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No increased mortality from donor or recipient hepatitis B- and/or hepatitis C-positive serostatus after related-donor allogeneic hematopoietic cell transplantation

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Abstract

Limited data exist on allogeneic transplant outcomes in recipients receiving hematopoietic cells from donors with prior or current hepatitis B (HBV) or C (HCV) infection (seropositive donors) or for recipients with prior or current HBV or HCV infection (seropositive recipients). Transplant outcomes are reported for 416 recipients from 121 centers who received a human leukocyte antigen-identical related-donor allogeneic transplant for hematologic malignancies between 1995 and 2003. Of these, 33 seronegative recipients received grafts from seropositive donors and 128 recipients were seropositive. The remaining 256 patients served as controls. With comparable median follow-up (cases, 5.9 years; controls, 6.7 years), the incidence of treatment-related mortality, survival, graft-versus-host disease, and hepatic toxicity appears similar in all cohorts. The frequencies of hepatic toxicities as well as causes of death between cases and controls were similar. Prior exposure to HBV or HCV in either the donor or the recipient should not be considered an absolute contraindication to transplant.

Keywords

allogeneic transplantation; hepatitis B; hepatitis C

Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for hematologic malignancies and other bone marrow failure disorders. Serologic markers of exposure to hepatitis B virus (HBV) and hepatitis C virus (HCV) are generally checked before HCT. Both viruses are endemic in Asia and the Middle East (~5%), with lower prevalence in other regions, including the United States (<2%) (1). In some transplant centers in the Center for International Blood and Marrow Transplant Research (CIBMTR) network, serologic evidence of HBV or HCV infection in the recipient may be considered a contraindication for allogeneic HCT. Often, evidence of prior or current viral hepatitis excludes a donor as well. The National Marrow Donor Program (NMDP) excludes individuals with prior or current viral hepatitis from serving as unrelated donors or cord blood donors, limiting the available donor pool (2). Related donors are preferred for many reasons, and transplant physicians are sometimes faced with the choice of using a matched related donor with a positive hepatitis serology versus an unrelated HBV- or HCV-seronegative donor. Information on the risk of using a donor with a history of either hepatitis B or hepatitis C would help transplant patients and physicians in their decision-making. This information may eventually lead to expanding the unrelated donor pool for eligible transplant recipients who are unable to find a suitable donor.

The impact of past or current hepatitis infection on the outcomes of HCT remains uncertain and the data available are from case series and a few prospective clinical trials conducted in infected recipients in endemic regions (3–12). Published evidence shows clinical hepatitis, hepatitis B surface antigen (HBsAg) recurrence with evidence of detectable viral load, and loss of hepatitis B core antibody (HBcAb) in patients undergoing autologous or allogeneic HCT with prior positive HBcAb but negative HBsAg (3, 6, 10, 13–18). Evidence also indicates that prophylaxis with reverse transcriptase inhibitors, such as lamivudine or adefovir, or post-transplant vaccination may prevent hepatitis reactivation (19–22). However, clinical hepatitis with fulminant liver failure can occur as immunosuppression is tapered (13–16). Large studies with sufficient cases analyzing the impact of seropositive donors are lacking.

The CIBMTR Infection and Immune Reconstitution Committee performed this study to assess clinical outcomes in recipients of human leukocyte antigen (HLA)-identical allogeneic sibling HCT in which the recipient, donor, or both demonstrated serologic evidence of HBV and/or HCV.

Methods

Patients

We included all patients in the CIBMTR research database from 1995–2003 receiving an HLA-identical sibling transplant for acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, and non-Hodgkin's lymphoma. Patients received either a myeloablative or non-myeloablative conditioning regimen as well as a primarily calcineurin inhibitor-based graft-versus-host disease (GVHD) prophylaxis regimen. Patients were excluded if they underwent umbilical cord blood transplantation or received a T-cell depleted graft.

