Risk of hepatitis B reactivation and the role of novel agents and stem-cell transplantation in multiple myeloma patients with hepatitis B virus (HBV) infection

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Background: The purpose of the study is to analyse the prevalence of hepatitis B virus (HBV) infection and its incidence of reactivation among multiple myeloma (MM) patients treated in the era of novel therapy in an endemic Asian setting.

Patients and methods: From 2000 to 2008, 273 patients with newly diagnosed MM were screened for the presence of hepatitis B virus surface antigen and HBV core antibody. HBV-infected patients were prospectively followed for reactivation with serial monitoring of serum alanine transferase and HBV DNA load. The patterns of HBV reactivation in relation to treatment received, exposure to high-dose therapy with autologous stem-cell transplantation (HDT/ASCT) and novel agents were studied.

Results: The prevalence of HBV infection was 5.5%. Three cases of HBV reactivation despite lamivudine prophylaxis were reported. Two patients reactivated 3–5 months after HDT/ASCT while receiving thalidomide maintenance and one reactivated 3 years after HDT/ASCT and shortly after bortezomib salvage therapy. Emergence of a mutant HBV strain was documented in one patient.

Conclusions: Use of prophylaxis may reduce but will not preclude HBV reactivation. Highest risk occurs during immune reconstitution phase of HDT/ASCT. The role of immunomodulatory agents in HBV reactivation needs to be further elucidated. Separate HBV prophylaxis and surveillance guidelines ought to be developed for patients with MM.

Key words: hepatitis B, immunomodulatory, lamivudine, myeloma, thalidomide

Introduction

Hepatitis B virus (HBV) infection is endemic in Asia. Viral replication can be promoted in chronic carriers of hepatitis B virus surface antigen (HBsAg) receiving immunosuppressive chemotherapy, resulting in widespread infection of hepatocytes. When chemotherapy is stopped, the recovery of the host’s immune competence and an exaggerated, activated, T-cell-mediated immunological response to the increase in HBV viral load during the period of immunosuppression can result in liver damage of varying severity, including fulminant hepatitis that is often fatal [1–4]. In addition to the morbidity and mortality risks associated with viral reactivation, the ensuing delays and reductions in delivery of chemotherapy may hinder the continuation of the treatment schedule. The risk of reactivation is commonly related to the intensity of immunosuppression, with the highest incidence reported with lymphoma therapy [5]. A higher incidence of HBsAg positivity among patients with B-cell lymphoma has been reported in HBV-endemic areas. Whether this relates to the direct immunosuppressive effect of the lymphoma itself on susceptibility to HBV infection or an oncogenic role played by HBV in lymphoma is debatable [6–11]. Viral reactivation has also been reported to occur in HBsAg-negative but HBV core antibody (HBcAb)-positive patients in the rituximab era [12].

Primary prophylaxis with lamivudine, a purine analogue that effectively suppresses HBV replication, has been shown to reduce the incidence of chemotherapy-induced HBV reactivation [6, 13]. Although much has been reported in the literature about HBV infection and lymphoma, there is still a paucity of data pertaining to the incidence of HBV infection and the risk of HBV reactivation in patients with multiple myeloma (MM). As such, no specific guidelines exist for surveillance of HBV reactivation in HBV-infected MM patients receiving treatment.

The treatment strategy for MM has evolved very rapidly and differently from lymphoma over recent years. Bortezomib and immuomodulatory drugs (IMIDs) are now very integral components of MM treatment. In this article, we reported on the prevalence of HBV infection in patients...
with MM and the incidence and patterns of reactivation in patients treated in the era of novel therapy in an endemic region. The role of lamivudine prophylaxis will also be evaluated.

### patients and methods

#### patients

We identified 273 previously untreated patients with MM who presented to our institution from January 2000 to December 2008 for this retrospective analysis. Patient characteristics before treatment were evaluated overall and with respect to HBV carrier status. Every patient was staged by the International Staging System (ISS). As HBV is endemic in Singapore, HBsAg was documented among patients with MM. Screening for the presence of HBcAb was only added for the later cohort of patients following concerns of viral reactivation in patients with prior resolved HBV infection (negative for HBsAg but positive for HBcAb) in lymphoma patients receiving rituximab-based treatment [12].

