Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies

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Summary

The prevalence of hepatitis B virus (HBV) infection in patients with haematological malignancies is increased compared with the general population worldwide. HBV reactivation is common following chemotherapy and is associated with a high mortality despite prompt anti-viral treatment. HBV reactivation may necessitate interruption of chemotherapy with adverse prognostic consequences for the haematological disease. Chemotherapy-induced immune suppression may lead to increased HBV replication. Immune reconstitution within the weeks and months following recovery from chemotherapy may be associated with a flare of hepatitis B manifested by hepatocellular injury. Risk factors associated with HBV reactivation include detectable hepatitis B surface antigen (HBsAg), HBV DNA, Hepatitis B e (HBeAg) antigen, antibodies to hepatitis B core antigen (anti-HBc), treatment with corticosteroids, young age and male gender. Lamivudine is effective during HBV reactivation due to immune suppression. Clinical trials have demonstrated that pre-emptive antiviral treatment with lamivudine is superior to deferred treatment. Current recommendations emphasise screening for HBV infection in all haematology patients, particularly prior to chemotherapy. Patients who are HBsAg positive or HBV DNA positive should receive pre-emptive treatment with lamivudine before chemotherapy. The duration of lamivudine treatment may be prolonged commensurate with the degree of immunosuppression. HBV naïve patients should be immunised against hepatitis B, as should haematopoietic stem cell donors. In summary, overt and occult HBV pose a serious, but preventable, threat. Pre-treatment screening of patients at risk should be practiced diligently by all clinicians that treat patients with malignancies.

Keywords: immune suppression, leukaemia, lymphoma, anti-viral treatment, haematopoietic stem cell transplantation.

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The 'natural' course of hepatitis B virus infection as relevant to patients with a haematological malignancy

The evolution of chronic HBV infection often depends on the age at infection and is affected by the balance between the host immune response and viral replication. Vertical or perinatal transmission of HBV frequently results in immune tolerance to the virus. Infection during adulthood induces a neutralising immune response in over 90% of immunocompetent individuals, with spontaneous resolution of acute infection (McMahon, 2005; Yim & Lok, 2006). In this case, immune memory, comprising T helper cell type 1 (Th1) responses to nucleocapsid epitopes and antibodies to HBsAg (anti-HBs), persist for decades and generally prevent reinfection (Chisari, 1997; Bertoletti & Gehring, 2006). Patients who are unable to resolve an acute infection have an altered natural course of HBV infection, consisting of four phases: immune tolerance with enhanced viral replication; immune clearance characterised by the initial presence of hepatitis B e antigen (HBeAg) and variable viral load; inactive carrier state frequently associated with antibodies to HBeAg (anti-HBe) seroconversion with low viral replication, and HBV reactivation (Yim & Lok, 2006). Reactivation of HBV infection may occur in a known asymptomatic HBsAg carrier or in patients with occult or rarely with resolved hepatitis B. HBV reactivation, either spontaneous or following chemotherapy, can resolve, persist, recur or lead to liver failure and death (Fig 1). Such flares have been attributed to changes in equilibrium due to an enhanced immunological response to HBV during recovery from immune suppression, associated with quantitative variations in viral load. Serological recovery from HBV infection (defined as anti-HBs antibody titre >10 IU/l, also termed resolved HBV) usually signifies clearance of viraemia and complete resolution of hepatocellular injury. However, even after serological recovery, HBV may persist as an occult infection in serum, in the liver (with intra-hepatic covalently closed circular DNA, termed cccDNA) or in extra-hepatic sites, with resulting risk of reactivation (Yim & Lok, 2006). This is especially true during recovery from immunosuppression or disease-associated immunodeficiency (Puoti et al, 2006). Immune suppression allows enhanced viral replication with increased viral load and reduced clearance. Immune reconstitution may then lead to a vigorous host-derived inflammatory response towards HBV, with concomitant hepatic necrosis (Liaw, 1998).

Risk factors

Patients at risk are those with haematological malignancies (or solid malignant tumours) who are candidates for chemotherapy but also patients with non-malignant diseases, such as immune thrombocytopenic purpura (ITP) or autoimmune haemolytic anaemia, which require continuous immunosuppressive therapy. Most haemat-oncological patients should be considered at risk either for HBV reactivation or acute acquired HBV infection. Increased risk is due to increased exposure to potentially contaminated blood products (despite conventional screening) as well as disease- and treatment-related factors (Yeo & Johnson, 2006).

Haemat-oncological diseases reported in association with HBV reactivation are listed in Table I.

Studies on the clinical significance of HBV genotypes indicate that genotypes may correlate with key clinical events (Kao et al, 2000). Although data are scarce, the incidence of HBV reactivation seems to correlate with distinct HBV genotypes C and B, prevalent in East Asia, and the East Mediterranean (Lok & Lai, 1990; Lok et al, 1991; Jazayeri et al, 2004).

