Occult Hepatitis B viral infection (OBI) in patients on chemotherapy

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Hong Kong Association for the Study of Liver Diseases
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## Milestones in knowledge of OBI

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<tr>
<th>Year</th>
<th>Journal</th>
<th>Authors</th>
<th>Topic</th>
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<tr>
<td>1975</td>
<td>Gastroenterology</td>
<td>Wands et al</td>
<td>OBI reactivation in patients undergoing chemotherapy</td>
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<td>1978</td>
<td>NEJM</td>
<td>Hoofnagle et al</td>
<td>HBV transmission by blood transfusion from an OBI donor</td>
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<tr>
<td>1981</td>
<td>NEJM</td>
<td>Shafritz et al</td>
<td>HBV DNA integration in the hepatocyte genome of HBsAg-ve individuals</td>
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<td>1988</td>
<td>Lancet</td>
<td>Thiers et al</td>
<td>Acute hepatitis B in chimpanzees injected with HBV isolates from blood of OBI carriers</td>
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<td>1989</td>
<td>Proc Natl Acad Sci</td>
<td>Kaneko et al</td>
<td>PCR detection of HBV DNA in serum of HBsAg-ve individuals</td>
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<td>1994</td>
<td>Lancet</td>
<td>Chazouilleres et al</td>
<td>Liver transplant from OBI donors may induce hepatitis B in recipients</td>
</tr>
<tr>
<td>1994</td>
<td>J Clin Invest</td>
<td>Michalak et al</td>
<td>OBI in patients recovered from acute hepatitis B</td>
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<td>1996</td>
<td>Nature Medicine</td>
<td>Rehermann et al</td>
<td>A strong CTL-specific anti HBV response persists over the time in patients who recovered from acute hepatitis B</td>
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<td>1999</td>
<td>NEJM</td>
<td>Cacciola et al</td>
<td>OBI is associated with cirrhosis in patients with chronic HCV and the virus is wild type</td>
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<td>2002</td>
<td>Lancet Inf Dis</td>
<td>Torbenson and Thomas</td>
<td>First systemic review of the OBI field</td>
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<td>2004</td>
<td>Gastroenterology</td>
<td>Polliciono et al</td>
<td>Molecular analysis of a large series of liver tumor tissues confirmed the association between OBI and HCC</td>
</tr>
<tr>
<td>2008</td>
<td>J Hepatology</td>
<td>Raimondo et al</td>
<td>Statements on OBI by a large international panel of experts</td>
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[Raimondo G, Semin Immunopathol 2012]
HBV viral genome transformed by cellular DNA repair factors to the **covalently closed circular (ccc)** DNA. This form of the viral genome can **stay in the nucleus and replicate** via reverse transcription for the **entire life span of the infected hepatocyte**.
• Long lasting persistence of HBV cccDNA in the nuclei of hepatocytes

• HBsAg disappearance + anti-HBs production ≠ complete clearance of virus in the liver

• Strong suppression of viral replication gene expression with latent virus persistence in liver by host immune system
Occult HBV – Definition

• Presence of HBV DNA in the liver of individuals testing HBsAg-ve by currently available assays
• With detectable or undetectable HBV DNA in the serum
• When detectable, serum HBV DNA level is usually very low (<200 IU/ml)
• Seropositive OBI (anti-HBc and/or antiHBs +ve)
• Seronegative OBI (both anti-HBc & antiHBs -ve)

Raimondo G, J Hepatology 2008
OBI

- Seropositive
  - HBsAg lost after AH
  - HBsAg lost during CH

- Seronegative
  - Primary occult
  - Progressive antibody disappearance

- HBV DNA levels < 200 IU/ml

"false" OBI

- Infection with S gene escape mutants
- HBV DNA levels comparable to overt infection

[Raimondo G, J Hepatol 2008]
Typical course of acute resolving hepatitis B leading to occult persistent infection and selection of escape mutants

Gerlich W, Dig Dis 2010
5th Phase of Chronic HBV infection

• In the “‘HBsAg-negative phase’” after HBsAg loss, low-level HBV replication may persist with detectable HBV DNA in the liver.

• Generally, serum HBV DNA is not detectable, while anti-HBc antibodies +/-anti-HBs are detectable.

