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## How I treat

# How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation

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**Hepatitis B virus (HBV) reactivation is a serious but preventable complication of immunosuppression. Full HBV serologic profile must be obtained from all patients receiving intensive immunosuppressive therapy. In general, preemptive anti-HBV therapy is more effective than giving treatment after development of reactivation. Prompt lamivudine therapy should be given to at-risk patients who are hepatitis B surface antigen (HBsAg)-positive. It is recommended that lamivudine be continued until at least**

**6 months after the cessation of immunosuppression. Some patients requiring a longer duration of lamivudine therapy are at risk of developing drug resistance. The newer anti-HBV agents are effective in overcoming lamivudine resistance. Early use of these agents may be considered. HBV reactivation was observed in HBsAg-negative patients with occult HBV infection (HBV DNA-positive) who are on heavy immunosuppression. The optimal management of this group of patients is unclear. For pa-**

**tients receiving allogeneic HSC transplants, the HBV status of the donors requires special attention. To minimize the risk of transmission of infection to recipients, HBsAg-positive donors should receive adequate anti-HBV therapy before HSC donation. As the result of adoptive immune transfer, clearance of HBsAg is observed in HBsAg-positive patients receiving HSC transplants from donors who are positive for hepatitis B surface and core antibodies. (Blood. 2009; 113:3147-3153)**

## Introduction

In Hong Kong, a typical hepatitis B (HBV) endemic area, approximately 1 in 10 persons is serologically positive for hepatitis B surface antigen (HBsAg), and another 4 are positive for hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), or both.<sup>1</sup> We can conclude that at least one-half of the population has prior exposure to HBV. There is an early maternal-infant transmission of HBV during the perinatal period, and the infection tends to become chronic.<sup>2</sup> Successful HBV vaccination programs are now widely implemented in many HBV endemic areas and will decrease the proportion of chronic HBV carriers in the future.<sup>3</sup> Vaccinated persons are identified by a negative HBsAg, positive HBsAb, and negative HBcAb serologic results.

Cytotoxic chemotherapy, monoclonal antibody, and other intensive immunoablative therapies, including hematopoietic stem cell (HSC) transplantation, are widely used for treating various hematologic diseases. In places where HBV infection is prevalent, it is often necessary to give highly immunosuppressive therapy to chronic HBV carriers, and they are at risk of HBV reactivation.<sup>4</sup> The mortality rate is high if the reactivation is complicated by fulminant hepatic failure.<sup>5-9</sup> The chance of HBV reactivation is linked to the serologic profile and also the intensity of the immunosuppression. The risk is highest in HBsAg-positive patients and lowest in HBsAb-positive patients with a high anti-HBs titer.<sup>10</sup>

Lymphoma patients who are HBsAg-positive are noted to have a higher risk of HBV reactivation after chemotherapy than other cancer patients.<sup>7</sup> This may be related to the relatively more immunosuppressive chemotherapeutic drugs used for lymphoma and also possibly the intrinsic immunosuppressive effect of lymphoma.<sup>7</sup> A strong association between B-cell lymphoma and HBsAg positivity has also been reported in HBV endemic areas. A causal relation has been suggested but not firmly established. The

association may also be explained by the immunosuppressive effect of lymphoma, seroconverting some HBsAb- and HBcAb-positive patients to become HBsAg-positive.<sup>7,11-16</sup>

## Chemotherapy and HBV reactivation in HBsAg-positive patients

Chemotherapy is the mainstay for treatment of most hematologic malignancies. When immunosuppressive agents are given to patients who are also chronic HBV carriers, there is an increased risk of liver-related mortality and morbidity.<sup>4</sup> When standard combination chemotherapy is used to treat patients with lymphoma without specific anti-HBV prophylaxis, significant impairment of liver function with elevated liver transaminases is expected in 30% to 60% of the HBsAg-positive patients and more than one-half of these HB-reactivated patients may become jaundiced.<sup>6</sup> This results in an overall liver-related mortality of greater than 5%.<sup>4</sup> The cause of death is usually HBV-related fulminant liver failure.<sup>8,17</sup>