#### treatment

Treatment information updated as at the last follow-up date and before June 2009 when the data were censored was reviewed. For induction therapy, transplant-eligible patients received VAD (vincristine, adriamycin and dexamethasone) chemotherapy from 2000 to 2004 (27%), and this was replaced by thalidomide–dexamethasone combination from 2004 (31%). Transplant- ineligible patients received melphalan–prednisolone combination from 2000 to 2004 (7%) and thalidomide–dexamethasone or melphalan–prednisolone–thalidomide combination from 2004 (17%). Patients <65 years old were eligible for high-dose therapy with autologous stem-cell transplantation (HDT/ASCT; 28%). This entailed conditioning with melphalan 200 mg/m² followed by infusion of peripheral blood stem cells. All transplanted patients received thalidomide maintenance at 50–100 mg/day for 1–2 years after transplantation. Bortezomib became available as the standard of care for treatment of relapsed/refractory disease from 2004 and for upfront treatment of high-risk MM from 2007 (15%). Overall, 35% of the patients had been exposed to bortezomib. Lamivudine prophylaxis at a dose of 100 mg once daily was mandated for all patients who had HBV viraemia based on HBV DNA quantification. Initially, at the discretion of the treating physician, patients who were positive at diagnosis for HBsAg, but without HBV viraemia, and could not be reliably followed for regular HBV DNA surveillance were also eligible for lamivudine prophylaxis. From 2005, however, lamivudine prophylaxis was mandated for all HBsAg-positive patients regardless of the HBV DNA levels. Lamivudine was typically given before the commencement of induction treatment and maintained for 6–12 months after withdrawal of chemotherapy. Authorisation to carry out this retrospective analysis was approved by our institutional review board.

#### hepatitis B infection and reactivation

An HBV-infected patient was defined as someone who had detectable serum HBsAg at the time of MM diagnosis. Hepatitis was defined as a three or more fold increase in serum alanine transferase (ALT) that exceeded the upper limit of normal or an absolute increase of ALT to >100 U/L when compared with the baseline pre-chemotherapy value. Hepatitis attributable to HBV reactivation (HBV flare) was defined by the presence of a concomitant increase in HBV DNA levels of 10-fold or an absolute increase of 1000 x 10^6 genome equivalents/ml in the HBV DNA level, with the exclusion of other causes of hepatitis [2]. Patients tested positive for HBsAg at diagnosis were followed at regular intervals with serial ALT levels and HBV DNA load.

### analysis

Differences in baseline demographic and disease characteristics between HBV-infected and HBV-uninfected patients (Table 1) and the differences among HBV-infected patients who reactivated and those who did not are compared using the 2 sample t-test or chi-squared test for continuous or categorical variables, respectively. The risk factors for viral reactivation studied among HBV-infected patients included the HBV viraemia status and stage of disease at presentation and the treatment (induction, transplantation and maintenance) received. Survival curves were estimated using the Kaplan–Meier method [14]. The Kaplan–Meier curves were compared for statistical differences by using the log-rank test in the univariate analyses [15]. For overall survival (OS), the time interval was measured from the date of diagnosis to the date of death or last follow-up. Death from all causes was included.

### results

The prevalence of HBV infection among 273 MM patients was 5.5%. This was not statistically different from the prevalence of HBV infection in the Singapore population of 4.1% (P = 0.5) but lower than the 10.3% prevalence of HBV infection among lymphoma patients in Singapore [7, 16]. Apart from a significantly higher male predominance and a trend for a lower presenting platelet counts among HBV-infected patients (Table 1), other baseline characteristics between HBV-infected and -uninfected patients were comparable. The median OS of HBV-uninfected and -infected patients were 5.2 [confidence interval (CI) 3.6–6.7] and 4.4 years (CI 0.6–8.0), respectively (P = 0.52) (Figure 1).

Among the 15 HBV-infected patients, 7 (47%) had HBV viraemia, with detectable HBV DNA viral load of >3 logs at presentation. Among 10 patients who were tested for serum hepatitis B virus ‘e’ antigen/antibody status (HBeAg/HBeAb), 1 patient was positive for HBeAg, while 6 patients had anti-HBe antibody. None of the infected patients had elevated ALT levels at presentation. Eleven patients were started on lamivudine prophylaxis before commencing treatment of MM, while four patients treated before 2005 who did not have HBV viraemia at presentation did not receive lamivudine. HBV DNA levels decreased significantly in all seven patients with initial HBV viraemia. For induction treatment, six patients received VAD regimen, six received thalidomide–dexamethasone combination, two received bortezomib–thalidomide–dexamethasone and one was palliated with melphalan–prednisolone. Seven patients proceeded on to HDT/ASCT followed by maintenance thalidomide. Concurrent administration of lamivudine did not disrupt the planned induction treatment of MM nor affect stem-cell mobilisation and collection for patients intended for HDT/ASCT.

