HEMATOPOIETIC CELL transplantation (HCT) is performed annually in over 30,000 patients worldwide for a range of underlying disorders including hematologic malignancy, severe aplastic anemia, solid tumors, and genetic diseases. While the risk of acquiring hepatitis virus infection from transfusion of blood products is now extremely low, it is not uncommon for patients to come to transplantation already infected with hepatitis viruses from past exposure. Particularly in endemic areas, potential hematopoietic cell donors may also have evidence of hepatitis virus infection. Furthermore, there is a large group of long-term HCT survivors with chronic hepatitis B and/or hepatitis C infection, many of whom are unaware they are infected.

Clinical manifestation of hepatitis B and C infection are determined by host-virus interactions. In both infections, hepatocellular damage appears to be mediated primarily by host cellular immune responses. Inflammatory and fibrogenic cytokines, released by infiltrating T cells, potentiate inflammation, hepatocyte damage, and progression to fibrosis. The marked immunosuppression and subsequent immune reconstitution associated with HCT have the potential to significantly impact the pathobiology of hepatitis virus infection. Furthermore, there is a large group of long-term HCT survivors with chronic hepatitis B and/or hepatitis C infection, many of whom are unaware they are infected.

Hepatitis Viruses and Hematopoietic Cell Transplantation: A Guide to Patient and Donor Management

By Simone I. Strasser and George B. McDonald

Although the risk of acquiring hepatitis virus infection from transfusion of blood products is now extremely low, it is not uncommon for patients to come to transplantation already infected with hepatitis viruses from past exposure. Particularly in endemic areas, potential hematopoietic cell donors may also have evidence of hepatitis virus infection. Furthermore, there is a large group of long-term HCT survivors with chronic hepatitis B and/or hepatitis C infection, many of whom are unaware they are infected.

Clinical manifestation of hepatitis B and C infection are determined by host-virus interactions. In both infections, hepatocellular damage appears to be mediated primarily by host cellular immune responses. Inflammatory and fibrogenic cytokines, released by infiltrating T cells, potentiate inflammation, hepatocyte damage, and progression to fibrosis. The marked immunosuppression and subsequent immune reconstitution associated with HCT have the potential to significantly impact the pathobiology of hepatitis virus infection. So that appropriate management decisions can be made, it is important to understand the impact of recipient and donor hepatitis virus infection, on the short-term and long-term outcome of HCT.

Hepatitis B Virus

Transplant candidates with hepatitis B infection. Patients may come to HCT already infected with hepatitis B virus (HBV) (see Table 1). These patients potentially are at risk for venoocclusive disease (VOD) and/or recurrent HBV infection after transplantation. While transplantation is frequently avoided or delayed in candidates with abnormal serum aminotransferases, a finding of positive hepatitis B surface antigen (HBsAg) alone is not considered a contraindication and does not confer an increased risk for VOD. However, preexisting cirrhosis or marked hepatic fibrosis does increase the risk of severe VOD and multorgan failure and should be considered a contraindication to high-dose cytoablative therapy and HCT (G.B.M., unpublished observations).

Even in patients with very low levels of viral replication before transplantation and relatively normal liver function and histology, the impaired cellular immunity seen in the first 3 to 6 months after transplantation can result in HBV reactivation, often with progressive elevations in HBV levels in serum and liver. Reconstitution of cellular immunity posttransplant often leads to a biochemical hepatitis, however some patients rapidly develop acute hepatitis and fulminant hepatic failure.5-8

The risk of fatal HBV liver disease among patients who are persistently HBsAg-positive after transplantation is approximately 12%.5-12 Risk factors for an adverse outcome have not been identified; however, fatal cases may be related to infection with a precore mutant form of HBV.11,13,14 This variant HBV with one or more nucleotide substitutions in the precore region of the genome fails to produce hepatitis B e antigen (HBeAg); patients lack HBeAg, are anti-HBe positive, but have circulating HBV DNA.15 In hematopoietic cell transplant recipients who are anti-HBc ± anti-HBs-positive, but HBsAg-negative, reactivation of latent infection can occur and may lead to fulminant hepatic failure.6,8,16-18

