Hepatic complications of allogeneic hematopoietic cell transplantation
Allojeneik hematopoetik hücre naklinin hepatik komplikasyonları

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Abstract

Hepatic complications of allogeneic hematopoietic cell transplantation contribute substantially to the overall success of the procedure and represent a major cause of morbidity and mortality. Early hepatic complications consist of the sinusoidal obstruction syndrome, drug toxicities, infections, and acute graft-versus-host disease, while late hepatic complications consist of chronic graft-versus host disease, chronic viral hepatitis, and iron overload states. Successful management of the hepatic complications of allogeneic hematopoietic cell transplantation is dependent on several factors. These include the recognition and elimination of any pre-transplant risk factors for these problems and the development of strategies to evaluate and prevent them in both the early and later post-transplant periods. The aims of the present review are 1) to identify the early and late hepatic complications of allogeneic hematopoietic cell transplantation, in the chronological order in which they occur, 2) to characterize the diagnostic procedures used to identify them, and finally 3) to present the current therapeutic approaches used to manage these problems.

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**Introduction**

Allogeneic hematopoietic cell transplantation (alloHCT) has become the standard treatment for various hemato/oncological diseases as well as certain autoimmune disorders [1]. Current estimates of the number of alloHCT procedures performed annually worldwide are 12,000 to 15,000. The first year transplant-related mortality after alloHCT averages 30% in HLA-identical sibling transplants [1].

Hepatic complications are a well-known cause of early post-alloHCT morbidity and mortality, occurring in 80% of cases [2]. Infections, drug toxicity, the sinusoidal obstruction syndrome (SOS) and acute graft-versus-host disease (aGVHD) are the most frequent causes of liver abnormalities in the early post-transplant period. Chronic viral hepatitis, chronic GVHD (cGVHD) and iron overload states are the most frequent causes of late liver abnormalities [2-6] (Table 1). The aims of the present review are 1) to identify the causes of early and late liver abnormalities of alloHCT in the order that physicians are likely to encounter them, 2) to characterize the diagnostic procedures used to specifically identify them, and 3) to present the current therapeutic approaches used to manage these problems.

**Table 1. Early and late hepatic complications of allogeneic hematopoietic cell transplantation**

<table>
<thead>
<tr>
<th>Early Complications</th>
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<tr>
<td>Transient transaminitis</td>
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<tr>
<td>Drug toxicity</td>
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<tr>
<td>Sinusoidal obstruction syndrome</td>
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<tr>
<td>Acute graft-versus-host disease</td>
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<td>Infections</td>
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<td>Sepsis</td>
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<tr>
<td>Biliary problems (cholestasis, sludge, stone, obstruction)</td>
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<tr>
<th>Late Complications</th>
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<tr>
<td>Chronic viral hepatitis</td>
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<tr>
<td>Chronic graft-versus-host disease</td>
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<td>Iron overload</td>
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<td>Drug-related hepatotoxicity</td>
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<td>Infections</td>
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<td>Sepsis</td>
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<td>Biliary problems (sludge, stone, obstruction)</td>
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<td>Cirrhosis and its complications</td>
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<td>Hepatic malignancy</td>
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**Table 2. Pre-transplant risk factors that may be related with development of post-alloHCT liver abnormalities**

- The presence of elevated transaminase levels prior to transplantation
- The presence of pre-existing liver disease: HBV-, HCV-related liver disease
- Recipients with liver metastases
- Prolonged use of broad-spectrum antibiotic or anti-fungal drugs
- Intensive conditioning regimen use
- Prior abdominal radiation therapy
- Mismatched or unrelated donor transplant
- Re-transplantation

**A- Pre-transplant considerations**

Several studies have defined the pre-transplant risk factors that are associated with post-transplant liver-related morbidity and mortality [2,3,6]. Some of the risk factors, such as elevated transaminases levels, are well recognized, whereas some, such as presence of pre-existing occult liver disease, are often unrecognized and remain unsettled (Table 2).

Biochemical liver tests, including the serum aminotransferases (alanine aminotransferase-ALT, aspartate aminotransferase-AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), bilirubin and albumin levels, and prothrombin time assess hepatocellular necrosis, cholestasis, and hepatic synthetic capacity. These tests have limited sensitivity and specificity, do not all reflect liver function, and provide limited information regarding the presence or severity of complications of liver disease.

A hepatitis virus serology panel consisting of an assessment of hepatitis A (HAV), B (HBV), D (HDV) and C (HCV) virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) infections are routinely obtained in the pre-transplant period on both recipient and donor. Abdominal sonography should be performed to identify any abnormality of abdominal organs.

For the assessment of asymptomatic aminotransferases elevation: During pre-transplant evaluation, the establishment of asymptomatic individuals with mild-to-moderate elevations in aminotransferase levels represents a common

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**Figure 1. The algorithm of the evaluation of abnormal aminotransferase levels in recipient and donor prior to alloHCT**
clinical problem. However, the majority of these liver tests abnormalities do not indicate serious liver disease. The etiology of mild-to-moderate serum aminotransferase elevations varies depending on patient selection and geography. For example, hepatitis B and C are common causes of elevated serum aminotransferases in Eastern European countries, whereas hepatitis C, alcohol-related liver disease, hepatic steatosis and drug-induced liver disease are the most common causes in Western countries.

Before extensive evaluation of abnormal aminotransferase levels, these tests should lead to retesting. The evaluation of mild-to-moderate serum aminotransferase elevations should be guided by the history, physical examination and nature of test abnormalities (Figure 1). All individuals with abnormal aminotransferase levels should be advised to discontinue all medications if possible and abstain from alcohol. A liver biopsy should be considered in individuals with persistent abnormal aminotransferase levels prior to transplantation.

**For the assessment of HBV infection**, an assessment of hepatitis B surface antigen (HBs-Ag) positivity and hepatitis B surface antibody (anti-HBs) and core-antibody (anti-HBc IgG) positivity should be performed (Figure 2). Some centers also test for the presence of HBV-DNA, especially in cases that are anti-HBc-Ab positive, to identify occult HBV infections. HBs-Ag positivity identifies both asymptomatic carriers and those with an active infection. Hepatitis B e-antigen (HBe-Ag) positivity helps to distinguish between asymptomatic carriers and those with active infections in the absence of HBV-DNA data. HBV-DNA detection using polymerase chain reaction (PCR) documents active viral replication. Liver biopsy should be performed prior to transplantation in all HBs-Ag-positive recipients to assess the severity of the hepatic inflammation and the stage of the disease. Liver biopsy in cases of isolated Hbc-Ab positivity is recommended to identify the presence of active disease, the current stage of the disease, and to determine whether the liver is HBV-DNA positive or negative.