Cytotoxic chemotherapy is often given to patients with cancer according to an intermittent schedule. This allows periodic recovery from the myelosuppressive effect of the treatments. During periods of immunosuppression, there is an increase in HBV replication in liver, resulting in a corresponding increase in hepatic viral load and widespread infection of the hepatocytes.<sup>18,19</sup> This is reflected by an increase in serum levels of HBV DNA, hepatitis B e antigen (HBeAg), and HBV DNA polymerase.<sup>20</sup> On recovery of host immunity, there is then immune-mediated destruction of the virus-laden liver cells, resulting in acute reactivation of hepatitis. The severity of hepatocyte destruction is related to the viral load in liver and, when massive, may end up in fulminant liver failure.

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Intrahepatic covalently closed circular DNA (cccDNA) is a key intermediate in the replication of the virus and may therefore serve as a marker of HBV replication in liver. Although the reactivation is usually preceded by enhanced HBV replication, it has been shown that a high intrahepatic viral cccDNA is predictive of HBV reactivation in HBsAg-positive patients treated with chemotherapy.<sup>21</sup>

HBV reactivation may also occur when chemotherapy is given to HBsAg-positive patients with nonhematologic malignancies, such as breast cancer and nasopharyngeal cancer.<sup>22-28</sup> Their risk is probably lower because the chemotherapy used tends to be less immunosuppressive in general, and, unlike lymphoma, the tumors themselves do not usually have an immunosuppressive effect. HBsAg-positive patients with nonmalignant hematologic conditions, such as immune thrombocytopenia, receiving high-dose corticosteroids or other immunosuppression are similarly at risk.

Attempts have been made to identify reliable predictive markers of HBV reactivation after chemotherapy. A high serum HBV viral load before chemotherapy is consistently found to be the most important factor. It can be measured by quantitative serum HBV DNA assays.<sup>29</sup> The clinical significance of serum hepatitis e antigen is less certain because it may be affected by the precore/core promoter HBV mutants.<sup>30,31</sup>

The risk is expected to be higher if the treatment used is highly immunosuppressive.<sup>20</sup> For example, drugs such as cyclophosphamide, vincristine, doxorubicin, and corticosteroids are commonly used for lymphoma, and they often induce HBV reactivation. The use of high-dose corticosteroids seems to impose a substantially higher risk.<sup>32</sup> Fludarabine, a drug commonly used for treating follicular lymphoma and chronic lymphocytic leukemia, is also associated with significant immunosuppression and has been added to the list of drugs inducing HBV reactivation.<sup>31</sup> Other, less consistent risk factors identified for HBV reactivation include male sex and young age.<sup>6,10,28,33</sup>

High-dose chemotherapy and autologous HSC rescue is a standard therapy for patients with relapsed lymphoma, as well as selected high-risk patients with lymphoma in first remission. This treatment is also widely used for patients with plasma cell myeloma. For patients who are HBsAg-positive, the risk of HBV reactivation after this procedure is substantially higher than conventional-dose chemotherapy because of the more intensive immunosuppression.<sup>29</sup> The conditioning regimen for autologous transplantations typically includes at least one alkylator, such as cyclophosphamide, which is immunosuppressive when used in high doses. Similar to patients receiving conventional-dose chemotherapy, a high serum level of HBV DNA predicts HBV reactivation after high-dose chemotherapy.<sup>29</sup>

## Monoclonal antibody therapy

Modern therapy for lymphoid malignancies and immunologic conditions often includes the use of monoclonal antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52). These agents are highly immunosuppressive, and their use has been associated with HBV reactivation.<sup>10</sup>