Thus, the following recommendations can be made when a patient is found to be HBsAg positive before transplantation (Table 1). First, the replication status of the virus should be determined. Patients should be tested for HBeAg, anti-HBe and HBV DNA and have the level of HBV DNA quantitated if positive. Patients with replicating, wild-type HBV will usually be HBsAg, HBeAg, and HBV DNA positive. The presence of a precore mutant form of HBV is suggested by the finding of a positive HBsAg, HBV DNA and anti-HBe, and a negative HBeAg, and can be confirmed by polymerase chain reaction (PCR)-based mutation analysis15 or by direct sequencing. Pretransplant liver biopsy to assess for the presence of fibrosis or cirrhosis is recommended in patients with abnormal liver-associated enzymes or clinical stigmata of chronic liver disease. Patients with active viral replication, regardless of whether they...
<table>
<thead>
<tr>
<th>Patient Result</th>
<th>Donor Result</th>
<th>Interpretation</th>
<th>Recommendation</th>
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<tr>
<td>Hepatitis B Virus</td>
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<tr>
<td>Anti-HBs positive</td>
<td>Negative</td>
<td>Patient has had prior exposure to HBV or has been vaccinated</td>
<td>Proceed with transplantation</td>
</tr>
<tr>
<td>Negative</td>
<td>Anti-HBs positive</td>
<td>Donor has had prior exposure to HBV or has been vaccinated</td>
<td>Proceed with transplantation</td>
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<tr>
<td>Anti-HBc positive (HBsAg and anti-HBs negative)</td>
<td>Negative</td>
<td>Patient has had prior exposure to HBV and is at risk for viral reactivation after transplant</td>
<td>Test for HBV DNA by PCR from 2 weeks posttransplant; consider antiviral therapy if serum positive for HBV DNA.</td>
</tr>
<tr>
<td>Negative</td>
<td>Anti-HBc positive (HBsAg and anti-HBs negative)</td>
<td>Donor has had prior exposure to HBV</td>
<td>Test donor for HBV DNA by PCR; if the result is negative, there is a negligible risk of viral transmission. If positive, consider antiviral therapy.</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>Negative</td>
<td>Current HBV infection in patient</td>
<td>Assessment for liver disease in patient, as patients with cirrhosis have a high risk for fatal VOD. If recipient is HBV DNA positive, institute antiviral therapy before transplant. If negative, monitor HBV DNA posttransplant and institute antiviral therapy if becomes positive.</td>
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<td>HBsAg positive</td>
<td>Anti-HBs ≤ anti-HBc positive</td>
<td>Current HBV infection in the patient. Donor has immunity to HBV.</td>
<td>Assessment for liver disease in patient, as patients with cirrhosis have a high risk for fatal VOD. If recipient is HBV DNA positive, institute antiviral therapy before transplant. If negative, monitor HBV DNA posttransplant and institute antiviral therapy if becomes positive.</td>
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<td>HBsAg positive</td>
<td>HBsAg positive</td>
<td>Current HBV infection in the patient and the donor</td>
<td>Assessment for liver disease in recipient, as patients with cirrhosis have a high risk for fatal VOD. Assessment for liver disease in donor, as there is an anesthesia risk during marrow harvest if the donor has cirrhosis. If recipient is HBV DNA positive, institute antiviral therapy before transplant. If negative, monitor HBV DNA posttransplant and institute antiviral therapy if becomes positive.</td>
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<tr>
<td>Negative</td>
<td>HBsAg positive</td>
<td>Current HBV infection in the donor</td>
<td>Assessment for liver disease in donor, as there is an anesthesia risk during marrow harvest if the donor has cirrhosis. Consider an alternate donor. Consider antiviral treatment of donor before stem cell harvest. Monitor recipient HBV DNA levels posttransplant and consider antiviral therapy if patient develops viremia.</td>
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<td>Hepatitis C Virus</td>
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<tr>
<td>Anti-HCV positive but HCV RNA negative</td>
<td>Negative</td>
<td>Patient has had passive acquisition of HCV antibody or has recovered from prior HCV infection or has a falsely negative HCV RNA</td>
<td>Repeat HCV RNA by a more sensitive method; check HCV RNA posttransplant.</td>
</tr>
<tr>
<td>HCV RNA positive</td>
<td>Negative</td>
<td>Current HCV infection in patient</td>
<td>Assessment for active liver disease or cirrhosis in patient before transplantation. Observe patient for development of chronic hepatitis after transplantation. Consider antiviral therapy in long-term follow-up.</td>
</tr>
<tr>
<td>Negative</td>
<td>HCV RNA positive</td>
<td>Current donor infection; HCV transmission is likely</td>
<td>Consider alternate donor; if this donor is the best available match, consider treatment of donor before marrow or stem cell harvest.</td>
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Abbreviations: anti-HBs, antibody to hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; VOD, venocclusive disease; PCR, polymerase chain reaction.
have evidence of the precore mutant form of HBV, should receive prophylactic antiviral therapy as discussed below.