When active HBV infection is identified, antiviral therapy must be initiated prior to alloHCT (Figure 2). Although several anti-viral agents are effective in reducing HBV viral replication, lamivudine, a reverse-transcriptase inhibitor of the HBV-DNA polymerase, has been used most widely [7]. Numerous studies have shown that lamivudine treatment of chronic hepatitis B results in clinical, biochemical and serological resolution of the HBV infection in immunocompetent individuals [7,8]. It is a remarkably safe drug with only rare adverse events. Unfortunately, the efficacy of long-term lamivudine treatment decreases progressively as a result of the emergence of mutant lamivudine-resistant HBV strains. In these cases, lamivudine plus adefovir can be utilized. Although lamivudine suppresses HBV replication within two weeks of initiation of therapy, both agents should be continued for several years and possibly indefinitely post-transplantation.

**Hepatitis B infection in the donor**: There is indisputable evidence that HBV infection can be transferred from donor to recipient [9]. The risks of using a HBV-infected donor depend on the HBV status of both the donor and the recipient. If the donor is HBV-DNA positive, the approach should be the same as that utilized in a HBV-positive potential recipient (Figure 3). The risk of severe hepatitis in recipients who become infected with HBV

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**Figure 2**: The management of HBs-Ag-positive recipient undergoing alloHCT

**Figure 3**: The management of HBs-Ag-positive donor who is candidate for donation
Hepatitis C infection in the donor: The transmission of a HCV infection from a donor ranges from 5 to 15% [2,10]; however, the risk of transmission is less from a donor who is only anti-HBc IgG antibody positive, but can still be substantial and severe if the alloHCT recipient is HBV-naive. In a case controlled study performed by Lau et al. [11] comparing the clinical and serological outcomes of recipients receiving donor marrow from HBV-positive or -negative donors, the occurrence of HBV-related hepatitis in the recipient of a HBs-Ag-positive marrow was substantial [11]. In contrast to this result, in the experience at our Bone Marrow Transplantation Unit, HBV-related hepatitis did not occur in the naturally HBV-immune recipients who received stem cells from inactive HBV carriers [12]. Based on these results, inactive HBV carrier donors can be used for alloHCT donation if the recipients of marrow have naturally acquired or active immunization-induced acquired HBV immunity.

The prevalence of HCV infection in individuals with hematopoietic malignancies who undergo alloHCT varies widely depending upon the HCV seroprevalence of the study population. Because HCV infection in alloHCT recipients always results in a chronic hepatitis [2,4,9], it is important to identify the presence of an infection prior to transplantation to prevent the development of post-transplant HCV-related liver morbidity and mortality. Negative anti-HCV serological testing prior to alloHCT is adequate to exclude the presence of a HCV infection in potential recipients of alloHCT. However, Locasciulli et al.[13] recommended that HCV-RNA testing be done as well. A liver biopsy should be obtained in all HCV-positive individuals regardless of the aminotransferases levels, as they have been documented to have no relationship with the severity of the histological findings in a given individual. Although there is no consensus regarding the pre-transplant treatment of a HCV infection in a HCV-positive individual who is candidate for alloHCT, it is recommended that if possible, HCV-positive individuals should be treated and the alloHCT be delayed until the individual is in a non-proliferative histological range and undetectable HCV-RNA in serum.

Hepatitis C infection in the donor: The transmission of a HCV infection from a HCT donor who is HCV-RNA positive to a recipient who is anti-HCV negative is essentially universal [2,4,9]. Recipients of such marrows become viremic with high viral load results in a chronic hepatitis [2,4,9], it is important to identify the presence of an infection prior to transplantation to prevent the development of post-transplant HCV-related liver morbidity and mortality. Negative anti-HCV serological testing prior to alloHCT is adequate to exclude the presence of a HCV infection in potential recipients of alloHCT. However, Locasciulli et al.[13] recommended that HCV-RNA testing be done as well. A liver biopsy should be obtained in all HCV-positive individuals regardless of the aminotransferases levels, as they have been documented to have no relationship with the severity of the histological findings in a given individual. Although there is no consensus regarding the pre-transplant treatment of a HCV infection in a HCV-positive individual who is candidate for alloHCT, it is recommended that if possible, HCV-positive individuals should be treated and the alloHCT be delayed until the individual is in a non-proliferative histological range and undetectable HCV-RNA in serum.

Liver test injuries are commonly seen after alloHCT (Figure 4). Determination of the cause of these injuries is helped by the fact that some liver diseases tend to occur within certain intervals following alloHCT.

Regiment-related hepatotoxicity

The type of conditioning regimen prior to alloHCT plays a critical role in the development of early hepatic complications occurring as a result of the development of a hepatic venous obstructive disorder (VOD), currently renamed the sinusoidal obstruction syndrome (SOS) or drug-induced hepatic injury.

Sinusoidal Obstruction Syndrome (SOS): The most serious early hepatic complication of HCT is SOS. This process represents a unique form of conditioning regimen-related hepatotoxicity. This condition occurs in 20% to 54% of HCT recipients [3,14-16]. SOS occurred in approximately 4.2% of alloHCT recipients in our Stem Cell Transplantation Unit between 1995 and 2005 (Unpublished experience). Historically, the term VOD has been used to describe a clinical syndrome of tender hepatomegaly, fluid retention, weight gain and the development of an increased serum bilirubin level as a result of obliterative fibrosis and occlusion of small hepatic venules occurring due to a prior conditioning regimen. With the recent recognition that the vascular injury is initiated in the hepatic sinusoid, the name of this syndrome has been changed to SOS. The clinical onset of SOS is typically recognized by day +20 after alloHCT. However, later onsets of this process have been reported [3,6]. Between 10-20 days after the initiation of the conditioning regimen, an increase in liver size, right upper quadrant abdominal tenderness and weight gain occur followed by hyperbilirubinemia. Patients with SOS manifest findings consistent with a diagnosis of the hepatoportal syndrome with intense sodium avidity, portal hypertension and multiorgan failure. SOS can range in severity from a mild reversible disease process to a severe syndrome associated with multiorgan failure and death [3,6,14-15].