Rituximab is an anti-CD20 humanized chimeric monoclonal antibody. It is an effective agent for treating B-cell tumors and has also been used for some autoimmune conditions, such as immune thrombocytopenia. For lymphoma, rituximab is efficacious as a single agent but is more commonly used in combination with other chemotherapy. It is used for treating both low-grade and high-grade non-Hodgkin lymphomas.<sup>34-37</sup> The antibody itself has minimal effect on blood counts. Although it depletes circulating B cells, the serum immunoglobulin levels are

usually well maintained. Treatment with rituximab is not commonly associated with severe opportunistic infections. Although normal B cells are depleted, antibody production by plasma cells continues during the lymphopenic period because they are usually CD20<sup>-</sup>. However, because more patients are being treated, there are increasing reports of HBV reactivation after rituximab therapy, either when used alone or in combination with chemotherapy. This complication may appear during or many months after the treatment.<sup>38-45</sup> A recent review of the literature showed that the most frequent viral infection complicating rituximab therapy for lymphoma was hepatitis B infection. HBV reactivation accounted for 39% of the reported cases, resulting in a high mortality rate of 52% as a result of hepatic failure.<sup>46</sup>

Rituximab plus CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) is now a standard treatment of diffuse large B-cell lymphoma.<sup>36</sup> The addition of rituximab significantly increases response rates. There are also improvements in survival and the chance of cure. Before preemptive anti-HBV therapy is widely used, treatment of HBsAg-positive lymphoma with CHOP chemotherapy alone is associated with an approximately 50% risk of HBV reactivation. Although the addition of rituximab to CHOP chemotherapy may give additional risk, the precise magnitude of the increase is not clear with the available data.<sup>45-47</sup> There are concerns that late HBV reactivation and liver failure may be more commonly associated with the use of rituximab.<sup>38-47</sup> There is, however, no apparent need to avoid the use of rituximab in HBV-infected patients with lymphoma. HBV reactivation is largely preventable by preemptive anti-HBV therapy, and these patients should not be deprived of a more effective treatment of their lymphoma.<sup>48</sup>

Alemtuzumab is a humanized monoclonal antibody that binds to CD52 antigen and is an effective treatment of chronic lymphocytic leukemia and some other lymphoid tumors.<sup>49</sup> It is also used in combination with other chemotherapy or as part of the conditioning regimen for patients undergoing autologous or allogeneic HSC transplantation. Alemtuzumab therapy is known to be associated with a high risk of serious bacterial, viral, and fungal infections and should be used with great caution.<sup>49,50</sup> Stringent anti-infective prophylaxes and monitoring are recommended. There have been multiple reports on the development of HBV reactivation after alemtuzumab therapy.<sup>49,51-53</sup>

Monoclonal antibody therapy is also widely used for treating various nonmalignant conditions. Rituximab and alemtuzumab are effective in treating immune thrombocytopenia and some other autoimmune diseases. Infliximab is an anti-TNF antibody and is being used for treating rheumatic or other immunologic diseases. HBV reactivation has been reported when these monoclonal antibodies are used alone or in combination with other immunosuppressive agents for nonmalignant conditions.<sup>54,55</sup>

## HBV reactivation in HBsAg-negative patients

HBV may persist in HBsAg-negative persons after infection. These persons usually have occult HBV infection if HBV DNA is detectable in the blood. HBsAg negativity may occasionally be due to the presence of mutant viruses missed by the commonly used HBsAg assays. In most other cases, it is the result of suppression of viral replication and gene expression.<sup>56</sup> The prevalence of occult HBV infection would depend on the sensitivity and specificity of the methods used for HBV DNA detection and also the populations being studied.<sup>56,57</sup>

With the use of nucleic acid amplification, 0.11% of the healthy blood donors in Taiwan, where HBV infection is endemic, were

found to be positive for HBV DNA.<sup>58</sup> A separate study in Taiwan has shown that 6% of their HBsAg-negative patients with B-cell lymphoma had occult HBV infection.<sup>16</sup> In a study of a cohort of 124 consecutive HBsAg-negative hematopoietic stem cell transplant donors in Hong Kong, where HBV infection is also endemic, the prevalence of occult HBV infection, as detected by a highly sensitive HBV DNA assay, was 15.3% (19 of 124 donors).<sup>59</sup> Sixteen (84.2%) of those 19 donors with occult HBV infection also tested positive for HbcAb, and 14 of them were HBsAb-positive (73.7%). Occult HBV infection may make a significant effect on the transmission of HBV infection through blood transfusion or organ transplantation.<sup>60</sup>