**Donors with hepatitis B infection.** The most suitable stem cell donor for an HCT recipient may be infected with HBV. The risks of using such a donor depend on the virological and serological HBV markers present in both the donor and recipient (see Table 1). Unfortunately precise risks are difficult to determine, as the HBeAg, anti-HBe, and HBV DNA status of HBsAg-positive donors are not always reported in the literature. These incomplete data, in part, explain the apparent low frequency of transmission from HBsAg-positive donors to recipients who have no serological markers of HBV infection. Of 22 such cases, nine remained uninfected, three were only transiently HBsAg positive, and 10 developed chronic HBV infection after transplantation.7,20,21 The lack of HBV transmission from many HBsAg-positive donors suggests either that the donors had no active viral replication (or circulating virus) or that their hematopoietic cells, a recognized site of HBV persistence, were not infected by the virus.22,23

If a recipient has had prior exposure to hepatitis B and has cleared the infection (ie, HBsAg-negative and anti-HBs-positive), there is an even lower chance of acquiring HBV infection from a HBsAg-positive donor. In series involving 14 such recipients, only one patient developed transient HBsAg, and one became a chronic carrier.7,20,24 There are, however, reports of rapid progression to cirrhosis and hepatic failure in anti-HBs-positive recipients transplanted from HBsAg-positive donors.21,25

To summarize, there is clear evidence that HBV can be transmitted from HBsAg-positive donors to either naive or anti-HBs-positive recipients. The subsequent infection is more likely to have severe consequences if the recipient has no serological markers of prior HBV infection. There is a small risk of HBV transmission from a donor whose only serum marker is a positive anti-HBc. Such donors may harbor latent HBV in their liver,26 but are unlikely to be viremic or transmit HBV through hematopoietic cell infusions, however, they should undergo testing for HBV DNA (by PCR) to exclude the remote possibility of viremia.27 The finding of negative HBV DNA by PCR in such a donor’s serum and hematopoietic cells should virtually eliminate the risk of transmission of HBV. There is a negligible risk of transmission from a donor who is anti-HBs and anti-HBc-positive.

These data suggest that a hepatitis B-infected individual can be used as a hematopoietic cell donor, if no alternative donor is available. Various strategies have been attempted to further reduce the risk of viral transmission. Attempts to protect the recipient by either prophylactic infusions of HB immune globulin or by active immunization of the recipient28 have been unsuccessful, probably because of prolonged absence of T-cell-dependent B-cell responses after myeloablative therapy. Several antiviral agents have been shown to be extremely effective in suppressing HBV replication. Treatment with interferon-alfa or nucleoside analogs such as lamivudine or famciclovir dramatically reduces circulating HBV DNA in most patients with chronic HBV infection.29-31 For instance, lamivudine at 100 mg or 300 mg per day results in total suppression of HBV DNA in 77% to 100% of patients by 3 to 6 months, with maximum suppression occurring within 2 weeks of starting therapy.32,33

Consideration should be given to treating HBsAg/HBV DNA-positive donors with antiviral therapy before hematopoietic cell collection, although there are currently no data to support this approach. Both lamivudine and famciclovir are well-tolerated and do not cause significant myelosuppression, a potential concern with the use of interferon.