Injury to the sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus appears to be a critical process in the development of SOS. In vitro studies have demonstrated that
No treatment strategies for SOS have been proven to be effective in the prospective, randomized, controlled studies [2,3,14,15]. Various prophylactic treatment modalities have been proposed that have focused on reducing the glutathione depletion occurring with conditioning. Other therapies act by modifying inflammatory mediators and altering the coagulation and fibrogenesis process. SOS is fatal in approximately 7% of individuals with the syndrome with no identifiable risk factors who have received a CY-based conditioning regimen following CY/TBI and in 5% of individuals following targeted oral BU and CY conditioning [24]. CY-based regimens are more likely to result in a SOS mortality in individuals who come to alloHCT with other risk factors that include hepatic fibrosis, chronic hepatitis C, nonalcoholic steatohepatitis and any infection before the start of the conditioning regimen [2,3,25]. The relative risk of a fatal SOS is approximately 10-fold higher in individuals with chronic hepatitis C as compared to individuals without any pre-existing liver disease [25].

Several approaches have been utilized to prevent a SOS-associated fatality. These are: first, to avoid higher doses of conditioning regimen; second, to monitor the levels of the drugs being used, minimizing drug-induced hepatic damage; and third, to use a nonmyeloablative regimen that is not recognized as producing hepatotoxicity.

A number of randomized trails have examined the effect of anticoagulation therapy in preventing SOS. Only one study conducted in low-risk patients has demonstrated a beneficial effect of heparin prophylaxis [26].

The prophylactic administration of ursodeoxycholic acid (UDCA) to prevent or reduce the severity of SOS has been studied in a number of randomized placebo controlled prospective studies [2,3,27-29]. Some of these have reported a reduced severity of SOS with UDCA therapy. The incidence of SOS in two older studies was reduced to 3% and 15% in the UDCA-treated groups as compared to values of 19% and 40% in the control groups [27,28]. However, a large randomized Scandinavian study failed to demonstrate any benefit of UDCA therapy [29]. Nonetheless, some transplant centers use UDCA routinely in an effort to reduce the severity and frequency of SOS. The effect of hepatic glutathione supplementation has been examined in experimental models, but it has been difficult to find a clinical rational for these findings. Currently, in our Transplantation Unit, we are not using a routine prophylactic medication in an effort to prevent or reduce the severity of SOS.

Because the precise pathogenesis of SOS remains unclear, no completely satisfactory treatment exists. The current treatment of SOS consists of minimizing any exposure to recognized hepatotoxins and avoiding nephrotoxins, the use of analgesia for pain, limiting the individual’s intake of sodium, diuresis and/or paracentesis, and the correction of any coagulopathy. Renal and pulmonary failure in individuals with severe SOS is managed with hemodialysis and mechanical ventilation.

Drug-induced hepatotoxicity: Drug-induced hepatotoxicity in the first week following alloHCT is probably more common than appreciated. Fortunately, severe liver damage due to drugs during this period is rare. In the pre-transplant and early post-transplant periods, patients receive a multitude of drugs, including the drug...
in the conditioning regimen as well as cyclosporin (CsA), methotrexate (Mtx), antibacterial, antifungal, and antiviral agents and various growth factors [2-3,6]. Total parenteral nutrition (TPN) is often implicated in the production of mild elevations of cholestatic enzymes as well as the level of bilirubin and aminotransferases in the serum. Liver biopsy is not particularly helpful in establishing a drug-induced hepatotoxicity, but is important in excluding other causes of liver disease such as SOS, aGVHD and sepsis.

**Infections**

Infections significantly contribute to the complications associated with alloHCT [2,6,30,31]. The particular type of infection at a given time is a function of the time after alloHCT. Before engraftment, bacteria are the most common pathogens and rarely involve the liver. Immediately after engraftment, viral infections become the principal agents responsible for infection [31].

The depressed T-cell mediated immune response occurring post-alloHCT persists for a period ranging from several months to more than a year and is a consequence of the underlying primary hematological disease process, the requirement for conditioning chemotherapy/radiotherapy, and the drugs used for infection prophylaxis and the treatment of GVHD [31-33]. The presence of specific antibodies such as anti-HBs is important in preventing infections with viruses, and loss of these antibodies over time after alloHCT enhances the risk of re-infection with viruses which the recipient had pretransplant exposure, prior to the alloHCT [31]. Reconstitution of an effective immune system following alloHCT plays an important role in the subsequent defense against viral infections [32,33].

**Hepatitis B virus infection**

The median prevalence of HBs-Ag-positive individuals requiring HCT has been reported to be 1% in American recipients, 3.5% in European recipients and 9% in Turkish recipients [34-36]. HBV infection in alloHCT recipients occurs in different ways: the progression of pre-transplant primary active disease, activation of a latent HBV infection or acquisition of a de novo HBV infection [3,6]. As a result of the immunosuppressive therapy required pre- and post-alloHCT, the HBV viral load increases in both the liver and blood of the HBV-positive recipient. This continues until either immune reconstitution occurs or the immunosuppression being used is reduced. A clinical flare-up of hepatitis (elevations in aminotransferases and increases in both the liver and blood of the HBV-positive recipient. This continues until either immune reconstitution occurs or the immunosuppression being used is reduced. A clinical flare-up of hepatitis (elevations in aminotransferases and jaundice) may be seen at the time of cellular engraftment. This response can distinguish between viral hepatitis and other causes of liver abnormalities such as GVHD seen post-alloHCT. A positive serum HBV-DNA assay is required to diagnosis and/or to confirm HBV infection. Anti-viral therapy should be used if a diagnosis of HBV is established as a result of a positive HBV-DNA test. The most appropriate treatment strategy and the dose and the duration of the HBV anti-viral therapy are unknown. The risk of fatal HBV-induced liver disease in an alloHCT recipient that is HBV-DNA positive is approximately 15% without specific anti-HBV therapy [2,9].