At a median follow-up of 2.8 years, three patients had relapsed or progressed and were salvaged with bortezomib-based therapy. Among four patients who did not receive lamivudine prophylaxis before induction treatment, two developed a rise in HBV DNA titres without hepatitis in the midst of induction treatment and were subsequently started on lamivudine. This successfully suppressed the viraemia. Patients who received prophylactic lamivudine did not develop viraemia during induction treatment. Three HBV flare events were documented among patients who were on lamivudine...
Table 1. Baseline characteristics of all patients with MM

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients, n (%)</th>
<th>HBV infected, n (%)</th>
<th>HBV uninfected, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>244</td>
<td>15</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>63</td>
<td>61</td>
<td>63</td>
<td>0.5</td>
</tr>
<tr>
<td>Range</td>
<td>25–93</td>
<td>48–79</td>
<td>25–93</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>124 (51)</td>
<td>10 (67)</td>
<td>114 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>119 (49)</td>
<td>5 (33)</td>
<td>115 (50)</td>
<td></td>
</tr>
<tr>
<td>MM subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>151 (62)</td>
<td>9 (60)</td>
<td>140 (61)</td>
<td>0.7</td>
</tr>
<tr>
<td>IgA</td>
<td>56 (23)</td>
<td>5 (33)</td>
<td>57 (25)</td>
<td></td>
</tr>
<tr>
<td>Light chain</td>
<td>37 (15)</td>
<td>1 (7)</td>
<td>32 (14)</td>
<td></td>
</tr>
<tr>
<td>International Staging System</td>
<td>N = 231</td>
<td>N = 15</td>
<td>N = 216</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>46 (20)</td>
<td>4 (27)</td>
<td>42 (19)</td>
<td>0.5</td>
</tr>
<tr>
<td>II</td>
<td>104 (45)</td>
<td>6 (40)</td>
<td>98 (45)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>81 (35)</td>
<td>5 (33)</td>
<td>76 (35)</td>
<td></td>
</tr>
<tr>
<td>Metaphase cytogenetics</td>
<td>N = 228</td>
<td>N = 15</td>
<td>N = 213</td>
<td></td>
</tr>
<tr>
<td>Diploid</td>
<td>119 (52)</td>
<td>6 (40)</td>
<td>113 (53)</td>
<td></td>
</tr>
<tr>
<td>Hyperdiploid</td>
<td>48 (21)</td>
<td>3 (20)</td>
<td>45 (21)</td>
<td></td>
</tr>
<tr>
<td>Non-hyperdiploid</td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Hypodiploid</td>
<td>41 (18)</td>
<td>5 (33)</td>
<td>36 (17)</td>
<td></td>
</tr>
<tr>
<td>Pseudodiploid</td>
<td>15 (7)</td>
<td>1 (7)</td>
<td>14 (7)</td>
<td></td>
</tr>
<tr>
<td>Near tetradiploid</td>
<td>5 (2)</td>
<td>0 (0)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Deletion 13</td>
<td>35 (17)</td>
<td>4 (26)</td>
<td>19 (18)</td>
<td>0.3</td>
</tr>
<tr>
<td>Interphase FISH</td>
<td>N = 100</td>
<td>N = 5</td>
<td>N = 95</td>
<td></td>
</tr>
<tr>
<td>High risk [t(4;14), del 17p or t(14;16)]</td>
<td>38 (38)</td>
<td>2 (40)</td>
<td>36 (38)</td>
<td>0.9</td>
</tr>
<tr>
<td>Median presenting platelet counts (&lt;10^9/l)</td>
<td>217</td>
<td>166 (54–294)</td>
<td>221 (27–511)</td>
<td>0.1</td>
</tr>
<tr>
<td>HDT/ASCT + maintenance thalidomide</td>
<td>63 (26)</td>
<td>7 (47)</td>
<td>56 (25)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

MM, multiple myeloma; HBV, hepatitis B virus; HDT/ASCT, high-dose therapy with autologous stem-cell transplantation.