**Donors with immunity to hepatitis B.** Immunity to HBV can be transferred from anti-HBs-positive donors to HCT recipients. Prolonged expression of anti-HBs has been documented in recipients after transplantation from donors whose immunity followed either natural infection or vaccination.34 In addition, the posttransplant infusion of peripheral blood lymphocytes obtained from donors who received hepatitis B vaccination after marrow donation has resulted in prolonged expression of anti-HBs in the recipient, which may be further boosted by subsequent immunization.35 There are a number of reports of clearance of HBV infection after marrow transplantation from anti-HBs-positive donors to HBsAg-positive recipients.3,5,6,38 Factors associated with sustained clearance of HBsAg include having a donor who is anti-HBs-positive after natural infection and negative pretransplant serum HBsAg and HBV DNA (by dot blot hybridization) in the recipient.39 In these cases, loss of HBsAg is seen between 3 and 10 months posttransplant; adoptive transfer of HBsAg-specific cytotoxic T lymphocytes is probably responsible for seroconversion in the recipients. Hepatitis B vaccination of a HBV-naive donor is probably insufficient to effect viral clearance in a HBV-infected recipient.39,40

The course of hepatitis B in the posttransplant period. Posttransplant HBV infection may arise in a number of ways. Patients may have active HBV infection before transplant or may reactivate latent HBV infection. Infection may occur during the transplantation process, either from an infected hematopoietic cell donor, or rarely from infected blood products, a risk currently estimated in the United States to be 1 in 63,000 units.41 In 1993 through 1994, three HCT recipients developed acute hepatitis B after receiving marrow or peripheral blood stem cells infected by storage in a contaminated cryopreservation tank.42

After cytoreductive therapy and before the return of cellular immunity, there is usually no clinical or biochemical evidence of viral hepatitis, although HBV DNA titers may increase to very high levels, particularly in patients receiving corticosteroids, cyclosporine (CyA), or other immunosuppressive drugs. This is in part because of suppression of immune mechanisms that normally serve to control viral replication, but in patients receiving corticosteroids, direct transcriptional regulation of the HBV genome is also likely to be important in increasing the level of viremia.43 At the time of immune reconstitution or during tapering of immunosuppressive drugs, a clinical flare of hepatitis may occur. In most cases, this flare is manifest by a transient increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Severe hepatitis with marked elevations of AST and ALT may culminate in fulminant hepatic failure and death in approximately 12% of HBV-infected transplant recipients.5,18 Patients at particular risk for fulminant hepatic failure are those harboring precore mutant HBV.13,14 These patients remain HBsAg-negative despite high
levels of viral replication, reinforcing the necessity to monitor HBsAg-positive patients with HBV DNA levels.

Progressive elevations of AST, ALT, and bilirubin at the time immunosuppressive drugs are being tapered in a hepatitis B-infected allograft recipient may be due to hepatic graft-versus-host disease (GVHD), HBV, a herpesvirus infection, or drug-induced liver injury. In this situation, liver biopsy should be performed to determine the dominant pathologic process. Even in the setting of marked thrombocytopenia, liver biopsy can be performed safely by a transvenous approach, using either a forceps-style biopsy instrument via the femoral vein or a needle via the jugular vein. If the biopsy shows characteristic changes of GVHD, then immunosuppression should be targeted to this disease, which has the effect of also suppressing the immune response to HBV infection. However, in the absence of antiviral therapy, this approach will usually lead to increasing levels of viral replication, putting the patient at further risk of a serious flare when the immunosuppression is finally reduced.