[ EASL 2012 ]
OBI virology & immunology

• Replication competent HBV but strong suppression of replication by host

• Rarely HBV mutant with defective replication activity

• Long lasting T cell immune response vs HBV epitopes
Mechanisms of OBI reactivation

Chemotherapy +/- Monoclonal Ab
Immunosuppression

Enhanced viral Replication

Beginning of chemoRx:
Intense intrahepatic mass of viral antigens

Direct cell damage → *Fibrosant cholestasis hepatitis*

Immune reconstitution during or post chemoRx → T cell immune reaction vs viral replication

→ *T lymphocyte mediated liver injury → lobular hepatitis*

rarely
Diagnosis of OBI

- Gold standard: analysis of DNA extracts from liver by PCR technique, liver specimen only available in minority

- HBsAg, anti-HBs, anti-HBc IgG, PCR based assays for serum HBV DNA

- 18% seropositive patient has detectable serum HBV DNA vs 8% seronegative patients has detectable serum HBV DNA
  
  [Minuk GY, J Hepatology 2005]

- General agreement to consider all anti-HBc +ve individuals as potential OBI carriers (pOBI)
  
  [Marzano A, Dig Liver Dis 2007]

- 7-20% of all OBI are -ve for all serum markers
  
AntiHBc Assay

- HA using Abbott ARCHITECT® anti-HBc II assay

- Sensitivity 99.1% (CI 94.2% - 100%)
- Specificity 99.1% (CI 96.6% - 99.9%)
- PPV 98.1% (CI 92.8% - 99.7%)
- NPV 99.6% (CI 97.3% - 100%)
OBI prevalence

- Prevalence higher in populations at high risk of parentally transmitted HBV
- Depends on the HBV endemicity in different areas
- Sensitivity of the HBV DNA detection method
- Hong Kong healthy hematopoietic stem cell donors with OBI: 15.3% [Hui CK et al, J Hepatol 2005]
- 21% seropositive OBI in a lymphoma patient cohort in Hong Kong [Cheung WI et al, HKMJ 2011]
HBV reactivation in OBI patient receiving chemotherapy

• First reported in 1975

• Median reported reactivation rate in OBI patients treated for haematological malignancies 4.5% (0.72%-50%)
  
  [Zullo A, World J of Gastrointestinal Oncology 2012]

No unified definition and heterogenous population

• HBV reactivation rate in haematological malignancies is higher in other oncology fields, because of immune system involvement (disease itself, duration and profound depletion of T/B lymphocytes associated with chemotherapy-immunotherapy)
Patient A

HBV DNA Log 10 (IU/ml)
ALT (IU/L)

ChemoRx Stopped
S-seroreversion
antiviral

Baseline 4 8 12 16 20 24 28 32 36 40 44

Time Duration (weeks)

[ Cheung WI et al, APDW 2012]
HBV reactivation in OBI patient receiving chemotherapy

• During reactivation:
  1. Virological breakthrough: serum HBV DNA > 1 log ↑ compared to nadir, reconfirmed in 2 consecutive serum tests
  2. s-seroreversion
  3. ALT > ULN

[Marzano A, Dig Liver Dis 2007]
Reactivation risk factors

- *Haematological malignancies e.g. lymphoma.*

1. Solid tumors do not usually have immunosuppressive effects
2. Chemotherapy in non-haemic malignancies tends to be less immunosuppressive.
Reactivation risk factors

• **Immunotherapy with monoclonal antibodies:**
  1. Meta-analysis of Rituximab use in OBI:
     HBV reactivation OR 5.73 (95% CI 2.01-16.33, \( p=0.0009 \))
     [Evens AM, Ann Oncol 2011]
  2. Alemtuzumab (anti-CD52)
     [Iannitto E, Eur J Jaematol 2005]

• **High risk immunosuppressive drugs:**
  1. Fludarabine alone or with other drugs
     [Picardi M, Haematologica 2003]
  2. Glucocorticoids and anthracyclines regimen
     [Lau GK, Hepatol Int 2008]
OBI reactivation risk factors

- Conflicting data

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<tr>
<th>Risk factors</th>
<th>Pros</th>
<th>Cons</th>
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<tr>
<td></td>
<td>Francisci D, Infection 2010</td>
<td>D’Andrea M, Dig Liver Dis 2009</td>
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<td>MatsueK, Cancer 2010</td>
<td>Ji D, Eur J Haematologica 2010</td>
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<td>Niitsu N, J Clin Oncol 2010</td>
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<td>Serum HBV DNA positivity</td>
<td>Ferraro D, Liver Int 2009</td>
<td>Koo YX, Cancer 2010</td>
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<td>Cheung WI, HKMJ 2011</td>
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<tr>
<td>Male</td>
<td>Yeo W, J Clin Oncol 2004</td>
<td>Persico E, Haematologica 2003</td>
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<td></td>
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<td>Ferraro D, Liver Int 2009</td>
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Sequelae of reactivation

- Self-limiting hepatitis to severe hepatitis with liver failure
- Mortality rate of HBV reactivation in OBI patients on chemotherapy 5% - 40%
- HBV reactivation causes progressive liver damage
- Potentially effective chemotherapy for the primary haematological malignancies has to be suspended, affecting the prognosis
Management controversies