Owing to small numbers of cases with varied characteristics, a case-cohort study, rather than a case-control study, was designed. Potential cases (n=360) were identified for which either the recipient or donor was reported to the CIBMTR as seropositive for HBsAg and/or HBcAb or hepatitis C antibody (HcAb) before HCT. Individuals who were hepatitis B surface antibody positive but HBsAg and HBcAb negative were excluded. A request for confirmation of viral hepatitis status and for supplemental data was sent; information on 161 patients was received and these were confirmed as cases. For descriptive purposes, the cases were divided into mutually exclusive groups based on hepatitis serostatus (Table 1). While supplemental data regarding information on serial viral loads and antiviral therapy were requested, limited data were provided.

After cases were identified, a comparable control cohort was selected from the database, based on the following criteria: 1) disease, 2) disease stage at HCT, 3) cytomegalovirus serostatus, and 4) age. A control was defined as both the donor and the recipient testing negative for HBsAg, HBcAb, and HcAb before HCT. Requests for confirmation of negative hepatitis serostatus for both recipient and donor were sent to centers of 387 potential controls, and confirmation was obtained in 256 patients. The final cohorts (161 cases, 256 controls) were obtained from 121 centers; 27 cases (17%) came from 23 centers that did not provide controls.

Data sources

CIBMTR is a research organization, formed through an affiliation of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and NMDP, and is comprised of a voluntary working network of more than 450 transplant centers worldwide. Detailed clinical data on consecutive allogeneic and autologous HCTs are reported to a Statistical Center associated with the Division of Hematology and Oncology in the Department of Medicine at the Medical College of Wisconsin (MCW), (Milwaukee, Wisconsin USA) and the NMDP Coordinating Center (Minneapolis, Minnesota USA). Data quality is maintained by on-site audits, computerized checks for error and physician review of submitted data. Observational studies conducted by CIBMTR are performed with informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined by the NMDP and MCW Institutional Review Boards.

CIBMTR collects data at two levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED data include disease type, age, sex, pre-transplant disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow- and/or

blood-derived stem cells), high-dose conditioning regimen, post-transplant disease progression and survival, development of new malignancy, and cause of death. All CIBMTR centers contribute TED data. More detailed disease and pre- and post-transplant clinical information are collected on a subset of registered patients selected for the CRF track by a weighted randomization scheme. TED and CRF-level data are collected pre-transplant, 100 days and 6 months after transplant, and annually thereafter or until death.

Definitions and endpoints

Conditioning intensity was defined as myeloablative or non-myeloablative using criteria defined by CIBMTR (23). Performance status at the time of HCT was defined according to the Karnofsky scale for patients 16 and older, or the Lansky scale for those younger than 16 years. Outcomes of interest included overall survival (OS), treatment-related mortality (TRM) defined as death without documented relapse, and incidences of acute and chronic GVHD. Acute GVHD was defined as the occurrence of grades II–IV skin, gastrointestinal, and/or liver abnormalities fulfilling the Glucksberg criteria of acute GVHD (24). Chronic GVHD events included symptoms in any organ system fulfilling the criteria of limited or extensive chronic GVHD. Additional liver-specific outcomes included frequencies of veno-occlusive disease (VOD), cirrhosis, and liver involvement with acute and/or chronic GVHD.

Statistical analyses

Patient-, disease-, and transplant-related factors and univariate outcomes for acute GVHD, chronic GVHD, and TRM are described for each group. The median and range of follow-up times were estimated by the Kaplan-Meier product-limit estimator. The probability of OS was calculated using the Kaplan-Meier estimator, with the variance estimated by Greenwood's formula. We were unable to perform a multivariate analysis owing to small numbers in each case group.

Median follow-up of survivors in the seropositive cases was 5.9 years (range, 0.3 – 11.1), and for controls 6.7 years (0.8 – 12.4). Supplemental data pertaining to hepatitis B envelope antigen (HBeAg) serostatus, viral load, and anti-hepatitis therapy are described.