Figure 1. Overall survival by HBV infection status. HBV, hepatitis B virus.
prophylaxis (Table 2). One patient reactivated with the emergence of an HBV variant with tyrosine–methionine–aspartate–aspartate (YMDD) mutation after 9 months of lamivudine prophylaxis (patient 2). The reactivation was treated successfully with a switch to adefovir. Two patients reactivated 3–5 months immediately after HDT/ASCT, while on both maintenance thalidomide and prophylactic lamivudine, with one of them dying of fulminant hepatitis. The last patient reactivated 3 years after HDT/ASCT and 4 months after a bortezomib–dexamethasone salvage therapy for a relapse. Baseline clinical and treatment parameters including age, gender, MM subtype, ISS stage, presence of HBV viraemia at diagnosis and the type of treatment received were compared between HBV-infected patients who developed HBV flare and those who did not. High-dose chemotherapy with stem-cell transplant followed by maintenance thalidomide emerged as the only significant risk factor for reactivation of HBV.

discussion

To our knowledge, this is the first systematic analysis investigating the prevalence of HBV infection and the incidence of HBV reactivation among MM patients. The prevalence of HBV infection among MM patients was not found to be higher than the endemic infection rate unlike lymphoma [7–11, 17]. It may be conceivable that the immunodeficiency related to MM, which is predominantly humoral, could be significantly different from that induced by lymphoma with regard to susceptibility to HBV infection.

HBV flare during chemotherapy is a major concern in HBV-endemic regions as the mortality rate can be high if the reactivation is complicated by fulminant hepatic failure [4, 18–20]. Our observation suggests that the risks with HBV reactivation may be reduced with upfront use of prophylactic lamivudine. Before mandating a prophylactic approach where all HBsAg-positive patients were given lamivudine before commencing MM treatment, we observed viral reactivation in two patients early in the course of induction treatment. The prompt introduction of empirical lamivudine before the onset of further hepatic injury was able to prevent further liver deterioration. However, after mandating a prophylactic approach regardless of the presenting HBV DNA titre in the later part of the study period, no incidence of HBV reactivation during induction was seen. This observation corroborates previous lymphoma studies that a prophylactic approach is preferred to deferring treatment till HBV reactivation has occurred [10, 21–23]. Any disruption to a planned induction regimen can hence be kept to a minimal in an HBV-infected patient. Although such an evaluation of prophylactic lamivudine in a retrospective manner has major statistical shortfalls, it is none the less highly informative since any randomised trial exploring the optimal dosing schedule of lamivudine could be ethically unfeasible.

Despite the use of prophylaxis, our experience shows that HBV reactivation could still occur since all three patients who developed HBV flare were on lamivudine at the time of reactivation. Unlike lymphoma patients, transplant-eligible MM patients undergo HDT/ASCT as a standard consolidative treatment. Common to these three patients who reactivated in our study was the prior exposure to HDT/ASCT and maintenance thalidomide. Two of them reactivated 3–5 months during the immediate post-transplant period. Interestingly, from immune reconstitution studies on patients undergoing ASCT, this is the time of recovery of the cellular immunity after peripheral blood stem-cell infusion [24–27]. Using the cellular immune response to another viral pathogen, Epstein–Barr virus (EBV) as a model, some of these studies have demonstrated that although the EBV-specific cytotoxic T cells are substantially reduced during the first 3 months after transplantation, they recover remarkably 3–6 months after transplantation [28, 29]. This corresponded to the onset of T-cell-mediated liver injury, with rising ALT levels in our patients. Although the reconstitution of cytotoxic HBV-specific T cells in the transplant setting has never been studied, it is unlikely to be any different from the reconstitution of the EBV immune response.

Immunomodulatory agents are now a very integral part of modern MM therapeutics. Thalidomide is the first of the kind and by far the most widely used IMID for MM in Asia. The finding that thalidomide acts as a T-cell co-stimulator suggests that this drug may boost the antiviral CD8+ T-cell responses. In vitro studies have demonstrated that thalidomide could enhance virus-specific CD8+ T-cell cytokine production and cytotoxic activity [30, 31]. A major concern for HBV-infected MM patients treated with IMIDs is hence the possible exaggeration of cellular response resulting in hepatic injury upon recovery of the immune function after suppressive chemotherapy. As current data support the use of IMIDs in the

