Management of chemotherapy-induced hepatitis B virus reactivation

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Abstract

Hepatitis B virus (HBV) reactivation induced by cytotoxic chemotherapy is an important issue in cancer patients. An elevated HBV viral load usually precedes hepatitis flare, and hepatic decompensation and eventual death is not infrequent once viral reactivation is initiated. Reverse seroconversion from hepatitis B surface antigen (HBsAg)-negative to HBsAg-positive would also occur in hepatitis B core antibody (anti-HBc)-positive patients. The risk of HBV reactivation can be attributed to patient viral status and the regimen of chemotherapeutic agents. Chemotherapeutic regimens that contain steroid and rituximab can increase the risk of viral reactivation in lymphoma patients. Consequently, routine HBV marker screening, including HBsAg and anti-HBc, is mandatory prior to chemotherapy for all cancer patients, and prophylactic antiviral treatment is highly recommended for HBsAg-positive cases. However, for patients who are anti-HBc-positive and HBsAg-negative, so-called resolved hepatitis B patients, regular HBV viral load survey during the course of chemotherapy is necessary to early detect HBV reactivation. Currently, the role of antiviral prophylaxis for resolved hepatitis B patients is still unsettled.

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1. Introduction

Chronic hepatitis B is a major public health and medical concern around the world.1 There are already 400 million people worldwide who are chronically infected with the hepatitis B virus (HBV).2 HBV often leads to chronic hepatitis if infection occurs during the neonatal or early childhood period. Although HBV universal vaccination for newborns has been routinely administered in Taiwan for two decades, management of chronic hepatitis B (CHB) is still an issue for Taiwanese adults. The interaction between host immune response and viruses plays an essential role in the pathogenesis of CHB.3 Based on clinical observations, CHB in patients evolves through four phases: immune tolerance, immune clearance, inactive, and reactivation phases after hepatitis B e antigen (HBeAg) seroconversion.4–6 HBV reactivation induced by immunosuppressive or cytotoxic chemotherapy is not uncommon in HBV carriers,7 and it can have a variety of outcomes from asymptomatic to severe hepatitis with fatal consequences. Reactivation not only occurs in hepatitis B surface antigen (HBsAg)-positive patients, as well as HBsAg-negative/hepatitis B core antibody (anti-HBc)-positive, so-called resolved hepatitis B cases.8–10

2. Causes of HBV reactivation

The causes of HBV reactivation are varied. Although HBV reactivation can be spontaneous, in most patients who develop viral reactivation, an “insult” has occurred which affects the balance between host immunity and HBV activity. This can be induced by immunosuppressants, cytotoxic chemotherapy, human immunodeficiency virus (HIV) infection, or sudden withdrawal of antiviral therapy. Usually, HBV viral loads...
increase when patients receive immunosuppressants or chemotherapy. Then, the host immune response rebounds, and hepatitis flare develops after withdrawal of such treatments.11

3. Definition of HBV reactivation

Currently, there is no consensus on the definition of HBV reactivation. Most clinical trials adopted the definition proposed two decades ago by Lok and colleagues.12 According to their report, HBV reactivation can be defined as a sudden increase (more than tenfold) in serum HBV viral loads or reappearance of HBV DNA in the serum.12 In addition, hepatitis was defined as a threefold rise in serum alanine transaminase (ALT) level that exceeds the reference range, or an absolute increase of serum ALT to more than 100 U/L.12–15 To diagnose hepatitis attributed to HBV reactivation, clinicians must exclude evidence of hepatic infiltration by underlying malignancy, hepatotoxic drugs, recent transfusion, and other systemic infections for all cases.12–15

For patients with resolved hepatitis B (HBsAg-negative, anti-HBc-positive), the definition of HBV reactivation is that same definition which applies to HBV carriers, excepting the inclusion of HBsAg reappearance (HBsAg reverse seroconversion).16

4. Incidence of HBV reactivation during chemotherapy in HBV carriers

HBV reactivation during cytotoxic chemotherapy occurs in a wide variety of cancers patients with underlying HBV infection, including lymphoma, breast, head and neck, lung, and gastrointestinal tract cancers. One study reported that the incidence of HBV reactivation was the highest in lymphoma (58%), followed by breast (41%), head and neck (30%), lung (23%), and gastrointestinal cancers (7%).17 The overall HBV reactivation rate was 26%.17 In the literature, lymphoma is the most frequently studied type of cancer associated with chemotherapeutic HBV reactivation, and the focus of the majority of randomized controlled trials which have been conducted.13,17–19