Acute HBV reactivation after immunosuppression has been observed in patients with occult HBV infection.<sup>61</sup> Those patients have prior immunity against HBV after past exposure to the virus (HbcAb- and/or HbsAb-positive). In a recent study, 244 HBsAg-negative lymphoma patients receiving cytotoxic chemotherapy were investigated.<sup>61</sup> Eight of them (3.3%) developed HBV-related hepatitis after therapy. They appeared to have a relatively higher tendency (3 of 8 patients, 37.5%) to develop fulminant hepatic failure. Direct DNA sequencing results confirmed all 8 patients having de novo HBV-related hepatitis from reactivation of previous occult HBV infection.<sup>57</sup> Those patients were initially HBsAg-negative, and HbsAb- and/or HbcAb-positive, and the serum liver enzymes were not elevated before. At the time of reactivation, they became HBsAg-positive. This was associated with a greater than 100-fold increase in their serum HBV DNA levels, occurring before an elevation of serum transaminases.<sup>61</sup>

HBV reactivation is also observed in HBsAg-negative patients after autologous HSC transplantation.<sup>62</sup> In Korea, 129 HBsAg-negative patients receiving autologous HSC transplants were studied. Of this group, 110 (85.3%) were HbsAb-positive, and 62 (56.4%) of the 110 were also HbcAb-positive. Eight patients (6.2%) were negative for both HBsAb and HbcAb. Seven (6.2%) of these 129 HBsAg-negative patients became HbsAg-positive after transplantation, and 5 of them developed acute hepatitis.<sup>62</sup>

HBV reactivation is seen in HBsAg-negative lymphoma patients after monoclonal antibody therapy (rituximab or alemtuzumab), given either alone or in combination with chemotherapy.<sup>41-43,49,51</sup> Data suggest that the risk of HBV reactivation in HBsAg-negative lymphoma patients after chemotherapy may be increased by the addition of rituximab.<sup>61</sup>

## Diagnosis and prognosis of acute HBV reactivation

Currently, no uniform diagnostic criteria are available for HBV reactivation.<sup>10</sup> It has been defined as an increase of HBV viral replication from a low to high level in patients with chronic or past HBV infection.<sup>20</sup> Many different ways of measuring HBV DNA are now available with different sensitivities.<sup>20</sup> The branched DNA hybridization assay (Quantiplex HBV DNA assay; Chiron, Berkeley, CA) has a detection limit of  $0.7 \times 10^6$  copies/mL, and the newer real-time polymerase chain reaction assays have a sensitivity down to 11 copies/mL.<sup>20,63,64</sup> HBV reactivation can be confirmed by an increase in serum HBV DNA level to more than 1 log higher than that of the baseline, an absolute increase exceeding  $6 \log_{10}$  copies/mL, or serum HBV DNA turning from negative to positive.<sup>20,63</sup>

Serologic evidence of chronic HBV infection would be useful. To serve this purpose, HBsAg positivity at least 6 months before the reactivation is required, but this information may not be

available if HBV markers are not previously tested.<sup>20</sup> For HBsAg-negative patients, positive HbcAb indicates immunity from natural HBV infection rather than vaccination.<sup>20</sup>

The timing of HBV reactivation may vary. It occurs most frequently after cessation of immunosuppression, but it may also be seen during chemotherapy. The median interval between the initiation of chemotherapy and the onset of reactivation is approximately 4 months (range, 4-36 months).<sup>4,10</sup> Although HBV DNA and liver transaminases may rise at the same time, more often the rising HBV DNA levels precede the elevation of liver transaminase.<sup>10</sup> There may be a lag of days or even weeks.<sup>20,63</sup> It is also possible that HBV DNA levels are already declining when liver enzyme levels start rising.<sup>63</sup>