Several specific risk factors for HBV reactivation have been proposed, but few were confirmed in multivariate analysis. In studies of 78 patients (Yeo et al, 2000, 2004a), univariate analysis identified an increased risk in younger males who had HBsAg positive/HBeAg positive lymphoma, while there was no association with pre-treatment alanine amino trans-

![Fig 1. Dynamics of viral load and alanine amino transferase (ALT) during the course of hepatitis B virus (HBV) reactivation following chemotherapy-induced immune suppression. Adapted from Xunrong et al (2001). ©John Wiley & Sons Limited with permission.](image-url)

### Table I. Haematological diseases reported in association with hepatitis B virus reactivation

<table>
<thead>
<tr>
<th>Group</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Acute leukaemia</td>
<td>Acute myeloid leukaemia</td>
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<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>Chronic myeloid leukaemia</td>
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<tr>
<td>Myeloproliferative disorders</td>
<td>Chronic lymphoblastic leukaemia</td>
</tr>
<tr>
<td>Lymphoproliferative disorders</td>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td></td>
<td>Hodgkin disease</td>
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<tr>
<td>Plasma cell dyscrasias</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Waldenström macroglobulinaemia</td>
<td>Plasmacytoma</td>
</tr>
<tr>
<td>Other</td>
<td>Aplastic anaemia</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic syndrome</td>
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<tr>
<td></td>
<td>Haematopoietic stem cell transplantation</td>
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ferase (ALT), bilirubin or HBV DNA. In contrast, in a study of patients with hepatocellular carcinoma and underlying liver disease, pre-treatment ALT elevation was shown to be a risk factor for HBV reactivation (Yeo et al, 2004b). In a study of 100 patients, male sex was the only risk factor (Lok et al, 1991). In contrast, a study of 137 autologous haematopoietic cell transplantation (HCT) patients found that pre-immune suppression HBV DNA level >10^5 copies/ml was the only significant risk factor (Lau et al, 2002a). This was also observed in 138 cancer patients for whom HBV viral load >3 x 10^5 copies/ml was a risk factor for reactivation (Yeo et al, 2004a). Zhong et al (2004) and Hui et al (2005a) confirmed that high titre viral DNA levels increase the risk of HBV reactivation.

Different chemotherapeutic agents have been reported in association with HBV reactivation (Table II), most importantly, corticosteroids and anthracyclines (Lok et al, 1991; Cheng et al, 2003; Yeo & Johnson, 2006). The HBV DNA contains a glucocorticoid responsive element that facilitates replication (Tur-Kaspa et al, 1986), while anthracyclines have been shown in vitro to stimulate HBV DNA secretion (Hsu et al, 2004). Most important, corticosteroids may also induce a flare, particularly upon abrupt withdrawal of treatment. ‘Steroid free’ chemotherapy has been proposed to minimise the risk of HBV reactivation (Lok et al, 1992; Nakamura et al, 1996), but is of dubious benefit. In a prospective study of 50 patients with aggressive non-Hodgkin lymphoma (NHL) (75% diffuse large B-cell NHL in both the steroid-free and the steroid-inclusive arms), the use of ‘steroid-free’ chemotherapy resulted in a significant decrease in the rate of HBV reactivation (73% vs. 38%, P = 0.03). However, patients in the ‘steroid-free’ arm had a significantly lower rate of complete remission and shorter overall survival, presumably due to suboptimal therapy (Cheng et al, 2003).

Theoretically, any form of immune suppression, including agents not mentioned in Table II, may lead to HBV reactivation. Standard chemotherapy has frequently been documented to cause HBV reactivation in HBsAg negative patients with occult HBV infection (Lok et al, 1991; Hui et al, 2006). Immune suppression of greater intensity may be a risk factor. One study found the incidence of HBV reactivation increased with second or third line chemotherapy (Kumagai et al, 1997), but this was not subsequently confirmed (Yeo et al, 2000). In contrast, mildly immune suppressive chemotherapy, such as

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents associated with HBV reactivation</th>
<th>Potential hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylators</td>
<td>Cyclophosphamide</td>
<td>VOD, hepatocellular injury</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>Hepatocellular injury</td>
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<tr>
<td></td>
<td>Chlorambucil</td>
<td>Hepatocellular injury</td>
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<tr>
<td></td>
<td>Carboplatin, cisplatin</td>
<td>hepatitis viral injury, cholestasis, peliosis</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Cytarabine</td>
<td>VOD, hepatocellular injury</td>
</tr>
<tr>
<td></td>
<td>Fludarabine</td>
<td>Hepatocellular injury</td>
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<tr>
<td></td>
<td>Gemcitabine</td>
<td>Hepatocellular injury</td>
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<td></td>
<td>Mercaptopurine</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>Hepatocellular injury, steatosis, fibrosis, hepatic neoplasm</td>
</tr>
<tr>
<td></td>
<td>Thioguanine</td>
<td>VOD, hepato-cellular injury, NRH, peliosis</td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>Anthracyclines</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td></td>
<td>Bleomycin</td>
<td>Steatosis</td>
</tr>
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<td></td>
<td>Mitomycin C</td>
<td>VOD, steatosis</td>
</tr>
<tr>
<td></td>
<td>Actinomycin D</td>
<td>VOD, steatosis</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone/dexamethasone etc.</td>
<td>hepatomegaly (rare association)</td>
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<tr>
<td>Immunotherapy</td>
<td>Rituximab (anti-CD20)</td>
<td>Hepatocellular injury</td>
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<tr>
<td></td>
<td>Alemtuzumab (anti-CD52)</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td></td>
<td>Infliximab (anti-TNF)</td>
<td>Hepatocellular injury, steatosis</td>
</tr>
<tr>
<td>Plant Alkaloids</td>
<td>Vincristine</td>
<td>VOD, hepatocellular injury</td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Others</td>
<td>Asparaginase</td>
<td>Hepatocellular injury, steatosis</td>
</tr>
<tr>
<td></td>
<td>Procarbazine</td>
<td>VOD</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>Hepatocellular injury</td>
</tr>
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<td></td>
<td>Etoposide</td>
<td>Hepatocellular injury</td>
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<td></td>
<td>Fludarabine</td>
<td>Hepatocellular injury</td>
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<tr>
<td></td>
<td>Imatinib Mesylate</td>
<td>Hepatocellular injury, cholestasis</td>
</tr>
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<td></td>
<td>Interferon alpha</td>
<td>Hepatocellular injury</td>
</tr>
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*Only predominant forms of liver injury are cited for the purpose of differential diagnosis of abnormal liver function tests.