Results

Patients

Table 2 provides the demographics of the study population. The median age for both cohorts was 37 years (range, 1 – 61). The predominant indication for transplantation across all groups was acute myeloid leukemia. Within each case group and the control cohort, the frequencies of myeloablative conditioning, use of total body irradiation, and GVHD prophylaxis were similar. No data were available on etiology of elevated aspartate aminotransferase (AST) for cases or controls or on the presence of liver fibrosis in the seropositive case groups.

HBsAg-positive donors

Fourteen siblings seropositive for HBsAg donated to HBV- and HCV-seronegative sibling recipients. Nine of these donors were also assessed for HBeAg and one was positive. Table 3 shows pertinent transplant-related outcomes. The cumulative incidence of 1-year TRM was 14% (95% confidence interval [CI], 2 – 36). The probabilities of grades II–IV acute GVHD at day 100 and chronic GVHD at 1 year were 14% (95% CI, 1 – 36) and 57% (95% CI, 31 – 80), respectively. Five-year OS was 59% (95% CI, 30 – 85), and was similar to the control cohort (48% [95% CI, 42–55]).

Of the 14 HBsAg-positive donors, only 3 had viral loads measured in the 6 months before donation, with values of undetectable, 27,000, and 800,000 IU/mL respectively. A post-transplant viral load was assessed in 2 recipients of these donors within 3 months after HCT. The recipient of the donor with undetectable viral load was treated with lamivudine peri-transplant and had an undetectable viral load. The recipient whose donor had a viral load of 27,000 IU/mL did not receive any peri-transplant antiviral therapy and demonstrated a viral load of 210 IU/mL at 3 months post transplant. This patient subsequently received lamivudine therapy; no data regarding response to treatment were provided.

HBsAg-positive recipients

Twenty-eight recipients, who received cells from HBV- and HCV-seronegative donors, were positive for hepatitis B surface antigen (Table 3). Fifteen of these patients were assessed for HBeAg, of whom 3 were positive. The TRM at 1 year was 17% (95% CI, 6 – 34), and appears similar to the control cohort (21% [95% CI, 16 – 26]). The probability of acute GVHD grades II–IV was 25% (11 – 42) and chronic GVHD at 1 year was 46% (95% CI, 28 – 64). Five-year OS was 35% (95% CI, 18 – 53). Of the 28 recipients who were HBsAg positive at the time of transplantation, 4 had viral loads assessed in the month before transplantation, with values ranging from undetectable to 4,806,000 IU/mL. An additional recipient had the viral load assessed 1 year before transplantation at 1780 IU/mL. In the first 6 months after HCT, data were provided for 5 HBsAg-positive recipients who demonstrated viral loads ranging from 700 – 1,400,000 IU/mL. All of these recipients were treated with lamivudine in the peri-transplant period.

HBcAb positive

A positive HBcAb test – the only serologic abnormality – was found in 7 (4%) donors and 27 (17%) recipients; the outcomes are shown in Table 3. Specifically, the probabilities of 1-year TRM, acute GVHD, and chronic GVHD, were similar to the control cohort. However, the 1-year OS in this cohort was only 28% (36 – 64), which appears lower than the control cohort (61% [95% CI, 55 – 67]).

For the 27 HBcAb-positive recipients, the transplant outcomes were similar to those of the control cohort (Table 3), including a 1-year OS rate of 77% (95% CI, 59 – 90). The frequency of liver-specific toxicities was not greater than the controls in patients who were HBcAb positive or who received a transplant from an HBcAb-positive donor. No information on viral loads was available for any recipients or donors in these groups, and HBeAg was assessed in 3 recipients (all negative) and no donors.

HCAb-positive donors

Evidence of hepatitis C exposure, denoted as a positive HCAb serology, was found in 12 donors who provided hematopoietic stem cells for their hepatitis B- and C-seronegative siblings. Table 3 describes the transplant outcomes of these sibling recipients. The 1-year TRM of 25% (95% CI, 5 – 52) and 1-year OS of 41% (95% CI, 16 – 69) appear similar to the control cohort (TRM: 21% [95% CI, 16 – 26]; OS: 61% [95% CI, 55 – 67]). The probabilities of acute GVHD and chronic GVHD also appear similar. Hepatitis C viral loads were assessed in 8 recipients who received cells from an HCAb-seropositive donor. For these patients, 6 recipients had detectable HCV post transplant. Only 1 of these recipients reportedly received antiviral therapy with ribavirin. For the 2 patients who did not report detectable HCV after transplant, 1 of the donors had undetectable viral loads before donation.