Hepatitis is defined as a greater than 3-fold increase in the liver transaminases on 2 consecutive determinations at least 5 days apart.<sup>20</sup> Icteric hepatitis is defined as hepatitis associated with clinical jaundice and a serum bilirubin level exceeding  $30 \mu\text{mol/L}$ .<sup>20</sup> Other causes of hepatitis, such as other hepatitis viruses or drugs, should be excluded at diagnosis of HBV reactivation. Hepatitis A, hepatitis C, hepatitis D, cytomegalovirus, and Epstein-Barr virus have to be considered.<sup>10</sup> A liver biopsy is not always essential for the diagnosis of HBV reactivation. However, it may be useful for the exclusion of other causes of liver injury.<sup>10</sup> The benefit of doing a percutaneous liver biopsy should be balanced against the associated risks, such as bleeding.<sup>20</sup> If the patient has thrombocytopenia or coagulopathy, a transjugular liver biopsy may be an alternative. However, the small sample size obtained with this approach often poses a challenge to the pathologist.

HBV reactivation may be symptomatic or asymptomatic.<sup>20</sup> Classical features of hepatitis, including fatigue, jaundice, ascites, hepatic encephalopathy, and coagulopathy, may be present.<sup>4,65</sup> Patients with preexisting cirrhosis are more likely to develop liver failure.<sup>20</sup> Although a proportion of the patients may recover spontaneously, the mortality rate of HBV reactivation reported ranges from 5% to 40%.<sup>4,10,20</sup> Furthermore, potentially effective chemotherapy for the primary hematologic malignancy has to be suspended. This disruption to treatment may affect the prognosis of the primary hematologic condition and hence the ultimate survival of the patient.<sup>10,20,60</sup> In addition, chemotherapy-related HBV reactivation has been associated with long-term deterioration of liver function on follow-up.<sup>66</sup>

## Management of HBV reactivation

When a clinical diagnosis of HBV reactivation is made, all chemotherapy must be suspended and hepatotoxic drugs stopped. Although some patients may recover spontaneously, prompt commencement of anti-HBV therapy is vital, and lamivudine is commonly used.<sup>10</sup>

Before the era of effective anti-HBV drugs, the treatment of HBV reactivation was mainly supportive.<sup>4</sup> Interferons and steroids were used but had never been shown to be beneficial. In contrast, the use of steroids might have detrimental effects.<sup>16</sup> When famciclovir, a drug with moderate anti-HBV activity, became available, it was used for treating HBV reactivation after HSC transplantations with some success.<sup>67</sup> However, it is now superseded by other more potent anti-HBV agents.

Lamivudine, a nucleoside analog, is an effective treatment of chronic HBV infection.<sup>68</sup> The drug is active in controlling viral replication and is therefore potentially useful for the treatment of HBV reactivation.<sup>69</sup> When given to patients with HBV reactivation after chemotherapy, sustained HBeAg seroconversion and rapid

suppression of serum HBV to undetectable levels are observed.<sup>70</sup> The drug is still effective, but to a lesser extent, in patients with hepatic decompensation.<sup>10,63</sup> Despite lamivudine, the mortality rate of HBV reactivation, once developed, remains high. This is probably due to the delay in starting lamivudine in many cases while the hepatic viral load is already high and massive immune-mediated hepatic damage has already occurred. A better outcome is expected if lamivudine can be promptly started at the initial rise of HBV DNA before the viral load is too great. However, this is only possible if there is a good system of close monitoring of HBV DNA levels.<sup>16</sup> Otherwise, it would be counterproductive. The monitoring system can be difficult to implement because of the demand on time and resources.<sup>20,70-72</sup>

A successful emergency living-related liver transplantation for fulminant HBV reactivation after an unrelated bone marrow transplantation has been reported.<sup>73</sup> This provides a treatment option for this desperate situation.