**HBV Vaccination:** The adoptive transfer of immunity to HBV infection can be accomplished in bone marrow transplantation (BMT) recipients from donors who are either naturally immune or have received active HBV immunization prior to donation [12,37]. In such cases, bone marrow-derived memory cells, capable of producing antibodies to the HBV envelope and/or nucleocapsid antigens, are transferred from the donor to the recipient [12,37]. This phenomenon prevents new HBV infections and can lead to the clearance of a pre-existing HBV infection in the recipient of stem cells from an anti-HBV-positive donor [12,37].

An experience of 16 allo-peripheral blood cell transplantation (PBCT) recipients and their donors, who were vaccinated against HBV at a dose of 40 mg administered for three consecutive months, has been reported [38]. Eighty-eight percent of these recipients seroconverted to anti-HBs antibody positivity (>10 mIU/ml). This rate of seroconversion (88%) in PBCT recipients is comparable to that reported by Ilian et al. [39] in BMT recipients and by Nagler et al. [40] in autologous BMT recipients. None of the HBV vaccinated recipients had either clinical or serological evidence of HBV-related hepatic events during the conditioning regimen or post-transplant follow-up period. Based on this experience, the vaccination of both HBV-naive recipients and donors results in the development of an effective antibody response to HBV infection in the alloHCT recipient.

The durability of this vaccine-induced immunity in alloHCT recipients, however, is not clear. Most transplants lose their immunity after transplantation. In the experience cited above [38], a substantial proportion of the HBV-vaccinated recipients (57%) lost their immunity over a period of time (a median of 236.2 days). Nagler et al. [40] reported that 37% of their HBV antibody-positive recipients lost their immunity within 17-45 days of transplantation as a result of defective immune reconstitution. Thus, systematic re-immunization is necessary following transplantation to maintain HBV immunity.

Immunity against HBV infection can be transferred from an anti-HBs-positive donor to a recipient of alloHCT [12,38-40]. Wimperis et al. [41] showed that immunization of the donor alone results in transfer of an antibody response to the recipient after T cell-depleted BMT. In our own experience [38], 83% of HBV-naive recipients with an HBV-immune donor seroconverted to anti-HBs antibody positivity after transplantation. In addition, two HBs-Ag-positive recipients having a HBV-immune donor seroconverted to anti-HBs antibody positivity after transplantation. Lau et al. [37] reported that 10% of the recipients with chronic hepatitis B who had an anti-HBs-positive donor sustained HBV clearance after alloBMT. The rate of seroconversion observed in these studies is higher than that reported as a consequence of either spontaneous resolution or as a result of anti-viral therapy. None of the HBs-Ag-positive recipients with HBV naive donors in each of these studies cleared HBV. These findings suggest that adoptive transfer immunity works not only in HBV-naive individuals, but also in HBV-infected individuals. Clearly, the HBV immune status of the donors plays an important role in seroconversion of recipients following alloHCT.

On the other hand, HBV-naive recipients of HBV-naive donor stem cells continue to be at risk for HBV infection in the post-transplant period. In our own experience [38], one HBV-naive recipient developed an active de novo post-alloHCT HBV infection and three others developed an asymptomatic HBV infection manifested by seroconversion to anti-HBs and
HBV Reactivation: Reactivation of HBV infection is a well-recognized complication of immunosuppressive therapy in individuals who are HBs-Ag-positive inactive carriers or those with recognized chronic HBV infection as well as those with an occult HBV infection [9,42,43]. Reactivation of HBV infection occurs in 14% to 50% of such individuals [9,42,43]. The mortality associated with viral reactivation varies between 3.7% and 60% [2,9,42,43]. Several factors contribute to the development of viral reactivation in HBV carriers receiving chemotherapy [42,44,45] (Table 3). HBV infection after organ transplantation can occur because of either reactivation of a latent endogenous HBV infection or acquisition of HBV infection from the donor or acceptance of contaminated transfused blood and blood products [2,3,6]. Such HBV infections have been associated with rapid liver disease progression to liver decompensation and even fulminant hepatitis and death [2,3,6].

Lamivudine used as prophylaxis of HBV reactivation

Lau et al. [35] evaluated the efficacy of lamivudine to prevent recurrent HBV-related hepatitis in alloHCT recipients. Only one recipient given lamivudine experienced HBV reactivation after transplantation. In contrast, 45% of the individuals in the control group experienced HBV reactivation and 15% of these individuals experienced HBV-related hepatitis failures [35]. The authors concluded that preemptive lamivudine therapy reduced the HBV reactivation rate in HBV-positive recipients after alloHCT and improved survival [35]. Seven HBs-Ag-positive alloHCT recipients who did not receive anti-viral prophylaxis were reported in 1999 [12]: one died 30 days post-transplant because of HBV-induced fulminant hepatic failure. HBV-induced chronic active hepatitis occurred in three [12]. Based on these results, lamivudine prophylaxis in HBV-positive recipients undergoing alloHCT appears to prevent immunosuppressive-induced HBV-related post-alloHCT morbidity and mortality and has become the standard of therapy.

The optimal duration of lamivudine prophylaxis in alloHCT recipients at risk for HBV reactivation has been investigated [46]. Unfortunately, there are no clear data in the literature to indicate how long prophylactic lamivudine therapy should be continued in HBV-positive recipients who continue to receive immunosuppression. Long-term (>1 year) antiviral therapy is required to eradicate HBV infection in immunocompetent individuals because of the high rate of HBV replication (plasma half-life of HBV, 24 hours) and the relatively slow turnover rate of HBV-infected hepatocytes (half life, 10-100 days) [7,8,46]. Lamivudine produces a rapid reduction in HBV replication within days of its initiation [7,8]. In immunosuppressed subjects, several investigators have suggested that lamivudine treatment in cases of inactive HBV infection should be continued for at least the duration of the immunosuppression and possibly longer [7,35,46]. Based on the experience in liver transplantation, long-term lamivudine prophylaxis in alloHCT recipients at risk for HBV reactivation seems reasonable.

The adverse effect profile of lamivudine does not overlap with that of the various immunosuppressive agents used in transplantation [35,46]. No hematological abnormalities, hepatic enzyme flares or reductions in immunosuppression dosage have been reported as a result of lamivudine in previous studies of transplant recipients.