Two randomized controlled studies compared the extent of antiviral prevention with lamivudine with the effect of deferred treatment in HBsAg-positive lymphoma patients undergoing chemotherapy.18,19 Results showed that the incidence of HBV reactivation was around 53%–65% in the controlled arm.18,19 The regimen of chemotherapy has an impact on the risk of HBV reactivation. Glucocorticoids can enhance HBV replication by activating steroid-response element of the HBV genome.20 One clinical trial demonstrated a decrease in the risk of reactivation (73% vs. 38%) with steroid-free regimen (etoposide, cyclophosphamide, and etoposide) for non-Hodgkin lymphoma HBV carriers.13 Rituximab, a chimeric mouse human anti-CD20 monoclonal antibody that can reduce B cell numbers and antibody levels, has been adopted for combination cytotoxic therapy for CD20-positive lymphomas, such as diffuse large B cells lymphoma (DLBCL) and follicular lymphoma.21 However, rituximab itself is associated with HBV reactivation. A recent meta-analysis confirmed that rituximab-based therapy significantly increased the risk of HBV reactivation compared with non-rituximab treatment in anti-HBc-positive cases with an odds ratio of 5.7.22

5. Incidence of HBV reactivation during chemotherapy in patients with resolved hepatitis B

The risk of HBV reactivation is associated with the intensity of the applied immunosuppression.23 HBV reactivation in patients with resolved hepatitis B is not unusual in postbone marrow transplanted cases, with the risk of HBsAg reverse seroconversion to be as high as 50%.11 Based on one review article, the rate of reactivation ranges from 3% to 50% in HBsAg-negative, anti-HBc-positive (anti-HBs positive or negative) patients with hematological malignancy who undergo chemotherapy with cytotoxic agents or immunosuppressant therapy.10,24 Fatal HBV reactivation following chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab in lymphoma patients negative for HBsAg has been reported9,10,25,26 Rituximab is still a major risk factor of HBV reactivation in HBsAg-negative lymphoma patients.27 One study from Hong Kong suggested a high proportion (~23.8%) of cases of HBV reactivation developed in lymphoma patients with resolved hepatitis B undergoing rituximab-based chemotherapy.16 Among 21 DLBCL patients who were HBsAg-negative and anti-HBc-positive, five patients developed HBV reactivation (including HBsAg reverse seroconversion) after receiving R-CHOP chemotherapy, including one patient who died of hepatic failure. All of these five patients with HBV reactivation were negative for anti-HBs. By contrast, none of the patients who were HBsAg-negative and anti-HBc-positive developed HBV reactivation after receiving CHOP alone. Male sex, absence of anti-HBs, and use of rituximab were factors associated with HBV reactivation. Two recent studies from Singapore and Taiwan reported that the rates of HBV reactivation in patients with resolved hepatitis B following rituximab-based regimen were 1.5% and 4.2%, respectively.28,29 Additionally, two studies from Japan suggested that the HBV reactivation rates were 9%–12% among HBsAg-negative cases.30,31 Therefore, HBsAg-negative and anti-HBc-positive patients still have the risk of HBV reactivation when they are exposed to intensive chemotherapy or immunosuppressant agents. The risk is further increased in the absence of anti-HBs during rituximab-based chemotherapy. However, the actual rate of HBV reactivation in HBsAg-negative but anti-HBc-positive lymphoma patients following rituximab-based chemotherapy is still unresolved.

6. Benefit of antiviral prophylaxis during chemotherapy

Lamivudine is the first approved nucleoside analog in the treatment of CHB.32,33 The preventive effect of lamivudine on chemotherapy-induced HBV reactivation in HBV carriers has been demonstrated in two randomized controlled trials.18,19
Liver Disease for patients with high viral loads at baseline and HBsAg loss for HBeAg-negative patients), and is positive; sustained HBV DNA suppression to undetectable points are reached (HBeAg seroconversion for HBeAg-negative patients). Before chemotherapy or at least 6 months after completing chemotherapy. The incidence of severity of hepatitis flare and mortality was 0% and 31% compared with 53% to 65% in controls.18,19 The incidence of severity of hepatitis flare and mortality was also significantly reduced by lamivudine prophylaxis.4,5 It is noteworthy that HBV reactivation developed after the completion of chemotherapy and withdrawal of lamivudine prophylaxis, the so-called delayed HBV reactivation, which is not uncommon.19,36 Adequate duration of antiviral prevention is important to confer the protective effect. Besides lamivudine, entecavir, telbivudine, and tenofovir are currently available antiviral agents for both treatment of CHB and for chemoprevention.7 Regarding patients with resolved hepatitis B, the data for antiviral prophylaxis are limited.