Consideration should be given to the use of antiviral therapy as a means of preventing progression to high levels of viremia and the risk of a clinical flare of hepatitis when immunity is restored after HCT. A number of nucleoside analogues have efficacy against HBV. These include ganciclovir, famciclovir (and its active component, penciclovir), and lamivudine. Ganciclovir has been used to manage hepatitis B in liver transplant recipients, and renal transplant recipients, however, it is not universally effective in suppressing HBV replication and is myelosuppressive. In one reported HCT recipient, ganciclovir, given for treatment of cytomegalovirus (CMV) disease, completely suppressed HBV DNA levels, although after ganciclovir was discontinued, an abrupt increase in HBV DNA levels led to acute hepatitis and liver failure. Both famciclovir and lamivudine have been used in clinical trials of immunocompetent patients with chronic HBV infection and for prophylaxis and treatment of HBV infection in liver transplant and renal transplant recipients. Both agents are very effective at suppressing HBV replication, however, their use has been associated with the emergence of drug-resistant variant viruses, which have mutations in the HBV polymerase gene. The clinical impact of these mutations remains to be determined, however, in one study of patients treated with lamivudine after liver transplantation, breakthrough hepatitis associated with a lamivudine-resistant mutant resulted in only mild elevations of ALT levels. In the future, higher doses of antiviral drugs or therapy with combinations of antiviral drugs may well reduce the rate of emergence of variant viruses.

There is little experience in the use of antiviral therapy to control HBV after HCT. Lau et al. reported their experience with the use of oral famciclovir, starting at least 1 week before marrow transplantation and continuing for 24 weeks after transplantation. This strategy reduced the incidence of posttransplant hepatitis due to HBV compared with historical controls. An alternative approach is to carefully monitor posttransplant HBV levels in patients at risk for HBV infection. Increasing levels of HBV DNA can usually be detected as early as 1 to 2 weeks after transplantation and antiviral therapy with famciclovir or lamivudine could be introduced at that time. It is important not to wait until a clinical flare of hepatitis has developed, before instituting antiviral therapy. This preemptive approach appears to be effective in preventing HBV liver disease after orthotopic liver transplantation, but has not been reported in the HCT setting. The aim should be to completely suppress viral replication to minimize the risk of viral mutation. The most appropriate antiviral strategy (monotherapy versus combination therapy), drug dosage, and treatment duration are unknown at this time. Based on the liver transplantation experience, anti-HBV therapy may need to be continued long-term.

Chronic hepatitis B in long-term survivors. The prevalence of chronic HBV infection among transplant survivors varies widely around the world. Most of the series examining the long-term effects of HBV infection are from Asia and southern Europe, where the seroprevalence of hepatitis B in the general population is high. The serologic patterns of HBV infection may be atypical in transplant survivors, probably as a consequence of immunosuppression. Clearance of antigenemia is commonly observed and is particularly likely if the hematopoietic cell donor was anti-HBs-positive. Once they are stable and off all immunosuppression, long-term survivors who remain HBsAg-positive generally exhibit only mild liver disease. However, in the presence of chronic GVHD and added requirements for immunosuppressive drugs, patients with chronic HBV infection remain at risk for acute flares of hepatitis whenever immunosuppression is tapered or ceased. Such flares in activity may result in hepatic failure and death. Cirrhosis due to chronic hepatitis B has not emerged as a major problem in long-term survivors, although this may be due to an inadequate period of follow-up.

Hepatitis C

Transplant candidates with hepatitis C. Before the introduction of routine blood donor screening for hepatitis C, many patients with disorders such as hematologic malignancy, aplastic anemia, or thalassemia, came to transplant already infected with hepatitis C virus (HCV). For example, during 1987 to 1988, 32% of patients presenting in Seattle for marrow transplantation for acute myeloid leukemia had elevations of serum aminotransferases and hepatitis C viremia. HCT centers continue to see patients who acquired HCV infection either from a transfusion before 1991, or from other parenteral exposure, such as injecting drug use. Serological testing for hepatitis C antibodies is inadequate for exclusion of HCV infection among immunocompromised patients, such as those with hematologic malignancy, therefore, at-risk individuals should be assessed for the presence of viremia by PCR. Transplant candidates who received blood products before 1991, who have a history of injecting drug use or intranasal cocaine use, who have had multiple sexual partners, who are spouses or close household contacts of hepatitis C patients, or who have an elevated serum AST or ALT levels should be tested for hepatitis C, with a PCR test for HCV RNA performed in a reputable laboratory.