The risk of developing lamivudine-resistant HBV increases with the duration of lamivudine treatment [7]. Most cases of resistance are associated with mutations in the YMDD motif of the HBV polymerase gene [7]. Resistance rates between 15% and 40% have been reported after two years of lamivudine treatment in immunocompetent individuals [7]. In immunosuppressive individuals, Chan et al. [47] reported a cumulative resistance rate of 41% after 31 months in HBs-Ag-positive kidney allograft recipients. Lau et al. [35] reported a single alloHCT recipient (1/20) case treated with lamivudine who developed lamivudine resistance after 40 weeks of therapy.

The development of HBV resistance has been a limiting factor in the durability of lamivudine treatment. Adefovir dipivoxil, a monophosphate nucleotide analogue approved by the United States Food and Drug Administration, represents the newest approach to the treatment of HBV infection [48]. In contrast to lamivudine, viral resistance to adefovir as a result of prolonged therapy occurs at a 3-4-fold reduced rate in immunocompetent individuals [48]. Moreover, adefovir is effective against mutant HBV lamivudine-resistant virus. There are no data available concerning the efficacy, safety and tolerability of adefovir dipivoxil when used to treat lamivudine-resistant HBV reactivation in alloHCT individuals. Additional studies are required to clarify the precise role of adefovir dipivoxil (or other nucleotide analogues) in immunosuppressed individuals in order to clearly define its efficacy and to identify potential adverse hematological side effects of its use.

Hepatitis C virus infection

Unlike HBV infection, HCV-related hepatitis is unusual in alloHCT recipients. Post-transplant HCV infections in alloHCT recipients may arise in two ways: progression of pre-transplant HCV infection or acquisition of a de novo HCV infection from either a HCV-infected donor or via having accepted a transfusion of HCV-infected blood and blood products [2,3,6,9]. A minimal increase in liver-related mortality in the first 10 years as a result of a HCV infection has been reported after alloHCT [3,9]. Asymptomatic mild to moderate transaminitis not exceeding a level of 300 U/L is seen frequently in the post-transplant period of HCV-positive alloHCT recipients and coincides with the

**Table 3. Factors predisposing to HBV reactivation in HBV carriers who receive chemotherapy**

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<th>1. Host-related</th>
<th>Primary hemato/ oncological disease (lymphoma)</th>
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<td>Preexisting liver disease</td>
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<td>Young age</td>
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<td>Male gender</td>
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<tr>
<td>2. Virus-related</td>
<td>High serum HBV-DNA levels</td>
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<td>3. Treatment-related</td>
<td>High dose of chemotherapy</td>
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<td>Corticosteroid treatment</td>
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tapering of the immunosuppressive drugs used to prevent GVHD. During this time, it may be difficult to determine whether a flare of hepatitis C or GVHD is responsible for the observed increase in serum transaminase values. Differentiation of these two disorders, however, is crucial for appropriate therapy. HCV-RNA detection using PCR documents active viral replication. A liver biopsy should be obtained before any specific therapeutic decision is made.

With longer periods of observation, HCV-induced cirrhosis is emerging as an important late complication of alloHCT. It can result in liver failure and HCV-induced hepatocellular carcinoma. In contrast to the 20-40 year period of HCV-induced liver disease experienced in immunocompetent individuals, HCV-related liver disease in alloHCT recipients runs an accelerated course to cirrhosis that can occur as soon as 4-5 years post-transplantation.

The reported sustained response rates to combination anti-viral therapy (interferon (IFN) plus ribavirin) in alloHCT recipients with HCV infections are similar to those reported in immunocompetent individuals [2]. IFN therapy is contraindicated in the early post-transplant period because of its myelosuppressive effects and the possibility of inducing or exacerbating GVHD. HCV-positive recipients should be evaluated for anti-viral therapy after all of their immunosuppressive therapy has been discontinued and there is no current evidence of GVHD. The combination of pegylated (PEG)-IFN and ribavirin therapy should be used in the treatment of HCV-induced hepatitis in alloHCT recipients, but it needs to be administered carefully with particular attention to its myelosuppressive effects.

**Fungal liver infection**

Fungal infections usually occur in the first weeks post-transplant and in recipients treated for GVHD or in those with primary disease activation, in whom they can occur at any time [3,6]. *Candida albicans* is the most frequently identified fungal pathogen in alloHCT recipients [3,6]. Hepatic and splenic abscesses are a common presentation in such cases. Hepatic involvement usually occurs in the context of a systemic disease process, although isolated hepatic involvement has been reported. The clinical presentation of hepatic candidiasis consists of tender hepatomegaly, persistent fever and elevated serum alkaline phosphatase levels.

The prophylactic use of fluconazole has virtually eliminated hepatic candidiasis in alloHCT recipients. The incidence of candida infections in older series has been reported to be as high as 28%. With fluconazole prophylaxis, the incidence of this infection has declined to 7% [3,49]. Unfortunately, with fluconazole prophylaxis, an increase in the incidence of infections with candida species other than *Candida albicans* has occurred [3]. These non-albicans species are resistant to fluconazole and other agents need to be utilized for their successful treatment.

A specific diagnosis of a fungal infection is critical when it occurs, as systemic anti-fungal therapy before and during alloHCT is mandatory. A raised alkaline phosphatase is suggestive but non-specific for the diagnosis. The most sensitive imaging modality is magnetic resonance imaging.

Serological tests such as fungal antibody detection and determination of fungal DNA in serum may be useful. It is important to clearly identify the specific pathogen. This often requires a liver biopsy with a culture of the liver tissue. The choice of subsequent anti-fungal therapy needs to be tailored to the specific fungal species isolated and its sensitivity to the available anti-fungal drugs. AlloHCT recipients with disseminated disease need to be treated aggressively for a prolonged period. Restoration of granulocyte counts is critical to their recovery and may require the use of granulocyte colony-stimulating factor.