7. Management of chemotherapy-induced HBV reactivation: international HBV treatment guidelines

Based on three major HBV treatment guidelines proposals originating from America, Europe, and the Asia-Pacific region, all cancer patients should check HBV markers, including HBsAg and anti-HBc, prior to initiation of chemotherapy (Table 1).2,7,37,38 To avoid the risk of life-threatening HBV reactivation in HBV carriers, routine prophylactic antiviral therapy is recommended for individuals who are positive for HBsAg before the start of cancer chemotherapy.7,37,38 The duration of antiviral prophylaxis must extend at least 6 months after completing chemotherapy to avoid delayed HBV reactivation.7 It would be ideal to have a longer duration of antiviral therapy until treatment end points are reached (HBeAg seroconversion for HBeAg-positive; sustained HBV DNA suppression to undetectable level and HBsAg loss for HBeAg-negative patients), and is recommended by the American Association for the Study of Liver Disease for patients with high viral loads at baseline (>2,000 IU/ml).7 Antiviral drugs with low genetic barrier, such as entecavir or tenofovir, are preferred.7,37 There is no established recommendation for routine antiviral prevention prior to chemotherapy for patients who are positive for anti-HBc, but negative for HBsAg.7,37,38 However, HBV DNA should be checked if a patient is positive for anti-HBc regardless of anti-HBs status.10 Continuing HBV DNA monitoring must be performed to early detect HBV reactivation, and antiviral treatment should be started as soon as HBV DNA has increased tenfold compared with baseline, and >2000 IU/ml during the course of chemotherapy.9,10 In Conclusion, the risk of HBV reactivation during chemotherapy in HBV carriers is high, especially if the regimen of steroid and rituximab is used. Consequently, HBV marker screening is important for all patients before they receive chemotherapy. In addition, all HBsAg-positive cancer patients should receive antiviral prophylaxis before starting chemotherapy, and prophylaxis against HBV reactivation should continue for at least 6 months after completing chemotherapy. Although the role of antiviral prophylaxis in resolved patients remains unsettled, regular HBV DNA monitoring is still strongly suggested for resolved hepatitis B patients during chemotherapy.

Table 1
Comparison of treatment guidelines for patients receiving chemotherapy among AASLD, EASL, and APASL.

<table>
<thead>
<tr>
<th>Prechemotherapy screen</th>
<th>AASLD7</th>
<th>EASL37</th>
<th>APASL38</th>
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<tbody>
<tr>
<td>HBsAg</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Antiviral prophylaxis for HBsAg (+) patients</td>
<td></td>
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<tr>
<td>When to start antiviral prophylaxis</td>
<td>Before chemotherapy</td>
<td>Before chemotherapy</td>
<td>Before chemotherapy</td>
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<tr>
<td>When to stop antiviral treatment</td>
<td></td>
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<tr>
<td>For HBV DNA &lt; 2000 IU/ml: 6 mos after completing chemotherapy</td>
<td>Entecavir or tenofovir for high viral load at baseline and/or lengthy cycles of chemotherapy</td>
<td>Lamivudine</td>
<td></td>
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<tr>
<td>For HBV DNA &gt; 2000 IU/ml: reach treatment end point for CHB</td>
<td>Yes, if HBV viral load is detectable</td>
<td></td>
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<tr>
<td>Antiviral prophylaxis for HBsAg (-)/anti-HBc (+) patients</td>
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<td></td>
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<tr>
<td>No recommendation</td>
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</table>

AASLD = American Association for the Study of Liver Disease; APASL = Asian Pacific Association for the Study of the Liver; CHB = chronic hepatitis B; EASL = European Association for the Study of the Liver; HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

References