HCAb-positive recipients

Twenty-nine recipients were HCAb seropositive before receiving cells from an HBV- and/or HCV-negative sibling. The cohort of HCAb-positive recipients had a higher median AST value pre-transplant (HCAb positive recipients: 43 U/L [range, 13 – 153]; controls: 24 U/L [range, <1 – 806]), but otherwise was similar to the control cohort (Table 2). Five of 29 HCAb-positive recipients (17%) were diagnosed with VOD of the liver by day 100 (Table 3), which appears slightly higher than the control group (n = 24 [9%]). One-year TRM was similar for both cases and controls (Table 3). Five-year OS was 41% (range, 23 – 60) for seropositive recipients, and this did not differ from the 5-year OS of the control cohort (48% [95% CI, 42 – 55]).

Five of the HCAb-seropositive recipients had viral load levels assessed within 3 months before HCT, with values ranging from undetectable to 9,275,291 IU/mL; of these, 2 had values checked within 1 year post transplant (pre: 552,000 and 1,306,000 IU/mL; post: 512,000 and 118,250 IU/mL). An additional 4 seropositive recipients without pre-transplant viral load assessments were reported with levels ranging from undetectable to 170,000,000 IU/mL in the first year post-transplant. Four patients received peri-transplant therapy with interferon +/- ribavirin.

Recipient and/or donor seropositive for HBV and/or HCV

Forty-four cases (27%) had >1 hepatitis virus present or evidence of viral hepatitis in both the recipient and donor (Table 1). Assessment for HBeAg occurred in 14 recipients and 15 donors; of these, 5 recipients and 2 donors had serologic evidence of HBeAg. Transplant outcomes for this cohort showed slightly higher 5-year TRM (38% [95% CI, 24 – 53]) and slightly lower 5-year OS (30% [95% CI, 17 – 44]) compared with the control cohort and cases in which only one virus was present (Table 3). Interestingly, the frequencies of VOD, hepatic acute GVHD, and hepatic chronic GVHD were similar in this cohort compared with the controls (Table 3), suggesting that infection or other organ toxicities may be causing the slightly higher TRM in this setting.

Causes of death

At the time of last follow-up, 97 cases (60%) and 136 controls (53%) had died. The most common cause of death was relapse or progression of the primary malignancy, accounting for 94 deaths (40%) (41 cases and 53 controls). Infections were the primary cause of death for 18 cases (19%) and 19 controls (14%). Liver-specific causes of death, including liver failure and VOD, occurred with similar frequency between the seropositive cases (n = 6, 6%) and controls (n=7, 5%). Other causes of death included GVHD (n=32, 14%); acute respiratory distress syndrome/idiopathic pneumonitis (n=18, 8%); and other complications including non-hepatic organ failure, hemorrhage and new malignancies (n=39, 17%).

Discussion

This analysis represents the largest population of HBV- and/or HCV-exposed donors providing cells for allogeneic HCT reported in the literature. Although 2 prior analyses examined outcomes in patients receiving cells from 24 and 18 HBV-exposed donors, respectively, our study reports outcomes in recipients who received cells from 61 donors who were previously exposed to HBV and/or HCV (25, 26). It also examines a large number of HBV- and/or HCV-seropositive recipients. No detrimental effect on transplant outcomes was identified when recipients were compared to a control population with confirmed seronegative status for HBV and HCV in both the recipient and donor.