• Monitor and treat
  I) Parameters to monitor
  1. Serum HBV DNA ? Frequency (1-3 months)
  2. HBsAg (Not all OBI reactivation cases had s-seroreversion)
  3. LFT
  II) When to start treatment

• Check and treat (universal prophylaxis)

• Duration of therapy / end point
<table>
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<th><strong>Monitor and treat</strong></th>
<th><strong>Check and treat (UP)</strong></th>
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<td>AISF 2007 (BVI, CVI)</td>
<td>Low immuno-suppression: monitor HBsAg (q1-3m)</td>
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<td></td>
<td>1) Intense immuno-suppression</td>
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<td></td>
<td>2) Baseline HBV DNA +ve</td>
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<td></td>
<td>3) Chronic liver disease</td>
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<td>AASLD 2009</td>
<td>Monitor HBV DNA</td>
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<tr>
<td>EASL 2012 (C1)</td>
<td>Baseline HBV DNA -ve: monitor HBV DNA (q 1-3 m)</td>
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<td></td>
<td>Detectable HBV DNA</td>
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<tr>
<td>APASL 2012 (IVA)</td>
<td>Use of biologics: monitor HBV DNA</td>
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Baseline detectable serum HBV DNA

Retrospective:
75 HBsAg –ve with oncohematological diseases

18 baseline serum HBV DNA +ve
13 no reactivation
5 reactivation

57 baseline serum HBV DNA -ve
6 reactivation
51 no reactivation

Reactivaton defined as HBsAg turned positive

Baseline HBV DNA +ve reactivation: 27%
Baseline HBV DNA –ve reactivation: 10%

[Ferraro D, Liver Int 2009]
Retrospective: 58 HBsAg–ve and anti-HBc +ve Patients with lymphoma

3 baseline serum HBV DNA +ve

0 reactivation

55 baseline serum HBV DNA -ve

1 reactivation

54 no reactivation

Reactivation defined as serum HBV DNA > 1 log ↑ compared to baseline or absolute ↑ > 10^5 cpm

Reactivation rate in baseline HBV DNA +ve group: 0%
Reactivation rate in baseline HBV DNA-ve group: 1.8%

[Koo XY, Cancer 2010]
Prospective: 28 seropositive HBsAg –ve Patients with lymphoma

8 baseline serum HBV DNA +ve
0 reactivation
8 no reactivation

20 baseline serum HBV DNA -ve
3 reactivation
17 no reactivation

Reactivation defined as serum HBV DNA > 1 log ↑ compared to baseline reconfirmed in consecutive serum test at least 4 weeks apart

Reactivation rate in baseline HBV DNA +ve group: 0%
Reactivation rate in baseline HBV DNA-ve group: 15%
Monitor +/- Treatment

- Baseline serum HBV DNA positivity not necessarily predict HBV reactivation in OBI patients receiving chemotherapy

- Small sample size, need to confirm with larger prospective studies

Universal Prophylaxis

- ¼ HBV DNA +ve patients has reactivation, pre-emptive treatment should be considered

- PPV ~ 27.8 %, NPV 89.5%

- about ¾ will receive needless, costly treatment

- In depth cost/efficacy analysis warranted
Management strategies

- Local OBI prevalence and reactivation rate

- Cost- effectiveness of monitoring + targeted prophylaxis vs universal prophylaxis

- Turn around time and costs for serum HBV DNA tests

- Patient factors:
  1. comorbidities e.g. chronic liver disease
  2. duration and type of chemotherapy
  3. use of monoclonal antibodies/ strong immunosuppressants
  4. high baseline serum HBV DNA ? False OBI
Future studies

- Duration and interval of monitoring (esp those on monoclonal antibodies)
- Optimal timing of initiation of antiviral
  1. Serum HBV DNA turned from undetectable to detectable
  2. Serum HBV DNA absolute level
  3. Serum HBV DNA > 1 log ↑ compared to nadir, reconfirmed in consecutive serum test
- End point of antiviral treatment
Conclusion

- HBsAg disappearance and anti-HBs production is not equal to the complete clearance of virus in the liver
- General agreement to consider all anti-HBc +ve individuals as potential OBI carriers
- Patient at high risk of reactivation: haematological malignancy, receiving immunotherapy or certain strong immunosuppressants
- Two management trends: monitor & treat vs check & treat
- Cost/efficacy analysis on universal prophylaxis according to baseline HBV DNA detectability is warranted
- Individual patient factors should be considered in management strategy
- No consensus on definition of HBV reactivation in OBI patients, optimal treatment duration.
Thank you
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