positive despite the cessation of chemotherapy. Others have reappeared of HBsAg, and two remained persistently HBsAg in their anti-HBs titre; five developed 'seroreversion', with malignancies (Wands disease. In a report of 17 patients with haematological lead to asymptomatic rise of ALT, which may progress to overt these patients are not absolutely protected against reactivation. While anti-HBs positive patients are at low risk (Lok 1991; Lau 1993; Martin et al, 1999; Picardi et al, 1998; Strasser & McDonald, 1999; Iwai et al, 2000; Nordbo et al, 2000; Goyama et al, 2002); the rate of HBV reactivation varies between 14% and 50% (Chen et al, 1990; Dhedin et al, 1998; Seth et al, 2002; Knöll et al, 2004; Onozawa et al, 2005). Suggested risk factors include corticosteroid use, lack of anti-HBs in the donor, and graft versus host disease (GVHD). Conversely, in autologous-HSCT, there have been fewer reports (Webster et al, 1989; Goyama et al, 2002). One case series showed that one of 37 patients developed non-fulminant hepatitis B (Lau et al, 2002a).

Newer therapeutic monoclonal antibodies, such as Rituximab (anti-CD20) (Westhoff et al, 2003; Law et al, 2005; Niccola et al, 2005; Sarrecchia et al, 2005), Alemtuzumab (anti-CD52) (Iannitto et al, 2005) and infliximab (anti-TNF) (Calabrese et al, 2006) have been associated with HBV reactivation in HBsAg carriers as well as in HBsAg negative patients, which may progress to fulminant hepatitis. These agents cause profound and long-lasting immunosuppression (Osterburg et al, 1997; van der Kolk et al, 2002), which may account for the risk of HBV reactivation following treatment.

The patient’s HBV serological profile is linked to the risk of HBV reactivation. HBsAg positive patients are at highest risk; patients with anti-HBs levels >10 IU/l are at the lowest risk. HBsAg positivity, previously considered to signify high level viral replication, has been replaced by more sensitive viral load assays (Locarnini, 2004) that have a threshold of detection of as low as 300 copies/ml and a wide dynamic range (Gish & Locarnini, 2006). HBV DNA assays are also useful in HBsAg negative/anti-HBe positive patients in whom viraemia can still be significant. Even in patients who have cleared HBsAg and undergone seroconversion, residual HBV DNA, in the form of cccDNA ‘hidden’ in hepatocytes, can be used as a template for reactivation following immune suppression (Hui et al, 2005b). Furthermore, HBV DNA has been found in peripheral blood mononuclear cells recovered from immune suppressed transplanted patients with a serologic profile anti-HBc positive/ HBsAg negative/anti-HBs negative, in the absence of HBV DNA in the serum (Mason et al, 1998; Locarnini, 2004). A similar rule applies for patients following treatment for HBV. Even with successful therapy, some patients remain at lifelong risk for reactivation (Osborn & Lok, 2006). Therefore, while anti-HBs positive patients are at low risk (Lok et al, 1991; Lau et al, 2002a; Knöll et al, 2004; Onozawa et al, 2005), these patients are not absolutely protected against reactivation. Subclinical changes in the immune profile of such patients may lead to asymptomatic rise of ALT, which may progress to overt disease. In a report of 17 patients with haematological malignancies (Wands et al, 1975), 12 had a marked reduction in their anti-HBs titre; five developed ‘seroreversion’, with reappearence of HBsAg, and two remained persistently HBsAg positive despite the cessation of chemotherapy. Others have reported changes in the HBV serological profile following chemotherapy (Iannitto et al, 2005; Avetand-Fenoel et al, 2006).

In summary, proven risk factors include: positive HBsAg (especially when associated with high viral load), positive HBeAg, positive anti-HBc in the absence of HBsAg and anti-HBs, use of corticosteroids or anthracyclines, higher intensity chemotherapy (such as for HSCT), male gender and young age.

Clinical manifestations and laboratory diagnosis of a hepatitis B flare in the immune suppressed patient

Hepatitis B virus reactivation is characterised by two main parameters: rising serum HBV DNA levels followed by rising ALT. Monitoring of HBV DNA requires an available sensitive assay with a wide dynamic range (Gish & Locarnini, 2006). Reactivation may be symptomatic or remain asymptomatic. Rising HBV DNA levels usually precede ALT elevation, which frequently lags by several days (range 1–11 weeks) after an increase in viral load (Lau et al, 2003). Furthermore, HBV DNA levels may be declining or undetectable by the time a rise in ALT is noticed (Xunrong et al, 2001; Yeo & Johnson, 2006) (Fig 1). Therefore, there are no clear cut diagnostic criteria for HBV reactivation. One proposed definition was a sudden rise in serum ALT more than five times the upper limit of normal or more than three times baseline level, whichever was higher (Lok et al, 1987). Other definitions include a 10-fold rise in viral load or HBV DNA levels exceeding approximately 6 log10 copies/ml (Yeo et al, 2000). Essentially, measuring viral load (Gish & Locarnini, 2006) and ALT are the key to diagnosing and monitoring reactivation. A liver biopsy, although usually not imperative, can potentially yield important information, by excluding other or concomitant factors involved in liver injury. It may also reveal a potentially wide spectrum of histological changes associated with HBV infection. If present, coagulopathy or thrombocytopenia may necessitate a transjugular approach.

