
      - Immigrant to the US
    - **Setting:**
      - Disease: NHL
      - Chemotherapy: R-CHOP

- Hepatitis B reactivation related acute liver failure in the setting of NHL and R-CHOP exposure

- How to treat this patient?

- Is this preventable?
HBV Reactivation

• **Definition:**
  
  – An abrupt rise in HBV DNA levels among patients who are HBsAg-positive
  
  or
  
  – the reappearance of serum HBV DNA in those with serologic evidence of resolved HBV infection (negative HBsAg and positive anti-HBc antibody) also called as reverse seroconversion
Why does HBV reactivation occur?

Reactivation occurs as HBV persists even after HBsAg clearance by integrating with the host DNA by forming covalently closed circular (ccc) DNA. Upon immunosuppression the host immune system’s control may disrupt leading to active HBV replication.
Clinical setting

- Liver Transplantation
- Bone Marrow Transplantation
- Non-Liver Solid Organ Transplantation
  - Kidney, Heart, Lung or other transplantation
- Non-Transplantation setting
  - Cancer chemotherapy
  - Immunosuppression
    - Anti-B cell therapies
    - TNF blockers
    - High dose steroids
Clinical Presentation

• Hepatitis B viremia
• Biochemical Hepatitis
• Decompensated Liver disease
• Reverse Seroconversion (Seroreversion)
Reactivation of Hepatitis B

Hoofnagle JH. Hepatology 2009;49:S156
Risk of reactivation by country of birth: Prevalence of HBV Infection
Prior to 2008:
Does anti-HBV therapy improve outcomes in HBV reactivation
Lamivudine prevents HBV-reactivation

Lamivudine prevents HBV-related hepatic failure

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Lamivudine Group, n/n</th>
<th>Control Group, n/n</th>
<th>Relative Risk (95% CI)</th>
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### Hepatitis B mortality

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Summary I

• Pre-emptive lamivudine therapy reduced the risk of
  – HBV reactivation from 35.6% to 2.8% (p<0.0001)
  – HBV-related liver failure from 5.7% to 0.5 % (p = 0.0002)
  – HBV-related mortality from 7.0% to 0.5 % (p < 0.0001)

• NNT to prevent one death is 15 patients with pre-emptive lamivudine
Status

- Anti-HBV therapy prevents HBV reactivation, HBV related death and mortality

Key question that emerges:
- Should we check all patients for HBsAg prior to cancer chemotherapy?
- Should we pre-emptively treat all patients?
CDC September 2008
CDC Recommendations

• All patients undergoing cancer chemotherapy should be tested for hepatitis B prior to initiation of cancer chemotherapy
Prevention and Treatment of Reactivation

- Antiviral prophylaxis
- Active treatment
AASLD Practice Guidelines 2009: Antiviral Prophylaxis of Hepatitis B Carriers Who Receive Immunosuppressive or Cytotoxic Chemotherapy

* HBsAg and anti-HBc testing should be performed in patients who are at high risk of HBV infection, prior to initiation of chemotherapy or immunosuppressive therapy.
  – Screening Yes

* Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy.
  • Patients with baseline HBV DNA<2,000 IU/mL level should continue treatment for 6 months after completion of chemotherapy or immunosuppressive therapy.
  • Patients with high baseline HBV DNA (>2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients.
  • Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (<12 months) and baseline serum HBV DNA is not detectable.
  • Tenofovir or entecavir is preferred if longer duration of treatment is anticipated.
  • IFN- should be avoided

EASL Guidelines 2010: Immunosuppressed Patients

- Patients undergoing immunosuppressive treatment or chemotherapy, even for short-term courses:
  - Screening: Yes

- HBsAg-positive patients (inactive carriers) should be tested for HBV DNA levels and treated with lamivudine

- Duration: Up to 12 months after cessation of immune suppression or chemotherapy.

- Anti-HBc positive carriers (HBsAg negative ± anti-HBs, past infection) should only be closely followed without pre-emptive anti-HBV treatment.
  - HBV viraemia and ALT levels should be tested bimonthly and in case of HBV DNA reactivation (even without ALT elevation) a potent drug should be urgently added to avoid hepatic flares.
American Society of Clinical Oncology Provisional Clinical Opinion: Chronic Hepatitis B Virus Infection Screening in Patients Receiving Cytotoxic Chemotherapy for Treatment of Malignant Diseases

• **No routine screening prior to cancer chemotherapy**
  - The evidence is insufficient to determine the net benefits and harms of routine screening for chronic HBV infection in individuals with cancer who are about to receive cytotoxic or immunosuppressive therapy or who are already receiving therapy.

• Individuals with cancer who undergo certain cytotoxic or immunosuppressive therapies and have HBV infection or prior exposure to HBV may be at elevated risk of liver failure from HBV reactivation. Physicians may consider screening patients belonging to groups **at heightened risk for chronic HBV infection or if highly immunosuppressive therapy** is planned. Highly immunosuppressive treatments include, but are not limited to, **hematopoietic cell transplantation and regimens including rituximab**. Screening based on a high risk of prior HBV exposure or risk of reactivation due to planned therapeutic regimens should include testing for HBsAg as a serologic marker for HBV infection. In some populations, testing for anti-HBc should also be considered. There is no evidence to support serologic testing for anti-HBs in this context. When evidence for chronic HBV infection is found, antiviral therapy before and throughout the course of chemotherapy may be considered to reduce the risk of HBV reactivation, although evidence from controlled trials of this approach is limited. Screening and/or treating HBV infection should not delay the initiation of chemotherapy.

Current status

• No uniform recommendations if testing should be performed

• A recent meta-analysis restricted to patients with solid tumors and receiving cancer chemotherapy
  – Confirmed reduction of risk with anti-HBV therapy

• What to do if you find someone has prior exposure to hepatitis B?
  – HBsAg negative and anti-HBc positive
  – HBV DNA negative
  – Anti-HBS negative

Paul et al. The Annals of Internal Medicine 2015
Lo Re V et al. The Annals of Internal Medicine 2015
What about HBsAg-negative and anti-HBc positive patients?
Risk of reverse seroconversion

• Rate of reverse seroconversion is linked to the degree of immunosuppression and the setting

• Rate of reactivation without Rituximab (or anti-B cell therapies) is 2-3%

• High risk therapies
  – Rate of reactivation with CHOP-Rituximab is 7%-25%
    • FDA Black Box warning regarding risk of reactivation
  – Tyrosine kinase inhibitors (Imanitinib/nilotinib)
  – Anthracyclines (Doxorubicin/epirubicin)

• Risk of HBV-related liver failure is as high as 33% in those who reactivate

• Unclear if pre-emptive versus close monitoring of HBV DNA or serum ALT

Clinical and research priorities to improve outcomes

• **All should be tested prior to immunosuppressive therapy**
  – Increased funding for research dissemination
  – Education
  – Change in guidelines and physician behavior
  – Community effectiveness research

• **HBsAg-positive**
  – Pre-emptive therapy is needed
    • Trials: Newer anti-virals vs. Lamivudine
  – Duration
  – When and how to stop treatment

• **HBsAg-negative and anti-HBc positive**
  – Rituximab/Tyrosine kinase inhibitors/Anthracyclines
  – Studies are needed- Prophylaxis vs. monitoring HBV DNA/HBsAg/other biomarkers
  – Duration
  – When and how to stop treatment
Thank you!

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