**Graft-versus-host disease**

GVHD is a major complication of alloHCT and contributes substantially to the overall transplant-related morbidity and mortality [50,51]. Both acute (aGVHD) and chronic GVHD (cGVHD) affect the skin, liver and gut [50,51]. Because the histological findings of GVHD are non-specific, diagnosis often requires the utilization of both clinical and histological criteria [50,51].

aGVHD of the liver develops within 2 to 10 weeks of alloHCT and occurs in approximately 40-60% of HLA-identical transplants [2,3,6,50,51]. aGVHD occurred in approximately 30% of alloHCT recipients in our Transplantation Unit between 1995 and 2005. Liver involvement usually occurs in association with skin and intestinal GVHD. The liver dysfunction associated with aGVHD is primarily a cholestatic pattern and is characterized by an elevation of serum alkaline phosphatase, bilirubin and to a lesser extent the aminotransferases levels. However, it needs to be remembered that transaminase levels can be markedly elevated (up to 10 times of normal) in aGVHD. In contrast, in cGVHD, these same liver injury tests are usually only slightly increased. The hepatic manifestation of GVHD can present with nausea, vomiting, abdominal pain, and massive diarrhea with/without blood. The cholestasis in aGVHD can range from a mild biochemical disease process to overt jaundice. Moderate to marked elevations in the serum alkaline phosphatase level are usual and precede hyperbilirubinemia. Although elevations in serum alkaline phosphatase have been proposed as a sensitive identifier of GVHD, progressive jaundice is the most common presenting feature [3]. In alloHCT recipients, aGVHD can present as an acute hepatitis with serum aminotransferase levels over 1000 IU/L during the tapering of the immunosuppressive therapy being utilized to enable successful engraftment [50,51]. Features of severe hepatocellular dysfunction are terminal manifestations of liver disease seen in individuals with severe multisystem GVHD.

Although a liver biopsy is usually not necessary to establish a diagnosis of aGVHD when the other clinical findings of aGVHD are present, it may be required to establish the diagnosis of isolated hepatic GVHD and to rule out the other etiologies for the observed liver abnormalities, such as acute viral hepatitis, SOS, drug toxicity or sepsis. The histologic findings of hepatic aGVHD depend upon when in the course of the disease the biopsy is obtained [3,6,50,52]. In the early phase, the findings are characterized by a mixed lymphocytic and eosinophilic infiltration of small bile ducts with nuclear pleomorphism, minimal lobular inflammatory infiltrates and bile duct

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**References**


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**Keywords**

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destruction. Non-specific parenchymal changes that include scattered acidophilic bodies, lobular disarray and cholestasis may be present. The extent of these abnormalities varies with duration of the aGVHD. In the later phase, there is destruction of small bile ducts accompanied by ductular proliferation and an endothelialitis affecting the terminal hepatic veins. This endothelialitis is a relatively specific feature of GVHD [3,6,50,52].

Treatment of aGVHD of the liver usually involves the addition of methylprednisolone (MP) at a dose of 2 mg/kg/day to the existing immunosuppressive regimen [3,6,50]. Treatment with doses greater than 2 mg/kg/day does not improve the response rate but does increase the rate of infectious complications. In a large retrospective study [53], the liver abnormalities associated with GVHD improved in only 30% of the individuals with aGVHD [53]. There is no proven second-line treatment for steroid-refractory aGVHD, including the use of tacrolimus or antithymocyte globulin. The prognosis is poor if steroids fail to control aGVHD because secondary treatment regimens induce disease control in only a minority of the cases so treated [2,3,6].

cGVHD of the liver is a complex multisystem disorder that develops at or after day +100 post-alloHCT [2,3,6,50,54,55]. It is usually seen with other manifestations of cGVHD such as dry eyes, oral mucositis, and a scleroderma-like skin disease. The incidence of cGVHD after alloHCT ranges from 27% to 72% [2,3,6,50,54,55]. Liver involvement is reported in 73% to 86% [2,3,6,50,54,55]. cGVHD occurred in approximately 60% of alloHCT recipients in our Stem Cell Transplantation Unit between 1995 and 2005: 55% had limited stage cGVHD and the remaining 40% had extensive stage cGVHD.

cGVHD represents a manifestation of profound immune dysfunction. In most of these cases, the deaths observed are a result of an acquired infection [2,3,6,50,54,55]. cGVHD can either follow or progress from aGVHD or develop de novo in 20% of the cases [2,3,6,50,54,55]. The pathogenesis of cGVHD is different from that of aGVHD. Although its precise pathogenesis remains unknown, cGVHD bears a resemblance to a variety of immune-mediated autoimmune disorders. Several B- and T-cell-mediated abnormalities have been described in cGVHD. These include diminished T-cell responsiveness, decreased B-cell proliferation, impaired antibody production, a reduced number and function of CD4+ cells, and an increased number of CD8+ suppressor cells. The induction of increased histocompatibility antigens and leukocyte adhesion molecule expression on tissues such as bile ducts identifies these cells as the targets for the alloreactive donor T-cells. These CD8+ T-cells proliferate and secrete inflammatory cytokines (IL-2, IL-1 and TNF-α) which contribute to the tissue injury [2,3,6,50,54,56].

The clinical presentation of cGVHD of the liver is similar to that of primary biliary cirrhosis (PBC). Specifically, the serum liver injury tests reveal a cholestatic pattern with elevations of alkaline phosphatase, at least 5-15 times the upper limit of normal, as well as increased levels of GGTT and bilirubin with or without an increase in the serum aminotransferases levels. The increases in the serum alkaline phosphatase and GGTT usually precede the development of jaundice by weeks to months.

The diagnosis of cGVHD is made on the basis of combined clinical and laboratory parameters. It is important to confirm the diagnosis by liver biopsy and thereby exclude other possible liver diseases. The histologic criteria for cGVHD include the findings of bile duct damage and/or ductopenia with infiltration of the smaller bile ducts with lymphocytes and eosinophils, portal area expansion with both lymphocytes and plasma cells and the presence of cholestasis [57,58].

The current system of grading cGVHD as either limited or extensive has severe limitations [57]. This grading system provides little information about prognosis; is of limited clinical utility; and does not correlate well with either the degree of clinical manifestation or the extent of histopathological abnormalities. Several investigators have developed a revised grading system for cGVHD [3,6,50]. Recently, Akpek et al. [59] reported a new prognostic grading system for cGVHD. Using this system, patients are categorized based on the presence or absence of extensive skin involvement, thrombocytopenia and progressive disease [59]. Shulman et al. [58] also developed a histopathological grading system for hepatic cGVHD. Their histopathological grading system has a positive predictive value of 86%, a sensitivity of 66% and a specificity of 91% [58,59]. Currently, there is debate as to which grading system is best.