Table 2. Patients who developed HBV flare

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis/ISS</th>
<th>Viraemia at diagnosis</th>
<th>Lamivudine at diagnosis</th>
<th>Induction regimen</th>
<th>Viraemia during induction</th>
<th>HDT/ASCT + MT</th>
<th>Reactivation; outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IgG/III</td>
<td>No</td>
<td>No</td>
<td>VAD × 6</td>
<td>Yes (cycle 2)</td>
<td>Yes</td>
<td>5 months after HDT/ASCT; died</td>
</tr>
<tr>
<td>2</td>
<td>IgG/I</td>
<td>No</td>
<td>No</td>
<td>Thal–dex × 8; VAD × 6</td>
<td>Yes (cycle 3)</td>
<td>Yes</td>
<td>3 months after HDT/ASCT; alive</td>
</tr>
<tr>
<td>3</td>
<td>IgA/II</td>
<td>No</td>
<td>Yes</td>
<td>VAD × 6</td>
<td>No</td>
<td>Yes</td>
<td>At relapse, 3 years after HDT/ASCT; alive</td>
</tr>
</tbody>
</table>

HBV, hepatitis B virus; ISS, International Staging System; HDT/ASCT, high-dose therapy with autologous stem-cell transplantation; MT, maintenance thalidomide; VAD, vincristine, adriamycin and dexamethasone; thal–dex, thalidomide–dexamethasone.
maintenance setting, the impact of T-cell stimulation during this immune recovery phase will be even more profound. The fact that two of these patients who reactivated were on maintenance thalidomide despite the use of prophylaxis raises the concern on the possible role of thalidomide in inducing hepatic injury. Lenalidomide is a second-generation IMID with an even more potent immunomodulatory and T-cell-stimulating effect but more acceptable toxicity profile than thalidomide. Although the role of IMIDs in the pathogenesis of hepatitis B reactivation has yet to be firmly established, it is, however, advisable to practise due caution when using IMIDs in HBV-infected patients. In the frontline setting, although HBV reactivation among our patients receiving thalidomide–dexamethasone induction was observed, no hepatic injury was reported. This could be a result of prompt administration of lamivudine upon detection of HBV viraemia. Another postulation, however, could be the suppression of the immunostimulatory effects of thalidomide when high-dose dexamethasone was concomitantly administered. This is based on recent in vitro studies elucidating the mechanism of action of the lenalidomide–dexamethasone combination [32, 33]. A meta-analysis conducted by Ziakas et al. [34] has demonstrated that the probability of HBV reactivation while on prophylaxis is significantly lower at 8.6% compared with 50.6% among patients without prophylaxis. In our study, the incidence of HBV reactivation despite lamivudine prophylaxis was a higher than expected 27%. In addition, we observed the emergence of the YMDD mutant strain in one patient on lamivudine. Although the high incidence reported here can be confounded by the low number of HBV-infected patients in the study, it is, however, conceivable that unlike lymphoma, the true probability of reactivation and the incidence of emergence of resistant strains among MM patients will be expected to be higher as MM is incurable, but the rapid advancement in MM therapy is allowing patients to survive longer, and consequently, protracted courses of HBV prophylaxis may be required. In time to come, this may constitute a major problem for MM physicians treating patients in HBV-endemic areas. Hence, upfront use of newer antivirals such as entecavir or tenofovir, which are more potent and have lower rates of drug resistance than lamivudine, could be considered in MM patients.

The association of HBV reactivation in MM patients with bortezomib has never been previously studied. One patient in our study had HBV reactivation 4 months after salvage treatment with bortezomib and dexamethasone. Whether bortezomib adds further to the reactivation risk associated with dexamethasone remains unknown. Before the routine use of antiviral prophylaxis, bortezomib was reported to be associated with an increased reactivation of varicella-zoster virus (VZV) [35]. Although data are limited, it has been suggested that bortezomib may alter the number and function of specific lymphocyte subsets, in particular the CD8 T cells and CD56 natural killer cells. The consequent suppression of the cellular-mediated immunity (CMI) that plays an important role in the suppression of VZV reactivation may have a role in the unchecked replication of VZV during bortezomib treatment [36]. As HBV is another DNA virus that remains dormant in the human host, whether HBV reactivation can be attributable to bortezomib’s impact on CMI remains to be defined.

In summary, with improved survival of MM patients, HBV reactivation and the emergence of resistant strains will be a growing concern in endemic areas. Highest risk of HBV flare seems to occur during the immune reconstitution phase of HDT/ASCT. Separate HBV prophylaxis and surveillance guidelines ought to be developed for MM patients. The use of prophylaxis may reduce but will not preclude HBV reactivation. The optimal choice and duration of HBV prophylaxis has not yet been determined. Further elucidation of the underlying mechanisms of HBV reactivation in the context of modern anti-MM agents like IMIDs and proteasome inhibitors will further help inform prophylactic strategies.

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disclosure

The authors declare no conflict of interest.

references