Reactivation most frequently follows cessation of chemotherapy, but may occur during chemotherapy. The reported interval ranges from 4 to 36 weeks (median, 16 weeks) from initiation of chemotherapy (Liang et al, 1999; Lau et al, 2003). An acute flare may also be induced by HBV genotypic variations, such as precore or DNA polymerase mutants as well as superinfection by other hepatotrophic viruses, such as hepatitis D, hepatitis C and hepatitis A as well as cytomegalo virus (CMV) and Epstein–Barr virus (EBV). Interaction with HIV or hepatotoxicity of anti-HIV agents may also contribute (Puoti et al, 2006). An acute flare may be indistinguishable from acute viral hepatitis B including the detection of anti-HBc IgM, potentially leading to a misdiagnosis of acute HBV infection in patients with previously undiagnosed chronic disease. HBV-reactivation can easily be missed, particularly in early stages, when salvage anti-viral therapy could be life saving. Reactivation can also be associated with an
increase in alpha-feto-protein, raising concern about the development of hepatocellular carcinoma (Lok & Lai, 1989).

Hepatitis B virus reactivation may resolve spontaneously. Symptomatic patients may develop the classical symptoms of hepatitis, including fatigue, jaundice, ascites, hepatic encephalopathy and coagulopathy. Patients with underlying cirrhosis may rapidly develop liver failure; their mortality ranges from 4% to 41% (Lok et al., 1991; Kumagai et al., 1997; Liang et al., 1999; Markovic et al., 1999; Tillman et al., 2003).

Since many patients are asymptomatic, regular monitoring of ALT and HBV DNA is essential although there is no consensus regarding frequency of testing. As reactivation may be transient, more frequent HBV DNA and ALT monitoring will lead to a higher rate of diagnosis.

**Differential diagnosis of a hepatitis flare**

Most hepatitis flares in patients with chronic HBV are of viral aetiology. However, there are a number of other causes for liver dysfunction including chemotherapy or other drug-induced toxic hepatitis, veno-occlusive disease (VOD), peliosis, hepatic steatosis, hepatic fibrosis and nodular regenerative hyperplasia (NRH). Table II lists various types of chemotherapy agents involved in HBV reactivation that may also induce toxic hepatocellular or cholestatic dysfunction. Hepatotoxicity of anti-cancer agents may frequently result from an interaction between two or more agents. ALT elevation can also be caused by bacterial, viral or fungal infection [i.e. sepsis, CMV, EBV, herpes or human immunodeficiency virus (HIV)]. Superinfection with other hepatitis viruses, i.e. delta virus (HDV) infection in HBsAg carriers, hepatitis C or even hepatitis A can cause as many as 20–30% of flares (Perrillo, 2001). HBV-related fibrosing cholestatic hepatitis and GVHD are reported to be more frequent in HBsAg carriers (Lau et al., 1999). Other causes of hepatocellular or cholestatic injury should be considered where appropriate, such as exposure to alcohol, total parental nutrition, acalculous cholecystitis, tumour infiltration, or radiation toxicity. About 12% of ALT elevations remain unexplained (Yeo et al., 2000).

Haemato-oncological patients previously treated for HBV are at risk for developing resistance against the antiviral agent, such as reported for lamivudine for which 16–60% of recipients develop a mutation known as the YMDD motif within 1–4 years of treatment, respectively (Locarnini, 2004; Osborn & Lok, 2006; Wong & Lok, 2006). Hepatitis flares in such patients with a high viral load despite lamivudine treatment, must therefore be evaluated for this mutation, followed by optional treatment with adefovir or entecavir (see below).

**Hepatitis B reactivation: screening and prevention**

Prevention of HBV reactivation is superior to intervention at the time of reactivation. Preventive measures start with proper screening for HBV markers before initiation of chemotherapy followed by active immunisation of all HBV susceptible patients (also including bone-marrow and stem cell donors). Candidate patients with overt or occult HBV must be identified and protected against HBV by an anti-viral agent.

**Screening of haemato-oncological patients prior to initiation of chemotherapy**

All patients diagnosed with a haematological disease should be screened for HBV infection. Initial screening is based on serological tests for anti-HBc antibodies, HBsAg and anti-HBs antibodies (see flow chart: Fig 2). Seronegative patients should be actively vaccinated against HBV. HBsAg positive patients are considered carriers and should be protected pre-emptively against HBV reactivation by an anti-viral agent before initiation of chemotherapy (see below). Frequently, the diagnosis of an HBsAg carrier state cannot be verified at time of initiation of chemotherapy, as it is based on 6 months’ observation. In such a situation, the presence of a positive HBsAg test should be interpreted as representing an HBsAg carrier state, provided there is no evidence for acute hepatitis B which may result in delay of cytotoxic treatment. All HBsAg positive patients should be further tested for HBeAg, anti-HBc, HBV DNA and if possible, anti-HBc IgM. A liver biopsy may be considered in patients with pre-chemotherapy abnormal liver function tests, the result of which may have implications on the selection and dosing of chemotherapy. HBsAg negative patients who are anti-HBc positive, require further testing. A positive anti-HBs test in this context signifies a patient who recovered from HBV infection; while a negative anti-HBs test may signify either occult HBV infection, recovery from infection with a waning antibody titre or a false positive anti-HBc result. Differentiation between these fundamentally different states may be accomplished by repeating the serological profile after administration of an HBV vaccine booster dose to anti-HBc positive patients negative for HBsAg and anti-HBs (Fig 2). A rise in the anti-HBs antibody titre above 10 IU/l (and preferably >100 IU/l) within 2–4 weeks is a result of an anamnestic immune response and signifies immunity to HBV. In anti-HBc positive non-responders to the HBV vaccine, HBV-DNA should be measured by a sensitive polymerase chain reaction (PCR) assay. Detectable HBV-DNA implies occult HBV infection which will require pre-emptive antiviral therapy before initiation of chemotherapy (Fig 2). Since a patient’s serological profile may change during the course of chemotherapy (i.e. seroreversion from a state of anti-HBs positivity to HBsAg positivity) it is advised to perform serologic re-testing before the continuation of chemotherapy in case ALT levels rise (Wands et al., 1975; Chen et al., 1990; Dhedin et al., 1998; Seth et al., 2002; Knöll et al., 2004; Onozawa et al., 2005). In cases where urgent chemotherapy treatment is required this may be accomplished by saving an adequate blood sample for serological analysis prior to the institution of therapy and making a decision on anti-viral treatment once results are available.
Immunisation against hepatitis B infection