Allogeneic transplantations are increasing because of older acceptable recipient ages, reduced-intensity regimens, and the use of alternative donors. However, it is estimated that only 30% of patients have an HLA-identical related donor, and the probability of finding a suitable HLA-identical unrelated donor varies widely, from 12–70% depending on recipient race and ethnicity. Therefore, to safely increase the numbers of potential donors, it is necessary to determine the potential negative impact of using less-desirable donors who carry transmissible blood-borne diseases. If transplant outcomes are reasonable, despite prior or current viral hepatitis in a donor, it may extend the donor pool for certain patients who would otherwise not be able to undergo allogeneic transplantation.

Our cases likely represent a cohort in whom the transplant center determined the patients were otherwise suitable for transplantation, despite the issue of viral hepatitis in the donor or recipient. Based on this possible bias, the outcomes may not apply to an unselected group of patients. Furthermore, our analysis is limited to related-donor transplantation, as unrelated donors are excluded if there is evidence of prior viral hepatitis; however, our results suggest that transplant outcomes are not impaired by using these seropositive donors.

As with all observational studies, certain limitations apply. There were no prospective protocols in place across centers to dictate criteria for proceeding to transplantation, therapy of the donor or recipient, or surveillance measures. Furthermore, the analysis is limited by small numbers in each case group and the sparse supplemental data provided beyond the standard data reported to CIBMTR. In fact, the HCAb-seropositive group is likely heterogeneous with only a portion having detectable HCV RNA that would potentially impact outcomes. We cannot comment on the post-transplant management of these patients or the impact of that management on viral loads or transplant outcomes. In addition, long-term complications such as cirrhosis may not have occurred or not been reported to the transplant center, which limits the applicability of this analysis to long-term effects of donors or recipients with viral hepatitis exposures.

Our data suggest similar frequencies of liver toxicities, such as VOD, GVHD, and death due to liver failure, in the case and control cohorts. One possible reason for this may be that our case population was relatively healthy and carefully selected for transplant, and did not have elevated liver function tests pre-transplant. In addition, information regarding active viremia was available in too few cases and could not be included in the outcomes analysis. A median follow-up of almost 6 years showed no cases of cirrhosis for our analysis, despite a known risk of cirrhosis in persons with chronic viral hepatitis B or C. Prior studies have reported incidences of cirrhosis of 10–16% between 7 and 16 years after allogeneic transplantation in recipients seropositive for HBV or HCV (4, 5, 8, 27). Other studies show that the development of cirrhosis appears accelerated in HCV patients receiving allogeneic HCT compared with untransplanted HCV-infected controls (8, 27). Our data may differ because the transplant center was not informed about the cirrhosis diagnosis or because of a shorter follow-up period. Our data suggest that there is no increased risk of hepatic toxicity after allogeneic transplantation in appropriately selected recipients, when the donor or recipient is seropositive for viral hepatitis.

Viral hepatitis reactivation rates for persons with hepatitis B after either autologous or allogeneic HCT are 5–50% (5, 10, 11, 15, 16, 21, 28). This rate decreases in the setting of prophylactic therapy with lamivudine for persons with HBV infections. One study suggests that vaccination against HBV in seropositive recipients post-transplant may lessen the risk of viral reactivation (3, 22). The impact of treatment of HCV post HCT is unclear. One study reported that sustained viral response was obtained in 20% of patients treated with a combination of interferon and ribavirin (29); however, patients with GVHD, mixed chimerism, or cytopenias were not offered therapy. The minimal data available on viral load,

anti-hepatitis therapy, and lack of data on aminotransferase enzymes limit our ability to comment on viral reactivation, clinical hepatitis, or the optimal management of seropositive donors and recipients. However, similar frequencies of liver complications and liver-related causes of deaths occurred between cases and controls, suggesting that viral hepatitis reactivation was limited or controlled and did not negatively impact survival.