## Prevention of HBV reactivation

Prevention is probably a better approach than intervention at the time of reactivation.<sup>10</sup> Preemptive anti-HBV therapy should be given to all at-risk patients, and the benefit of this approach has been clearly shown for HBsAg-positive patients receiving chemotherapy or HSC transplants.<sup>70-72</sup>

A panel of serologic HBV markers, including HBV surface antigen and antibody (HBsAg and HBsAb), HBV e antigen and antibody (HBeAg and HBeAb), and HBV anticore antibody (HBcAb), should be tested on all at-risk patients, before they receive chemotherapy or intensive immunosuppression, including HSC transplantation.<sup>20</sup> This is important, especially when one is managing patients coming from or living in HBV endemic areas.

Active HBV immunization has been recommended to HBV-naive (HBsAg, HBsAb, and HBcAb-negative) patients.<sup>10</sup> For HBsAg-positive patients, a baseline HBV DNA level needs to be performed. Preemptive anti-HBV therapy should be given as soon as possible, regardless of the patient's initial HBV DNA levels, before commencement of chemotherapy or other intensive immunosuppressive therapy.<sup>10,70-72</sup> Lamivudine is commonly used, and the drug is associated with minimal toxicity.<sup>10,74</sup> Even for patients with high initial serum HBV DNA, the level can usually be brought down quickly. Although it is preferable to start lamivudine as soon as possible, it is usually not necessary to delay the chemotherapy.<sup>10</sup>

The optimal duration of anti-HBV treatment remains uncertain. Lamivudine therapy probably needs to be continued for at least 3 months (range, 3-12 months) after the cessation of all immunosuppression.<sup>59,61,63</sup> For patients receiving conventional chemotherapy, lamivudine therapy until 6 months after cessation of chemotherapy has been recommended, and this seems to be reasonable.<sup>10</sup> A longer duration of lamivudine of 12 months or longer after stopping all immunosuppression may be necessary for patients receiving monoclonal antibodies, such as rituximab or alemtuzumab, or HSC transplants because of the late immune recovery of these patients.<sup>63,70-72</sup> In addition, patients with high baseline HBV DNA before chemotherapy may also need more prolonged lamivudine. Late HBV reactivation has been observed as the results of premature drug termination.<sup>10,75,76</sup>

The above strategy should protect most patients (> 90%).<sup>10</sup> However, HBV reactivation may still occur while the patients are already on lamivudine. This is usually due to the develop-

ment of drug resistance.<sup>10</sup> When it happens, a surge in HBV DNA level is observed. It is therefore necessary to monitor patients on lamivudine with HBV DNA and liver transaminases levels.<sup>20,63</sup> Drug resistance is due to the YMDD mutant.<sup>77,78</sup> The development of mutant is more commonly associated with prolonged lamivudine administration, and it becomes a greater concern when the drug needs to be given for a prolonged time of more than 1 year.<sup>10,78</sup>

Other newer nucleoside analogues, such as adefovir, entecavir, telbivudine, and tenofovir, are now available for the treatment of hepatitis B infection.<sup>79,80</sup> These drugs have a different drug resistance profile. They have been shown to be useful for lamivudine-resistant hepatitis B infection.<sup>79-82</sup> Adefovir gives a low incidence of drug resistance and is active against lamivudine-resistant HBV infection.<sup>53</sup> The newer drugs, including entecavir, telbivudine, and tenofovir, are more potent than lamivudine.<sup>80</sup> However, a relatively high drug resistance is still associated with telbivudine.<sup>80</sup> In addition, both telbivudine and entecavir are noted to have decreased efficacy against lamivudine- and adefovir-resistant HBV.<sup>80</sup> However, tenofovir, a new member in the list, is potent in both newly and previously treated patients.<sup>80</sup> At this time, it remains uncertain whether any of these newer agents should be routinely used instead of lamivudine as first-line preemptive anti-HBV treatment or be reserved for second-line therapy. Early use of these new agents however may be appropriate and justifiable when prolonged anti-HBV therapy is necessary for patients requiring prolonged immunosuppression.<sup>10,79-82</sup> Further clinical trials would be useful to define their precise roles.