It is important to identify HCV-infected patients before transplantation so that the severity of underlying liver disease can be assessed and posttransplant abnormalities of liver function can be interpreted. Assessment of disease severity should include physical examination to identify signs of chronic liver disease, hepatosplenomegaly or portal hypertension, and review of laboratory values, particularly serum aminotransferase levels, serum albumin, and prothrombin time. Liver biopsy
should be considered in (1) patients in whom there is a clinical suspicion of cirrhosis, (2) patients who are likely to have had hepatitis C infection for more than 15 years and have elevated serum aminotransferase levels, and (3) patients with hepatitis C who have a history of excessive alcohol intake. Patients with established cirrhosis or marked hepatic fibrosis should not proceed to high-dose cytotoxic chemotherapy and HCT because of the high risk of severe VOD, multiorgan failure, and death (G.B.M., unpublished observations). Even in the absence of cirrhosis, HCV infection may increase the risk of severe VOD.

The inclusion of pretransplant HCV RNA status in the previously published multivariable analysis of risk factors for severe VOD identified hepatitis C infection associated with AST elevation in the pretransplant period as a major risk factor for severe VOD, with a relative risk of 9.6. Other investigators have not found an association between HCV infection and an increased incidence of severe VOD.

The presence of chronic hepatitis C without cirrhosis is not considered a contraindication to HCT, as the risk of severe VOD in individual patients is difficult to predict, and in general, the posttransplant course of hepatitis C is benign. Currently, there is no effective way to treat HCV infection before transplant or in the immediate posttransplant period. Interferon-α is usually contraindicated at these times because of its myelosuppressive effects and the possibility of inducing or exacerbating GVHD. Ribavirin has been reported to result in clearance of HCV RNA in three marrow transplant patients, a finding that is not supported in studies of the use of ribavirin as a single antiviral agent in other patients with chronic hepatitis C.

**Donors with hepatitis C infection.** Hepatitis C is universally transmitted from HCV RNA-positive allogeneic or syngeneic donors to their recipients (see Table 1). Recipients become viremic within days of hematopoietic stem cell infusion, however they do not immediately develop clinical or biochemical hepatitis, probably because of lack of cellular immunity after myeloablation and transplantation. It is the general policy in Seattle to use hepatitis C-infected donors in preference to less well HLA-matched donors who are not HCV-infected, as the risks of acute and chronic GVHD far outweigh those of HCV infection, at least in the 5- to 10-year period after HCT. Transmission of HCV from an infected hematopoietic cell donor to a recipient may be preventable by pretreatment of the donor with interferon-α, so that serum HCV RNA is not detectable at the time of harvest. It is our recommendation that if time permits, HCV RNA-positive donors should be treated with interferon-α before marrow or peripheral blood stem cell harvest. The dose and duration of interferon therapy that would be optimal in this setting is not known. The administration of 3 million units, 3 times a week results in irradication of viremia at 6 months of treatment in 29% of patients with chronic HCV, with almost all responding patients having undetectable viremia by 3 months. Suppression of HCV replication is dose-dependent, so higher and daily dosing may be more effective. The addition of ribavirin to interferon may increase the chance of eliminating viremia. The presence or absence of viremia can be monitored by PCR. Interferon should be stopped at least 1 week before marrow harvest to avoid engraftment problems in the recipient. However, complete irradication of hepatitis C infection in the donor requires 6 to 12 months of antiviral therapy; therefore interferon or ribavirin of the donor should be recommenced after hematopoietic cell harvest.