Although various immunosuppressive drugs including CsA, tacrolimus, Mtx, MP and mycophenolate mofetil have been used to reduce the incidence and severity of cGVHD in alloHCT recipients [2,3,6,50], the results of such therapies have not been particularly successful.

When a diagnosis of cGVHD has been made, the extent of involvement must be ascertained. Because cGVHD can affect virtually any organ system, the most successful treatment of such recipients results when a systematic approach in discussing documentation and management is undertaken by a multidisciplinary team including transplant physicians, gastroenterologists, pathologists, dermatologists, pulmonologists and ophthalmologists. The specific treatment of cGVHD in a given individual is determined in part by the severity of the disease process. First-line therapy consists of the administration of immunosuppressive agents [2,3,6,50]. The use of immunosuppressive drugs (MP: 1 mg/kg/day, CsA: 10 mg/kg/day) is successful in 50-80% of cases [3,6,50]. Even with widespread involvement, the institution of appropriate immunosuppression can result in a very gradual but complete recovery. After the start of immunosuppressive therapy, a decline in the serum alkaline phosphatase level can be expected within 2-4 weeks. It may not return to normal even if there is complete improvement in other target organs. The immunosuppressive drugs used to treated cGVHD can be tapered and discontinued only after full resolution of the disease manifestations. Once this occurs, the dose of immunosuppressive agents being used can be tapered at regular intervals. In 50% of cases with cGVHD, immunosuppressive treatment can be discontinued after 9-12 months. If an individual with cGVHD does not respond within three months of the institution of specific therapy or progresses while on therapy, an alternative salvage regimen, such as the addition of CsA, tacrolimus, mycophenolate mofetil or rapamycin, should be instituted [3,6,50]. In some cases, liver transplantation can be used to treat cGVHD-induced end-stage liver disease.
Ursodeoxycholic acid (UDCA)

UDCA is a hydrophilic, non-toxic bile acid that induces a choleretic [60]. UDCA constitutes less than 5% of the total bile acids in normal bile. This can be increased to approximately 40% of the total bile acid pool by the oral administration of UDCA [60]. UDCA has been used successfully in the treatment of a wide array of chronic cholestatic liver diseases such as PBC and primary sclerosing cholangitis [60-62]. UDCA also has some efficacy in the prevention of allograft rejection after liver transplantation [63]. The mechanisms responsible for the liver protective effects of UDCA are not completely understood but include stabilization of liver cellular membranes and its ability to stabilize HLA antigens deleting hepatocytes and bile duct expression of these antigens [60-62]. UDCA has also been shown to reduce the secretion and action of various inflammatory cytokines such as interleukin-1 alpha (IL-1α), IL-2, IL-4, tumor necrosis factor-alpha (TNF-α) and gamma interferon [60,62].

In a prospective randomized open-label multicenter study, it was reported that UDCA prophylaxis has a beneficial effect on abnormal liver test results, reduces the incidence of severe aGVHD, and improves patient survival [29]. UDCA prophylaxis may decrease transplantation-related hepatic complications of alloHCT, but further studies are needed to fully evaluate the effect of prophylactic UDCA in alloHCT recipients.

UDCA has been used as treatment for several liver problems. Fried et al. [64] reported that cholestasis secondary to hepatic GVHD after alloHCT improves in 33% of patients treated with a 6-week course of UDCA therapy. However, a significant worsening of all liver test results occurs after discontinuation of UDCA therapy. No data exist relative to the long-term effects of UDCA therapy in cGVHD of the liver. In a prospective study [65], the long-term effects of UDCA therapy in individuals with limited cGVHD of the liver following alloHCT were examined. Specifically, 15 alloHCT recipients were treated with UDCA at a dose of 13 mg/kg/day p.o. for one year. Nine of the 15 received UDCA as a sole therapy for hepatic cGVHD. The remaining 6 received UDCA along with a tapering dose of CsA. As compared to baseline values, all 15 patients experienced an improvement in their liver tests. The values for the mean serum alkaline phosphatase, GGT and aminotransferase levels at one year were all reduced statistically in those taking UDCA. No increase in serum liver enzyme levels was observed three months after completion of UDCA therapy. Symptomatic improvement (pruritus resolved in 7 of 9 recipients) as well as a biochemical response was observed after one year of UDCA therapy [65]. Based on this experience, it was concluded that the long-term administration of UDCA is effective in improving liver enzyme tests in patients with isolated cGVHD. Symptomatic improvement also occurred. Clearly, additional studies in a larger group of patients, including those with other manifestations of cGVHD, are warranted to evaluate the utility of UDCA therapy.

UDCA is an easy drug to use. It is taken orally and has few side effects. The most frequent UDCA adverse event is diarrhea, which is seen in less than 5% of individuals treated with the agent [29,64,65]. No drug-induced cytopenias occur. Discontinuation of UDCA therapy in alloHCT recipients is not followed by an exacerbation of disease signs or symptoms.

Iron overload

Iron overload is recognized as a common contributor to the liver abnormalities in the late post-transplant period. Hepatic hemosiderosis is found in approximately 90% of long-term survivors of alloHCT [3,66]. Hepatic hemosiderosis is caused by a combination of multiple blood transfusions, especially in thalassemic patients, and dyserythropoiesis. Although many marrow transplant recipients have a high hepatic iron content 50-100 days post-transplant, iron deposition stops and iron store falls slowly over time thereafter because transfusions are no longer required as the primary hematological disease process has been cured.

The mechanisms of tissue injury that occur in iron overload states have been investigated in several models [3,6,67]. One hypothesis is that iron-induced lipid peroxidation occurs in hepatocytes causing cell injury and death, Kupffer cell activation also occurs. These latter cells produce profibrogenic compounds that stimulate hepatic stellate cells to increase collagen production leading to fibrosis. Liver biopsy studies in alloHCT candidates have documented a high prevalence of portal fibrosis, cirrhosis and hepatocellular carcinoma occurring in association with marked hemosiderosis [3]. In addition extreme iron deposition in visceral organs results not only with hepatotoxicity but cardiac and endocrinological problems as well. The risk of opportunistic infections that include Listeria and Yersinia is increased in immunocompromised recipients with hepatic hemosiderosis as a result of an iron-induced reduction in the generation of T cells and impaired T-helper, natural killer cell and Kupffer cell function.