The cornerstone of prevention for patients who are HBV seronegative is immunisation. Currently available HBV vaccines are very safe and have an efficacy of >90% in immunocompetent young individuals. Non-response is associated with a number of factors including genetically determined resistance, advanced age, obesity, chronic liver disease, smoking, male gender and miscellaneous systemic diseases including renal failure (Shouval, 2003; Yu et al., 2006). Although universal vaccination of newborns has been implemented worldwide according to World Health Organisation recommendations, it will take several decades until the majority of the world’s adult population will be immune. Unfortunately, vaccination rates are low in many countries either due to lack of funding or because of the misconception that vaccination is only necessary in high-risk groups (Banatvala et al., 2006).

It is strongly recommended that all haemato-oncological patients be screened for HBV markers and immunisation against hepatitis B should be performed when appropriate (see algorithm, Fig 2). The conventional regimen for the HBV vaccine requires three doses at 0, 1 and 6 months. Delaying administration of the third dose in healthy individuals (up to 1 year) may increase anti-HBs antibody levels. Frequently, in haemato-oncological patients, urgent administration of chemotherapy does not allow completion of the three-dose regimen. In such cases, an effort should be made to immunise patients with at least two doses within a 3–4 week interval. The third dose can then be given a few months after chemotherapy is completed.

In most countries, immunity against HBV infection is defined as an anti-HBs titre >10 IU/l and in the UK the recommended titre is >100 IU/l. Non-response to HBV vaccines is not rare in haemato-oncological patients due to disease-associated or treatment-induced immune suppression. Thus, protection against HBV may not be achieved until all doses have been administered. Although immune-suppressed patients have significantly lower response rates to vaccination, successful anti-HBs seroconversion following a three dose vaccine schedule has been reported in 57% of cancer patients, 15–68% of bone marrow transplant recipients, and in 10% in acute lymphoblastic leukaemia (ALL) patients (Yu et al., 2006).

Documentation of post-vaccination anti-HBs seroconversion is recommended. There are a number of means to augment the immune response to HBV immunisation in non-responders, including adding three additional doses; doubling the vaccine dose; intradermal injection of the vaccine and use of new, more immunogenic HBV vaccines (Shouval, 2003; Yu et al., 2006). Finally, after allogeneic HSCT, immunity to HBV acquired through active immunisation may rarely be abolished by immune suppression and/or transplantation of HBV naïve bone marrow cells (Dhedin et al., 1998).
Agents for treatment of patients with occult or overt HBV infection

Recently, new and efficacious anti-viral agents have significantly improved our ability to intervene in and prevent HBV reactivation in immune suppressed patients (Osborn & Lok, 2006; Wong & Lok, 2006). Standard therapy currently consists of lamivudine, a nucleoside analogue introduced in 1995, which inhibits the viral DNA polymerase, thus rapidly and effectively interfering with viral replication, with minimal toxicity.

In addition, several new potent anti-viral agents have been developed and licensed for the treatment of chronic HBV, including adefovir dipivoxil in 2002 (Osborn & Lok, 2006), entecavir in 2005 (Chang et al, 2006; Lai et al, 2006) and others are awaiting approval. Both adefovir and entecavir are effective against YMDD mutants. While adefovir and lamivudine seem to suppress hepatitis B viral load equally well, entecavir is the currently most potent agent against HBV, leading to a 5–6 log suppression in viral load in HBsAg/HBeAg positive patients after 48 weeks of treatment with no HBV resistant strains reported thus far. There have been a few reports on the successful use of adefovir for HBV reactivation by a YMDD mutant during lamivudine therapy in haematological and immune suppressed patients (Nunez & Soriano, 2005; Cortelezziet al, 2006).

Interferon alpha, used for the treatment of chronic HBV, has been shown to control chronic HBV infection during chemotherapy to a certain degree (Lok et al, 1992; Kumagai et al, 1997; Leaw et al, 2004; Osborn & Lok, 2006). However, adverse effects, such as thrombocytopenia and or leucopenia, often limit its use during chemotherapy. A more serious concern is the enhancement of hepatocellular injury by augmentation of the host immune response against HBV. Thus, the use of interferon for an HBV flare has now been practically discontinued.

Protection and management of immune suppressed patients with overt or occult HBV against HBV reactivation

There are currently two approaches in management of patients at risk, namely intervention by treatment of HBV reactivation when it is diagnosed, or prevention through pre-emptive treatment prior to or upon initiation of chemotherapy.

Intervention upon diagnosis of hepatitis B reactivation

When HBV reactivation is diagnosed, prompt anti-viral therapy is vital. In patients who develop signs of HBV reactivation, end points of treatment include normalisation of ALT, suppression of HBV viral load to undetectable levels and HBeAg seroconversion to anti-HBe. In anti-HBe positive patients, ALT normalisation and viral load suppression are the main goals of treatment. Aggressive supportive therapy should be instituted and cessation of chemotherapy and withdrawal of potential hepatotoxic agents should be considered. Patients should be monitored, closely testing liver enzymes, coagulation function and viral load. Consultation with an expert hepatologist or early referral to a hepatology centre should be considered in patients with a severe course, although liver transplantation may not be feasible in patients with a malignancy.