The available data for viral loads did not allow us to determine the frequency of viral transmission from a seropositive donor to a seronegative recipient. Furthermore, the impact of HBeAg-positive serostatus was found in only 9 recipients and 3 donors, limiting any analysis of this factor on recipient outcome or viral transmission. For those few recipients in whom post-HCT viral loads were collected and who received cells from donors with either detectable HBV (n=1) or HCV (n=7), all recipients except one with HCV had detectable viral loads post transplant. Hui et al. (30) reported on the outcomes of 54 patients receiving marrow from HBsAg-positive donors, 29 of whom (54%) were treated pre-harvest with lamivudine. In this case, 33 recipients (61%) were also positive for HBV. With short follow-up, the recipients receiving cells from the lamivudine-treated donors had less post-HCT hepatitis and a trend towards lower mortality rates. Outcomes specific to patients who were also seropositive before transplantation were not reported. Our data suggest that despite viral transmission, there is no disadvantage to the seronegative recipient for OS, TRM, acute or chronic GVHD, or frequency of liver toxicities. However, it is possible that with larger numbers, a negative impact on TRM or OS may be found, if both the recipient and donor are seropositive for HBV and/or HCV.

In summary, HBV and/or HCV do not appear to have a negative impact in a selected population of allogeneic HCT recipients who were seropositive or received cells from a seropositive donor. The impact of systematic molecular monitoring and antiviral therapy on transplant outcomes for these patients in the current era remains unknown; however CIBMTR is now collecting real-time information on hepatitis viral load and anti-hepatitis therapy, to better assess the impact of therapy and incidence of HBV and HCV transmission in the future. Longer follow-up of this cohort of patients to ascertain later development of cirrhosis is planned. Meanwhile, we conclude that there is no clear contraindication to allogeneic sibling HCT if properly selected recipients and/or donors are seropositive for HBV and/or HCV. This finding can potentially expand the donor pool, providing increased access to allogeneic transplant for patients.

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Table 1

Categories of recipient and donor hepatitis B and hepatitis C serostatus in the 161 cases in this analysis

Recipient		Donor			N (%)
HBsAg	HBcAb	HCAb	HBsAg	HBcAb	
+	-	-	-	-	28 (17)
-	+	-	-	-	27 (17)
-	-	+	-	-	29 (18)
-	-	-	+	-	14 (12)
-	-	-	-	+	7 (4)
-	-	-	-	-	12 (7)
+	-	+	-	-	1 (<1)
-	+	+	-	-	6 (4)
-	-	-	-	+	3 (2)
-	+	-	-	+	8 (5)
-	+	-	+	-	3 (2)
+	-	-	-	+	7 (4)
+	-	-	+	-	7 (4)
-	-	+	-	-	5 (3)
-	+	+	+	-	2 (1)
-	+	+	-	+	1 (<1)
-	+	+	-	-	1 (<1)

+, seropositive status; -, seronegative status; HBsAg, hepatitis B surface antigen; HCAb, hepatitis C antibody; HBcAb, hepatitis B core antibody.

Table 2

Characteristics of patients receiving a sibling donor hematopoietic stem cell transplant (HCT) in which the recipient and/or donor were seropositive for hepatitis B virus (HBV) and/or hepatitis C virus (HCV), and confirmed controls