Because iron overload in alloHCT survivors can lead to multiple organ dysfunctions, all alloHCT survivors should be assessed for iron overload. It can be evaluated by measuring the serum ferritin level, which is a reliable indicator of tissue iron stores. Computerized morphometric analysis of bone marrow iron content is available for estimating the hepatic iron stores in alloHCT recipients. A liver biopsy is required to accurately quantify hepatic iron content.

Phlebotomy and/or chelation therapy with desferrioxamine can be utilized to reverse excessive hepatic iron load and to improve hepatic as well as other organ (cardiac) function. Iron depletion prior to transplantation may reduce post-transplant hepatotoxicity especially in individuals with thalassemia.

Cholestasis

Cholestasis results from interference with bile flow anywhere from the basolateral membrane of the hepatocyte to the entry of the bile duct into the duodenum.

Cholangitis lenta: Sepsis-associated cholestasis is a form of biliary tract inflammation without obvious extrinsic bile duct obstruction and is an important contributor to hyperbilirubinemia in the early post-transplant period. The cholestatic effects of bacterial infection are mediated directly by endotoxins and indirectly by endotoxin-induced cytokines [68]. The clinical presentation of cholangitis lenta is usually mild-to-moderate elevations of serum bilirubin in a febrile patient. The serum...
bilirubin level may be as high as 15 mg/dl and the serum alkaline phosphatase level may increase in some cases. The histopathological findings of cholangitis lenta are not-specific and are usually minimal. The diagnosis of cholangitis lenta is based entirely on clinical criteria. Frequently, the serum bilirubin level falls with appropriate antibiotic treatment.

**Drug-induced cholestasis:** Drug-induced cholestasis is a common entity, seen with several drugs that are used in alloHCT recipients [3,6]. Different clinical syndromes may be recognized, with variable degrees of hepatitis in association with cholestasis. CsA commonly causes a dose-related mild increase in the serum bilirubin level due to inhibition of canalicular bile flow and bile salt secretion [69]. This effect correlates positively with CsA blood levels. Thus, higher blood CsA levels result in higher total serum bilirubin values. Tacrolimus also causes cholestasis at high doses, but not as often as CsA [69]. A high index of suspicion is required for the correct diagnosis. The most important aspect of treatment of drug-induced cholestasis is prompt discontinuation of the offending drug.

**TPN:** TPN has been implicated as being responsible for some of the mild elevations of serum bilirubin, alkaline phosphatase and transaminase values seen after alloHCT [2,3,70]. Severe hyperbilirubinemia occurs in alloHCT recipients who have sepsis or hemolysis [70,71]. The histopathological findings of TPN-related liver toxicity are non-specific. Therefore, the diagnosis is a clinical one made by exclusion of other causes.

**Biliary sludge and gallstones:** Biliary sludge begins to appear three weeks after the initiation of TPN. Between 4 and 6 weeks of TPN, 50% of alloHCT recipients develop gallbladder sludge and after six weeks, almost all have ultrasound demonstrable biliary sludge. Gallstones are found in approximately 20% of alloHCT recipients within four weeks of transplantation [70,72]. The accumulation of biliary sludge is reversible within four weeks of the resumption of oral intake. Either a reduction or discontinuation of TPN and the initiation of enteral feeding improve the liver abnormalities occurring as a result of TPN.

**Extrahepatic biliary obstruction:** Extrahepatic biliary obstruction is rarely seen in individuals with alloHCT. Infiltration of the common bile duct with the primary hematologic disease process, CMV-related biliary disease, inspissated biliary sludge or an impacted gallstone in the distal common bile duct are the most common causes of extrahepatic biliary obstruction in alloHCT recipients. It is nearly impossible to distinguish between extrahepatic and intrahepatic cholestasis in alloHCT recipients based upon clinical and laboratory studies. Radiographic evaluation is essential.

**Cirrhosis**

Cirrhosis is an uncommon hepatic complication in alloHCT recipients. Long-term survivors of HCT may be at increased risk of developing end-stage liver disease as a result of multiple risk factors including viral infection, hepatic GVHD and iron overload. With long-term follow-up, cirrhosis and its various complications including portal hypertension and hepatocellular carcinoma become increasingly important disease confounds. Strasser et al. [73] reported cirrhosis in 0.8% of alloHCT recipients who had survived one or more years and in 1.2% of those who survived five or more years. A rate of 2.2% was reported in those who had survived 10 or more years and 3.8% in those who survived 20 or more years. HCV infection is the primary risk factor for cirrhosis in alloHCT recipients [73]. The rate of progression to cirrhosis in alloHCT recipients with chronic hepatitis C is more rapid than in other patient populations [25,73]. Liver transplantation in HCT survivors who develop liver decompensation is possible. The original alloHCT donor would be an ideal potential living donor if no contraindication for live donor transplantation is present in either donor or the recipient.

**Liver Biopsy:** Abnormalities of liver tests are common after alloHCT. Liver biopsy as an important but invasive procedure in such cases often helps in establishing a specific diagnosis or another more appropriate prognosis, and can be the ideal method for long-term monitoring of the liver disease. Liver biopsy is most useful in the evaluation of otherwise unexplained liver test abnormalities and at excluding other potential etiological causes of liver dysfunction. It is also important when a change in treatment is contemplated. Percutaneous liver biopsy in experienced hands is a remarkably safe procedure. In the early post-transplant period, the presence of severe thrombocytopenia, a concomitant hemorrhagic diathesis and highly elevated aminotransferases levels limit the performance of a percutaneous liver biopsy, because of the risk of intra-abdominal hemorrhage and/or liver capsule perforation. A transvenous liver biopsy may be a better choice in these cases. Recent developments in transvenous liver biopsy needles make this approach more attractive as adequate tissue specimens and multiple cores can be obtained. Clinically significant bleeding after a liver biopsy is reported to occur at a rate of 1.3% to 20.2%, with a mortality rate of 0.1% to 0.5% [74,75]. Bleeding after a liver biopsy is rarely seen if the platelet count is greater than 50 x 10^12/L at the time of the biopsy. A careful assessment of the potential risk and benefit of a liver biopsy must be made in each case.

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**References**