Currently lamivudine is the primary agent for treatment for HBV reactivation in the setting of immune suppression. Several reports have shown clinical improvement and effective control of viral replication (Clark et al, 1998; Picardi et al, 1998; Ahmed & Keeffe, 1999; Al-Taie et al, 1999; Vento et al, 2002). The true rate of HBV reactivation in immune suppressed patients is not known and spontaneous resolution may occur (Table III). Thus, the reported efficacy rates of antiviral treatment may be somewhat overestimated (Yeo & Johnson, 2006). None of the studies reporting the success of lamivudine for HBV reactivation in these patients is truly prospective, blinded, placebo controlled trial. Presently, it is unlikely that such a study is ethically feasible. Despite this caveat, there is no doubt that lamivudine is effective in suppression of HBV replication and thus has dual importance, as it may enable the continuation of chemotherapy without risking further hepatic deterioration. Lamivudine is efficacious for HBV reactivation but less so if hepatic decompensation has occurred (ter Borg et al, 1998; Clark et al, 1998). Mortality may be as high as 40% despite lamivudine (Markovic et al, 1999) if severe hepatic injury is present (Iwai et al, 2000; Yeo et al, 2000; Yeo & Johnson, 2006). Thus, it is imperative to begin antiviral therapy immediately once a flare is diagnosed.

As stated earlier, HBV DNA rises prior to ALT elevation (Fig 1). Ideally, in cases where lamivudine is not administered pre-emptively, viral load should be monitored periodically during chemotherapy, although there is no consensus as to how frequently. Once a rise in HBV DNA is identified, it is strongly advised to immediately administer lamivudine, prior to the appearance of clinical manifestations. However, this recommendation is difficult to implement due to cost and the time required for assessment of HBV DNA levels.

Pre-emptive anti-viral therapy against hepatitis B reactivation

Several reports have demonstrated the benefit of pre-emptive treatment with lamivudine in patients at risk of HBV reactivation. The rational for initiation of pre-emptive treatment with lamivudine in patients at risk is based on observations that viraemia, defined as HBV DNA >10⁴ copies/ml, usually precedes ALT elevation by a day to several months. Thus, early suppression of viral load prior to hepatic injury is superior to deferred intervention. Reports on the efficacy of pre-emptive treatment may be divided into retrospective studies and prospective studies with historical controls, listed in Table III. In 12 studies conducted in 208
Table III. Selected reports on the outcome of hepatitis B virus reactivation in patients with haematological malignancies treated by deferred or pre-emptive lamivudine*.

<table>
<thead>
<tr>
<th>Therapy with Lamivudine</th>
<th>Author</th>
<th>Diagnosis</th>
<th>Study type</th>
<th>Interval to reactivation</th>
<th>Total number of patients</th>
<th>Number of patients in each group: P/D/NT</th>
<th>Number of acute hepatitis cases (resolved)</th>
<th>Number of HBV-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Liang et al (1990)</td>
<td>Lymphoma</td>
<td>Retro</td>
<td>During and after C</td>
<td>105</td>
<td>NT</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Deferred</td>
<td>Yeo et al (1999)</td>
<td>NHL, other</td>
<td>Retro</td>
<td>During C</td>
<td>8</td>
<td>8-D</td>
<td>5</td>
<td>1-D (2 deaths from malignancy)</td>
</tr>
<tr>
<td></td>
<td>Petrelli et al (2001)</td>
<td>NHL, PC, AML, MM, KS, ALL</td>
<td>Retro</td>
<td>During C</td>
<td>10</td>
<td>5-D/5-NT</td>
<td>1</td>
<td>8 (1 death from malignancy)</td>
</tr>
<tr>
<td></td>
<td>Penisco et al (2002)</td>
<td>NHL</td>
<td>Retro</td>
<td>During C</td>
<td>12</td>
<td>9-D/3-NT</td>
<td>9</td>
<td>3-NT</td>
</tr>
<tr>
<td></td>
<td>Liao et al (2002)</td>
<td>NHL</td>
<td>Pro</td>
<td>During C</td>
<td>6</td>
<td>1-P/5-D</td>
<td>5</td>
<td>1-D</td>
</tr>
<tr>
<td></td>
<td>Simpson et al (2003)</td>
<td>BC, NHL</td>
<td>Retro</td>
<td>During C</td>
<td>4</td>
<td>4-D</td>
<td>2</td>
<td>2-D</td>
</tr>
<tr>
<td>Pre-emptive</td>
<td>Rossi et al (2001)</td>
<td>NHL, CLL, MM, AML</td>
<td>Pro</td>
<td>2 m after C and 1 m after LAM</td>
<td>20</td>
<td>19-P/1-D</td>
<td>1-P (post-LAM discont.)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Shibolet et al (2002)</td>
<td>Lymphoma, other</td>
<td>Retro</td>
<td>During C</td>
<td>18</td>
<td>13-P/5-D</td>
<td>0-P/2-D</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Lim et al (2002)</td>
<td>Haematological and solid tumours</td>
<td>Retro</td>
<td>10–105 d after C</td>
<td>35</td>
<td>16-P/19-NT</td>
<td>0-P/2-D</td>
<td>0-P/5-NT&amp;D</td>
</tr>
<tr>
<td></td>
<td>Lee et al (2003)</td>
<td>NHL</td>
<td>Retro + HC</td>
<td>NA</td>
<td>31</td>
<td>11-P/20-NT</td>
<td>1-P/17-NT/5-NT&amp;D</td>
<td>0-P/1-NT</td>
</tr>
<tr>
<td></td>
<td>Lau et al (2003)</td>
<td>NHL, HD</td>
<td>Pro</td>
<td>4 m – during C</td>
<td>30</td>
<td>15-P/15-D</td>
<td>0-P/7-D</td>
<td>0-P/0-D</td>
</tr>
<tr>
<td></td>
<td>Idilman et al (2004)</td>
<td>NHL, AML, ALL, CLL, HD, MM, BC</td>
<td>Pro§</td>
<td>4 m – during C</td>
<td>18</td>
<td>8-P/10-NT</td>
<td>0-P/5-D/5-NT&amp;D</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ozguroglu et al (2004)</td>
<td>NHL</td>
<td>Retro</td>
<td>NA</td>
<td>12</td>
<td>4-P/2-D/6-NT</td>
<td>0-P/2-D/2-NT</td>
<td>0-P/2-D/4-NT</td>
</tr>
<tr>
<td></td>
<td>Yeo et al (2004c)</td>
<td>NHL, other</td>
<td>Pro + HC</td>
<td>NA</td>
<td>258</td>
<td>65P/193D</td>
<td>3-P/42-D</td>
<td>0-P/5-D</td>
</tr>
<tr>
<td></td>
<td>Leaw et al (2004)</td>
<td>Lymphoma</td>
<td>Pro + HC</td>
<td>NA</td>
<td>64</td>
<td>11-P/53-NT</td>
<td>0-P/10-NT</td>
<td>0-P/7-NT</td>
</tr>
<tr>
<td></td>
<td>Hui et al (2005a,b)</td>
<td>NHL, HD, AML, MM</td>
<td>Pro</td>
<td>9–39 m after C</td>
<td>46</td>
<td>46-P</td>
<td>10-P (11 patients reactivated post LAM discont.)</td>
<td>1-P (post-LAM discont.)</td>
</tr>
<tr>
<td></td>
<td>Vassiliadis et al (2005)</td>
<td>NHL, ALL, CLL, AML, WM, AA</td>
<td>Pro</td>
<td>NA</td>
<td>10</td>
<td>10-P</td>
<td>0-P</td>
<td>0-P</td>
</tr>
<tr>
<td></td>
<td>Li et al (2006)</td>
<td>NHL, HD</td>
<td>Pro + HC</td>
<td>NA</td>
<td>156</td>
<td>40P/116NT</td>
<td>7-P/60-NT</td>
<td>0-P/6-NT</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukaemia; ALL, acute lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; MM, multiple myeloma; WM, Waldenstrom macroglobuliniaemia; AA, aplastic anaemia; BC, breast cancer; PC, plasmacytoma; KS, Kaposi sarcoma.