The best strategy of managing HBsAg-negative patients with occult HBV infection is less clear.<sup>83-85</sup> They are often HbcAb-positive. The HBsAb is either negative or positive at a low titer. Occult HBV infection is identified by a sensitive assay of HBV DNA.<sup>10</sup> Their chance of developing HBV reactivation is lower than that of HBsAg-positive patients. However, when it occurs, there appears to be a high mortality rate from liver failure.<sup>61</sup> Patients receiving monoclonal antibody therapy (rituximab or alemtuzumab) or HSC transplants are particularly at risk.<sup>39,41-43,51,61</sup> A similar strategy of preemptive anti-HBV therapy has been recommended for HBsAg-negative patients with detectable serum HBV DNA, who are on significant immunosuppression. The chance of HBV reactivation for each patient should be carefully assessed. For patients receiving more prolonged and more intensive immunosuppression, the risk is expected to be higher.<sup>10</sup> An alternative approach would be close monitoring of their serum HBV DNA and liver transaminases levels and prompt commencement of anti-HBV therapy at the first sign of HBV reactivation.<sup>65</sup> This strategy may be appropriate for the heavily immunosuppressed patients who are initially both HBsAg and serum HBV DNA-negative but HbcAb-positive. As discussed earlier, this latter approach can be logistically demanding. A quick turnaround time for the HBV DNA results is essential. Further clinical studies are necessary to clarify these uncertainties.

## Allogeneic hematopoietic stem cell transplantation

Patients receiving allogeneic HSC transplants have a more complicated situation; therefore, they warrant special consideration.<sup>86,87</sup> HBsAg-positive patients receiving allogeneic transplants are heavily immunosuppressed and are at high risk of developing severe HBV reactivation (14%-50%).<sup>10</sup> Risk factors identified include use of

steroids, HBsAb-negative donors, and graft-versus-host disease.<sup>10</sup> The intensive conditioning regimens normally consist of high-dose chemotherapy with or without total body irradiation, and they are immunoablative.<sup>88</sup> Patients are further immunocompromised by the routine use of prophylactic cyclosporine and methotrexate for prevention of graft-versus-host disease. When there is graft-versus-host disease, treatment with high doses of steroids or antithymocyte globulin or both would further suppress the host immunity.<sup>89</sup> Some infections, such as cytomegalovirus, are also immunosuppressive. The risk would be even higher if unrelated rather than sibling donors are used in the transplantation, because more intensive immunosuppression is often required.<sup>89-91</sup> The reduced-intensity or mini transplantations are associated with similar risk of HBV reactivation because they are equally immunoablative.<sup>52</sup> Patients receiving allogeneic transplants are expected to have a higher HBV reactivation rate than are patients receiving autologous transplants.<sup>92</sup> They should be carefully assessed before transplantation and closely observed with frequent HBV DNA monitoring after transplantation. An effective prophylactic anti-HBV treatment, such as lamivudine, is essential for patients with evidence of overt or occult HBV infection before transplantation.<sup>72</sup> The duration of lamivudine therapy probably needs to be more prolonged. It should be continued until there is a good immune recovery, that is at least 6 to 12 months after cessation of all immunosuppression.<sup>10</sup> Lamivudine must be continued if immunosuppressive therapy is still necessary, for example, in patients receiving treatment of chronic graft-versus-host disease.<sup>90</sup> Because a higher chance of drug resistance is associated with more prolonged use of lamivudine, the newer anti-HBV agents with lower risk of drug resistance may be preferred in this clinical setting.<sup>79</sup>