The course of hepatitis C in the posttransplant period. Regardless of whether patients come to HCT with preexisting HCV infection or acquire infection around the time of transplant, clinical or biochemical evidence of hepatitis is not seen in the immediate posttransplant period. Asymptomatic elevation of serum aminotransferases in recipients of allogeneic marrow does not occur until around days 60 to 120, coinciding with the return of cellular immunity and the tapering of immunosuppressive drugs used for GVHD prophylaxis. It might be expected that clinical hepatitis may occur earlier in recipients of peripheral blood stem cell transplants because of faster leukocyte engraftment. As flares of GVHD can also be seen during this time, it may be difficult to decide whether a flare of hepatitis C or GVHD is responsible for the elevations of AST and ALT. The differentiation of these two disorders is crucial, as GVHD of the liver usually requires increased immunosuppression, while acute exacerbations of hepatitis C are self-limited and do not normally require specific therapy. The presence of hepatitis C viremia, even in high titer, is insufficient to make the distinction between these two disorders. The absence of hepatitis C viremia, however, means that HCV is not a cause of AST/ALT elevations. Unless there is evidence of active GVHD in other organs, a liver biopsy may be required before a therapeutic decision is made. Pathologic distinction between hepatitis C and GVHD may be difficult, as both processes may be associated with portal lymphoid infiltration and bile duct injury, however, marked bile duct injury with epithelial cell drop-out and loss of interlobular bile ducts is more typical of GVHD. A flare of hepatitis C and hepatic GVHD may occur simultaneously. If, on the basis of liver biopsy, it is felt likely that both processes are present, patients should receive immunosuppressive therapy for GVHD of the liver, as ongoing lymphocytic attack leading to loss of interlobular bile ducts may result in severe and progressive cholestasis.

Fulminant immune-rebound hepatitis C has been reported only rarely after HCT and chemotherapy withdrawal. Patients with known hepatitis virus infection who develop a rapid, marked increase in serum aminotransferases at any time posttransplant, must also be fully evaluated for hepatic infection with viruses other than hepatitis viruses. In particular, hepatitis associated with herpes simplex virus, varicella zoster virus, or adenovirus, can result in rapidly progressive liver failure if not recognized and treated appropriately. Acute hepatitis can also be a manifestation of chronic GVHD, particularly after immunosuppressive therapy has been withdrawn. A rapid increase in aminotransferase levels due to hepatitis C may occur uncommonly, but usually does not progress to liver failure. In this situation, reconstitution of CyA may lead to a reduction in serum AST and ALT and may lessen the hepatocellular damage related to infiltration with cytotoxic T cells. The role of antiviral agents, such as ribavirin and interferon-α, has not been defined in this circumstance.

After the initial hepatitis flare with immune reconstitution, the AST and ALT may again normalize, but often settle into a pattern of chronic hepatitis seen in other patients with HCV.
infection. Therapy directed at chronic HCV infection should be considered once the patient has ceased all immunosuppressive drugs and has no evidence of active GVHD.

Chronic hepatitis C in long-term survivors. The prevalence of chronic hepatitis C in long-term HCT survivors ranges from 5% to 70%, depending on the endemic seroprevalence. Because of the high prevalence of HCV infection in most countries, screening for hepatitis C infection in all patients treated for hematologic malignancy before 1991 has been advocated. Long-term survivors with HCV infection commonly have fluctuating levels of AST and ALT; however, little impact on morbidity or mortality has been observed in the first decade of follow-up. The Seattle group has recently reported that patients in their second and third decade of follow-up are starting to present with cirrhosis and its complications. It is anticipated that with longer duration of follow-up, cirrhosis may emerge as an important late complication of marrow transplantation. Perhaps because of specific transplant-related factors such as myeloablation, immunosuppression, and iron overload, the rate of progression to cirrhosis after marrow transplantation seems to be accelerated in comparison to immunocompetent patients with posttransfusion hepatitis C. The rate of progression is comparable to that seen in HIV-infected individuals with fluctuating immunity, but slower than seen in hypogammaglobulinemic patients or some liver transplant recipients.