Variable	Recipient HBsAg positive (n=28)	Recipient HBcAb positive (n = 27)	Recipient HBcAb positive (n = 29)	Donor HBsAg positive (n = 14)	Donor HBcAb positive (n = 7)	Donor HCV positive (n = 12)	Recipient and/or donor positive for HBV or HCV (n = 44)	Control cohort (n = 256)
Age, years, median (range)	34 (1 – 60)	34 (3 – 55)	36 (2 – 61)	34 (22 – 60)	44 (16 – 52)	42 (19 – 56)	40 (6 – 61)	36 (<1 – 65)
Male sex, n (%)	19 (68)	16 (59)	20 (69)	6 (43)	4 (57)	5 (42)	24 (55)	150 (59)
Performance status at HCT, n (%)								
> 80%	24 (86)	19 (70)	20 (69)	11 (79)	2 (29)	7 (58)	31 (70)	176 (69)
80%	4 (14)	8 (30)	9 (31)	3 (21)	5 (71)	5 (42)	13 (30)	77 (30)
Unknown	0	0	0	0	0	0	0	3 (1)
Disease								
AML	15 (54)	13 (48)	12 (41)	3 (21)	3 (43)	5 (42)	19 (43)	112 (44)
ALL	5 (18)	7 (26)	7 (24)	2 (14)	1 (14)	2 (17)	8 (18)	41 (16)
CML	6 (21)	3 (11)	3 (10)	9 (64)	2 (29)	1 (8)	12 (27)	56 (22)
NHL	2 (7)	4 (15)	7 (24)	0	1 (14)	4 (33)	5 (11)	47 (18)
Conditioning intensity, n (%)								
Myeloablative	27 (96)	24 (89)	25 (98)	12 (86)	5 (71)	9 (75)	35 (80)	217 (85)
Reduced intensity	1 (4)	3 (11)	4 (14)	1 (7)	2 (29)	1 (8)	6 (14)	32 (13)
Unknown	0	0	0	1 (7)	0	2 (17)	3 (7)	7 (3)
Received TBI, n (%)	11 (39)	10 (37)	14 (48)	3 (21)	2 (29)	6 (50)	12 (27)	106 (41)
Graft type, n (%)								
Bone marrow	21 (75)	16 (59)	15 (52)	10 (71)	2 (29)	4 (33)	23 (52)	130 (51)
Peripheral blood	7 (25)	11 (41)	14 (48)	4 (29)	5 (71)	8 (67)	21 (48)	126 (49)
GVHD prophylaxis								

Variable	Recipient HBsAg positive (n=28)	Recipient HBcAb positive (n = 27)	Recipient HCAb positive (n = 29)	Donor HBsAg positive (n = 14)	Donor HBcAb positive (n = 7)	Donor HCAb positive (n = 12)	Recipient and/or donor positive for HBV or HCV (n = 44)	Control cohort (n= 256)
Tacrolimus + MTX ± other	0	1 (4)	2 (7)	0	2 (29)	1 (8)	3 (7)	19 (7)
Tacrolimus ± other	0	1 (4)	2 (7)	1 (7)	1 (14)	1 (8)	1 (2)	9 (4)
CsA + MTX ± other	24 (86)	20 (74)	18 (62)	12 (86)	4 (57)	6 (50)	33 (75)	168 (66)
CsA ± other	3 (11)	3 (11)	7 (24)	1 (7)	0	4 (33)	6 (14)	49 (19)
Other/Missing	0	2 (7)	0	0	0	0	1 (2)	11 (4)
Pre-HCT AST (U/L), median (range)	26 (9 – 68)	20 (6 – 41)	43 (13 – 153)	22 (5 – 49)	16 (4 – 42)	29 (4 – 97)	25 (13 – 213)	24 (<1 – 806)
Pre-HCT bilirubin (mg/dL), median (range)	1 (<1 – 2)	0 (<1 – 11)	1 (<1 – 2)	1 (<1 – 1)	1 (<1 – 1)	1 (<1 – 1)	1 (<1 – 2)	1 (<1 – 14)
Donor/recipient sex match, n (%)								
Female → Male	9 (32)	10 (37)	6 (21)	3 (21)	1 (14)	2 (17)	10 (23)	67 (26)
Other	19 (68)	17 (63)	23 (79)	11 (79)	6 (86)	10 (83)	34 (77)	189 (74)
Donor/recipient CMV serostatus, n (%)								
Negative/Negative	2 (7)	6 (22)	2 (7)	1 (7)	1 (14)	1 (8)	5 (11)	39 (15)
Other	26 (93)	21 (78)	27 (93)	13 (93)	6 (86)	11 (92)	39 (89)	217 (85)
Year of Transplant, n (%)								
1995 – 1996	5 (18)	7 (26)	8 (28)	1 (7)	1 (14)	4 (33)	14 (32)	74 (29)
1997 – 1998	7 (25)	8 (30)	5 (17)	2 (14)	2 (29)	1 (8)	9 (20)	66 (26)
1999 – 2000	8 (29)	5 (19)	8 (28)	7 (50)	2 (29)	4 (33)	6 (14)	48 (19)
2001 – 2002	7 (25)	7 (26)	6 (21)	3 (21)	2 (29)	2 (17)	12 (27)	56 (22)
2003	1 (4)	0	2 (7)	1 (7)	0	1 (8)	3 (7)	12 (5)

HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HCAb, hepatitis C antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; TB1, total body irradiation; MTX, methotrexate; AST, aspartate aminotransferase; CSA, cyclosporine; CMV, cytomegalovirus.