*Several case reports of successful deferred treatment with lamivudine for HBV reactivation not quoted.
†Some patients originally listed in NT groups were subsequently treated with lamivudine upon reactivation. These patients are marked as NT&D.
§Controlled.

Modified from Yeo and Johnson (2006) with permission from John Wiley & Sons, Inc.
patients at risk treated pre-emptively with lamivudine during chemotherapy for various malignancies, HBV reactivation could be reduced from 25–85% to 0–9%. Thus a large body of clinical trials strongly supports pre-emptive therapy in patients undergoing chemotherapy.

The optimal timing for beginning pre-emptive anti-viral therapy has not been established and requires further study. It is preferable to begin pre-emptive treatment 2–3 weeks prior to chemotherapy, and we suggest no later than the first day of chemotherapy.

The optimal duration of prophylactic anti-viral therapy in patients at risk is unclear. Various studies have reported lamivudine discontinuation within 1–12 months after cessation of chemotherapy (Hui et al, 2005a; Hsiao et al, 2006). Premature discontinuation may lead to delayed HBV reactivation, as shown in Fig 3. Re-treatment with lamivudine may be successful, but delay in intervention may lead to serious liver injury and may be life threatening (Dai et al, 2004). The natural history of patients who stopped prophylactic therapy has not been well-studied. Despite the absence of well-controlled trials we suggest that treatment be maintained for at least 6 months and preferably 12 months after completion of chemotherapy (Idilman, 2006). Extended treatment for >12 months after chemotherapy may be advisable in patients who initially had high serum HBV DNA levels, at the discretion of the treating physician. More definitive recommendations require a prospective controlled study.

Guidelines for screening, immunisation and pre-emptive anti-viral treatment for patients at risk are suggested in Fig 2.

A potential concern related to the use of prophylactic lamivudine is the development of resistant mutants. At present, reports on lamivudine resistance in haematological patients with HBV reactivation are scarce, probably because of the relatively short duration of therapy. Newer and more potent anti-viral agents described above will enable effective protection despite the emergence of escape mutants.

Thus, in case of emergence of YMDD mutant-associated hepatitis, adefovir or entecavir may be used for rescue.

It should, however, be remembered that HBV reactivation may occur in up to 9% of patients at risk, despite pre-emptive lamivudine treatment. The reason(s) for this breakthrough phenomenon are still not understood.

Adoptive transfer of immunity to hepatitis B through immunisation of haematopoietic cell donors

Candidates for allogeneic HSCT require special attention. They are very poor responders to conventional vaccination against hepatitis B. Such patients may benefit from the acquired immune memory obtained through transplantation of HBV immune lymphocytes from their human leucocyte antigen (HLA) matched donors. The donors can be either immunised against HBV or may be immune following natural HBV infection with seroconversion (anti-HBc positive/anti-HBs positive). Indeed, adoptive transfer of immunity to HBsAg was shown to occur in HBV naive bone marrow recipients and in recipients of peripheral lymphocytes and stem-cells transferred from immunised anti-HBs positive donors (Shouval & Ilan, 1995; Ilan et al, 2000). Immunity to HBsAg could be boosted after transplantation by HBV vaccination. Studies in various animals confirmed that immunity to HBV can be adoptively transferred, even under conditions of immune suppression (Shouval et al, 1993; Li et al, 2002; Dahmen et al, 2004).