To prevent progression to cirrhosis, antiviral therapy should be considered in any long-term HCT survivor with chronic hepatitis C infection. Interferon-alfa can be safely administered to patients who have been off all immunosuppressive agents for at least 6 months and have no evidence of GVHD or myelosuppression. While experience is limited, response rates to interferon-alfa appear no different from those seen in nontransplant patients with hepatitis C. A recent meta-analysis of all available randomized clinical trials of interferon alfa-2b in patients with chronic hepatitis C demonstrated an overall biochemical response that was sustained for at least 6 months after completing therapy in 23% of treated patients and a sustained virologic response in only 8%. When interferon-alfa is given in combination with oral ribavirin, sustained virologic response rates of 40% to 50% have been observed. Use of combination therapy has not been reported in HCT survivors with chronic hepatitis C, although patients with genotype 1 and with a higher viral load (both features commonly present in long-term survivors of HCT) are more likely to achieve a sustained response with combination therapy than with interferon alone. In May 1998, the US Food and Drug Administration (FDA) approved a combination of interferon-alfa 2b plus ribavirin for patients with chronic hepatitis C who have relapsed after receiving interferon monotherapy. Recent controlled clinical trials also support the use of combination therapy in previously untreated patients. It should be noted that ribavirin therapy is commonly associated with the development of hemolytic anemia, therefore patients with preexisting anemia or underlying coronary artery disease should not be treated. Ribavirin is a teratogen in animals, and female patients should not become pregnant while taking ribavirin, or for at least 6 months after discontinuing therapy. Nonribavirin containing alternative strategies associated with higher response rates than standard interferon monotherapy include higher or daily doses of interferon-alfa, or the use of consensus interferon (interferon alfacon-1), which was licensed by the FDA in 1997.

In patients with concomitant iron overload, phlebotomy or chelation therapy to reduce hepatic iron stores should be considered before interferon therapy; mobilization of liver iron may increase the chance of response. Hepatitis A vaccination should be offered to all long-term survivors of HCT with chronic viral hepatitis, because of an increased risk of fulminant hepatitis should they develop acute hepatitis A. Hepatitis A vaccination is safe and elicits an immune response in at least 94% of patients with chronic liver disease.

Hepatitis G virus, also referred to as GB virus-C or hepatitis virus GB-C, is a recently identified member of the flaviviridae family of viruses and shares significant homology with HCV. HGV RNA is found in 1.5% to 4% of routine blood donors and is readily transmitted by blood product transfusion. HGV RNA has been identified in serum of 31% to 65% of hematopoietic cell transplant recipients, most likely related to transfusion of contaminated blood products. However, accumulated evidence suggests this virus is not hepatotropic and has no role in either acute or chronic liver disease including after HCT. Some extrahepatic disease processes, including aplastic anemia, may be associated with HGV infection, although this association remains controversial.

**CONCLUSIONS**

Much is now known of the impact of hepatitis B and hepatitis C on the process of HCT. Compared with HCV, hepatitis B is more likely to result in severe clinical hepatitis and death from posttransplant liver disease, although these outcomes occur only in the minority of HBV-infected patients. Hepatitis C infection is a risk factor for VOD of the liver, but otherwise, has little short-term impact on outcome after HCT. In the long-term, however, HCV infection may prove to be a significant cause of morbidity and mortality, as some infected patients gradually progress to cirrhosis and liver failure. It is, therefore, important to screen all transplant candidates and donors for HBV and HCV infection so that appropriate counselling and management can be undertaken. Liver biopsy may be required before transplantation in potential HCT recipients found to have HCV or HBV infection, so that the severity of underlying liver disease can be considered when making decisions about transplantation regimens to be used. Appropriate guidelines for the use of antiviral therapies in the setting of HCT have not been established, however, with the availability of potent HBV-suppressive agents, the potential exists to significantly alter the natural history of HBV infection during the periods of profound immunosuppression and immune recovery. Antiviral treatment should be considered for all HBV- and HCV-infected survivors of HCT unless specific contraindications are present.

**ACKNOWLEDGMENT**

The authors are grateful to Drs Larry Corey and Robert Carithers for their critical review of this manuscript.
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