Table 3

Univariate probabilities of transplant outcomes and frequency of liver-specific toxicities based on recipient and donor serostatus for hepatitis B virus (HBV) and hepatitis C virus (HCV)

Variable	Recipient HBsAg positive (n=28)	Recipient HBcAb positive (n = 27)	Recipient HCAb positive (n = 29)	Donor HBsAg positive (n = 14)	Donor HBcAb positive (n = 7)	Donor HCAb positive (n = 12)	Recipient and/or donor positive for HBV or HCV (n = 44)	Control cohort (n= 256)
Grade 2 – 4 acute GVHD at 100 days, probability (95% CI)	25 (11 – 42)	40 (23 – 59)	38 (21 – 56)	14 (1 – 36)	42 (11 – 78)	25 (5 – 52)	27 (15 – 41)	38 (32 – 43)
Chronic GVHD, probability (95% CI)								
1 year	46 (28 – 64)	29 (14 – 48)	33 (17 – 52)	57 (31 – 80)	14 (0 – 47)	33 (10 – 61)	27 (15 – 41)	37 (31 – 43)
3 years	53 (35 – 71)	41 (23 – 60)	37 (20 – 55)	57 (31 – 80)	-----	33 (10 – 61)	31 (19 – 46)	41 (35 – 47)
5 years	53 (35 – 71)	41 (23 – 60)	37 (20 – 55)	57 (31 – 80)	-----	33 (10 – 61)	35 (21 – 50)	42 (36 – 48)
Treatment related mortality, probability (95% CI)								
1 year	17 (6 – 34)	15 (4 – 31)	25 (11 – 42)	14 (2 – 36)	29 (4 – 64)	25 (5 – 52)	23 (12 – 36)	21 (16 – 26)
3 years	21 (8 – 38)	23 (9 – 40)	25 (11 – 42)	14 (2 – 36)	-----	25 (5 – 52)	30 (17 – 44)	23 (18 – 28)
5 years	25 (11 – 43)	23 (9 – 40)	25 (11 – 42)	14 (2 – 36)	-----	25 (5 – 52)	38 (24 – 53)	25 (20 – 30)
Overall survival, probability (95% CI)								
1 year	57 (38 – 74)	77 (59 – 90)	54 (35 – 71)	78 (54 – 95)	28 (36 – 64)	41 (16 – 69)	56 (42 – 70)	61 (55 – 67)
3 years	39 (22 – 57)	50 (31 – 68)	46 (29 – 65)	71 (45 – 91)	-----	41 (16 – 69)	38 (24 – 53)	51 (44 – 57)
5 years	35 (18 – 53)	45 (27 – 64)	41 (23 – 60)	59 (30 – 85)	-----	41 (16 – 69)	30 (17 – 44)	48 (42 – 55)
Frequency of liver specific toxicities, n (%)								
VOD by 100 days	4 (14)	1 (4)	5 (17)	1 (7)	1 (14)	0	5 (11)	24 (9)
Cirrhosis	0	0	0	0	0	0	0	0
Hepatic acute GVHD	7 (25)	12 (44)	9 (31)	2 (14)	3 (43)	3 (25)	11 (25)	90 (35)
Hepatic chronic GVHD	8 (28)	5 (18)	4 (14)	5 (36)	0	1 (8)	8 (18)	45 (18)

HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HCAb, hepatitis C antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; GVHD, graft-versus-host disease; CI, confidence interval; VOD, veno-occlusive disease.