A number of studies have provided further evidence that immunisation of donors may induce HBV immunity in recipients within several days to weeks of transplantation (Ilan et al, 1993a; Lindemann et al, 2003; Shouval, 2007). Immunisation of stem cell donors is simple, practically risk-free and should be planned in advance, so that donors can be adequately vaccinated prior to harvesting. Both donor and recipient can then receive a booster vaccine. The optimal timing and the number of booster doses required depends on the immune status of the recipient and should be documented by anti-HBs testing (Ilan et al, 1993a). Administration of the third vaccine dose to the donor at 6 months should not be forgotten after the primary immunisation to maximise anti-HBs seroconversion if future cell donations are required. It is not yet established if a booster dose is required in transplant recipients from cell donors who had previously recovered spontaneously from HBV infection and were anti-HBc positive/anti-HBs positive at time of donation. However, there is a rational for administering a booster vaccine dose to such recipients once they recover immunologically.

If an HBsAg positive patient requires haematopoietic cell transplantation (HCT) or HSCT, it may be possible to adoptively transfer immunity to HBV by these procedures. A number of observations suggest that this is possible. Clearance of HBV was first documented in an HBsAg positive/anti-HBe positive/HBV DNA positive chronic lymphocytic leukaemia
(CLL) patient who received a bone marrow transplant from his anti-HBc positive/anti-HBs positive brother (Ilan et al, 1993b). Lau et al (1997, 2002a) confirmed and extended this observation in HBsAg positive transplant recipients in whom HBV clearance and anti-HBs seroconversion was achieved following receipt of an HBV immune bone-marrow, without serious adverse events. Furthermore, donor-derived core antigen reactive T-cells were linked to the clearance of HBV in the recipients (Lau et al, 1999, 2002b). The probability of identifying an HLA-matched HBV immune donor with an anti-HBc positive/anti-HBs positive serological profile for an HBsAg positive recipient is low, albeit not negligible, especially in HBV endemic countries. Utilisation of such donors, together with pre-emptive lamivudine treatment may therefore be beneficial in patients with chronic HBV infection. Finally, there already is a report suggesting anti-HBs seroconversion in HBsAg negative patients transplanted with livers from HBV immune donors (Shouval, 2007).

Summary of recommendations

1. All patients who are candidates for immune suppressive therapy should be screened for HBV markers.

2. All HBV naive patients, including potential bone marrow and stem cell donors, should be immunised against HBV as soon as possible with preferably three doses and no less than two. The quantitative anti-HBs response should be documented several weeks after the last injection. Non-responders should receive another course of three injections, when possible.

3. Early, pre-emptive anti-viral therapy is superior to intervention at time of HBV reactivation. Patients who are HBsAg positive should be evaluated for presence of liver disease and receive pre-emptive treatment with lamivudine at 100 mg/d, regardless of their HBeAg or HBV DNA status. Anti-viral treatment should be started preferably within 2–3 weeks prior to initiation and no later than the first day of chemotherapy. Lamivudine treatment should be continued for at least 6 months after discontinuation of chemotherapy and preferably for 12 months.

4. Patients who are anti-HBc positive/HBsAg negative/anti-HBs negative should receive one dose of a hepatitis B vaccine and quantitative anti-HBs response measured within 2–4 weeks. Those who develop an anti-HBs response will not require pre-emptive anti-viral treatment. Non-responders to the vaccine should be tested for HBV-DNA by PCR. Patients with viraemia should be started on pre-emptive lamivudine 100 mg/d.

5. Patients who are anti-HBc positive/HBsAg negative/anti-HBs negative/HBV DNA negative do not require pre-emptive lamivudine. However, continuous monitoring for ALT is advised. In case of ALT elevation, HBV DNA should be tested.

6. Antiviral treatment should be started promptly in immune suppressed patients who demonstrate symptoms compatible with a hepatitis flare attributed to HBV reactivation.

In conclusion, surveillance for HBV status is an integral part of the care of the haematology patient. By implementing good medical practice, virtually all patients should be prevented from contracting or reactivating HBV, in view of the potentially serious consequences of this infection.

Acute hepatitis B – Hepatic injury that resolves within 6 months after exposure to HBV or onset of symptoms. Elevated ALT and AST, HBsAg positive/anti-HBe IgM, positive.

Chronic hepatitis B – Hepatic injury which continues ≥6 months. HBsAg positive ≥6 months, elevated ALT and AST, HBV-DNA in serum positive or negative.

Inactive HBsAg Carrier state – ALT and AST levels persistently normal, HBsAg positive ≥6 months, HBV DNA negative or low positive <10⁵ copies/ml in serum.

Occult HBV – Normal or abnormal ALT levels, anti-HBc positive/HBsAg negative, anti-HBs positive or negative, HBV DNA positive (in serum or liver tissue).

Overt HBV – Clinically, biochemically and virologically apparent hepatitis B.

Resolved HBV – HBsAg negative, HBV DNA negative, normal ALT, history of HBV infection/anti-HBc positive/anti-HBs positive or negative.

References


Calabrese L.H., Zein N.N. & Vassilopoulos D. (2006) Hepatitis B virus reactivation with immunosuppressive therapy in rheumatic dis-


Vassiliadis, T., Garipidou, V., Tziomalos, K., Perifanis, V., Giouleme, O. & Vakalopoulou, S. (2005) Prevention of hepatitis B reactivation with lamivudine in hepatitis B virus carriers with hematologic ma-