The HBV status of the donors also needs to be considered.<sup>86,87</sup> A full HBV serologic profile should be obtained from them. HBV infection tends to cluster within families. For HBV-infected patients requiring a sibling donor transplant, the only suitable sibling donor available is often HBsAg-positive.<sup>93,94</sup> A previous analysis reported 18 patients receiving an allogeneic HSC transplant from HBsAg-positive donors. Nucleoside analogues were not routinely used at that time.<sup>93</sup> Eight (44%) of the 18 transplant recipients developed HBV-related hepatitis, including 6 hepatic failures. The risk was higher in those who were HBsAg-positive and had clinical evidence of hepatitis before transplantation. Another 6 transplant recipients in the study were initially HBsAb-positive. Despite intensive myeloablation and immunosuppression, 3 of them (50%) remained HBsAb-positive after transplantation, and their anti-HBV immunity was preserved. The remaining 3 patients became HBsAg-positive, and 1 of them developed HBV-related hepatitis after transplantation. This study also showed that a high HBV load in the donor predisposed the recipients to HBV-related hepatitis after transplantation.<sup>93</sup>

HBV can be transmitted from HBsAg-positive donors to HBsAg-negative recipients. The consequence is probably more severe in HBV-naïve (HbsAg-, HbsAb-, and HbcAb-negative) patients.<sup>93</sup> An HBsAg-positive donor should be avoided as far as possible. However, an HBV-infected donor is often the only choice. The current data suggest that an HBV-infected person can be used as an HSC donor if no better alternative donor is available, especially if the recipients are previously HBV-infected.<sup>94</sup> The HBsAg-positive donors, however, need to be assessed carefully for clinical evidence of chronic liver disease.<sup>86,87</sup> In addition, the serum HBV DNA levels of the donors before transplantation should be

obtained. The donors should be started on anti-HBV therapy as early as possible. This would bring down rapidly the donors' serum HBV DNA to an undetectable level before HSC donation, hence minimizing HBV transmission.<sup>86,87,94</sup> The recipients need to be monitored after transplantation for HBV serology and serum DNA levels. Anti-HBV therapy should also be administered.<sup>86</sup>

HBsAg-positive transplant recipients also tend to have HBcAb-, HBsAb-positive, or both sibling donors, because HBV infection often clusters within families. With the use of these donors for transplantation, there is a chance of seroconversion from HBsAg positivity to negativity in approximately 50% of the transplant recipients, as the result of adoptive immune transfer.<sup>95-100</sup> The recipients may be seroconverted to become HBsAb-positive. This phenomenon of HBsAg clearance and seroconversion is often preceded by a minor self-limiting clinical flare of hepatitis.<sup>98</sup> The HBsAg and HBsAb status may fluctuate with the intensity of the immunosuppression given to the recipients. For example, there may be a reappearance of HBsAg in the recipients after initial clearance, on increasing immunosuppression for graft-versus-host disease. Less-intensive immunosuppression and preemptive use of anti-HBV therapy would help to enhance the chance of HBsAg clearance by augmenting the graft's anti-HBV activity and lowering the recipient's viral load, respectively.<sup>97</sup> HBsAg clearance seems to occur only if the donors have acquired immunity from natural HBV infection previously rather than from vaccination. These donors are usually both HbcAb and HBsAb positive.<sup>97,99</sup> Some donors may have anti-HBV immunity acquired from vaccination and are therefore HBsAb-positive but HBcAb-negative. Transplants from this latter group of donors apparently do not result in HBsAg clearance in the recipients. Because HBV immunization is quite risk free, it has been recommended to all allogeneic transplant donors and recipients who are HBV naïve.<sup>10,86,87,101</sup> Routine use of booster HBV vaccine has also been recommended to the donors and recipients with HBV immunity already, but the clinical benefit is uncertain.<sup>10,86,87</sup>

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## Concluding remarks

HBV reactivation is a serious but preventable complication of immunosuppression. At-risk patients must be identified promptly. Preemptive anti-HBV therapy is effective. Lamivudine is commonly used, and the role of the newer anti-HBV agents needs to be better defined. For patients receiving allogeneic HSC transplants, the problem is more complex because the HBV status of the donors should also be considered.

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## Authorship

Contribution: R.L. was the single author of this paper.

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