HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2022 October 27.

Published in final edited form as:

Bone Marrow Transplant. 2022 July ; 57(7): 1095–1100. doi:10.1038/s41409-022-01689-4.

Low dose Unfractionated Heparin Prophylaxis is a Safe Strategy for the Prevention of Hepatic Sinusoidal Obstruction Syndrome After Myeloablative Adult Allogenic Stem Cell Transplant

Maria Sola[#,1,2], **Valkal Bhatt**[#,1], **Meighan Palazzo**[1], **Kathleen E. Cavalier**[1], **Sean M. Devlin**[3], **Molly Maloy**[1], **Juliet N. Barker**[1,4], **Hugo Castro-Malaspina**[1,4], **David Chung**[1,4], **Parastoo B. Dahi**[1,4], **Ann A. Jakubowski**[1,4], **Heather Landau**[1,4], **Esperanza B Papadopoulos**[1,4], **Miguel-Angel Perales**[1,4], **Craig Sauter**[1,4], **Roni Tamari**[1,4], **Nancy A. Kernan**[5], **Sergio Giralt**[1,4], **James W. Young**[1,4], **Jenna D. Goldberg**[1,4], **Doris M. Ponce**[1,4]

[1]Adult Bone Marrow Transplant Service, Division of Hematology/Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[2]Hematology Department, Hospital General Universitario Morales Meseguer, Murcia, Spain

[3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

[4]Weill Cornell Medical College; New York, NY

[5]Bone Marrow Transplant Service, Department of Pediatrics

Abstract

Hepatic sinusoidal obstruction syndrome (SOS) is a serious complication after allogeneic stem cell transplantation (allo-HCT). However, there is no uniform consensus on the optimal strategy for SOS prevention. Ursodeoxycholic acid is the most used regimen, even though its administration is challenging in recipients unable to tolerate oral medication. Defibrotide was recently studied in a phase 3 trial, but enrollment was stopped early due to futility. Low dose unfractionated heparin (UFH) is an alternative strategy. However, its efficacy is reputed but unproven increased risk of bleeding has not been fully established. We evaluated 514 adult allo-HCT recipients who received SOS prophylaxis with low dose UFH. Bleeding complications occurred in 12 patients 2.3% of patients of which only 2 (0.4%) had significant grade 3 bleeding. Only 14 patients were diagnosed with hepatic SOS. Univariate analysis showed that day 100 SOS was higher in recipients of unmodified grafts when compared to CD34+ selected *ex vivo* T-cell depleted grafts

Corresponding author: Doris M. Ponce Box 68, 545 East 73rd Street, New York, NY, 10021, Ph 646 608 3739; Fax 929 321 8163, ponced@mskcc.org.

[#]These authors contributed equally to this work.

Author Contributions: M.S. and V.B. interpreted the data and wrote the manuscript. J.D.G. and D.M.P. designed the study, interpreted the data and wrote the manuscript. S.M.D. analyzed the data and wrote the manuscript. M.P., K.E.C., M.M. collected the data. J.N.B., H.C.M., D.C., P.B.D., A.A.J., H.L., E.B.P., M.A.P., C.S., R.T., N.A.K, S.G., J.W.Y. wrote the manuscript.

Conflict of Interest: D.M.P. has served as advisory board member for Evive Biotechnology (Shanghai) Ltd (formerly Generon [Shanghai] Corporation Ltd), Kadmon Corporation, CareDx, Ceramedix, and Incyte Corporation, and receives research funding from Incyte Corporation. Otherwise, the authors have no relevant conflicts of interest to declare.

($p \leq 0.001$), and patients with hepatitis B and/or C exposure pre-HCT ($p = 0.028$). Overall, UFH was well tolerated and associated with a low incidence of subsequent hepatic SOS. Low dose UFH prophylaxis can be considered in select patients who cannot tolerate oral ursodiol.

Keywords

sinusoidal obstructive syndrome; unfractionated heparin; myeloablative adult allogenic stem cell transplant

INTRODUCTION

Hepatic sinusoidal obstruction syndrome (SOS) is a serious complication of hematopoietic stem cell transplant (HCT), associated with a high mortality risk[1–3]. The incidence of SOS is widely variable but is more common in recipients of myeloablative conditioning, second allo-HCT, prior infection with hepatitis B or C[4,5] and previous use of gemtuzumab ozogamicin or inotuzumab ozagamicin[6,7]. Overall, the median incidence is approximately 13%[8]. Prevention of SOS is critical for the improvement of allo-HCT outcomes the most accepted prophylaxis strategy is ursodeoxycholic acid or ursodiol. This strategy is associated with reduced proportion of SOS (relative risk 0.34; 95%CI: 0.17–0.66) and safety profile[9,10]. However, other studies have failed to demonstrated benefit[11,12]. Nonetheless, there is no uniform consensus on an effective strategy to prevent SOS[13,14].

Low dose unfractionated heparin (UFH) is an SOS prophylaxis strategy, which has been used in allogeneic HCT for decades[11,15,16]. Randomized-controlled clinical trials and cohort studies evaluating the efficacy of UFH for the prevention of SOS, however, have demonstrated conflicting results[15,17–22]. These findings may reflect small sample sizes[19], delayed introduction of low dose UFH after conditioning[17], comparison with historical controls, and lack of a uniform conditioning regimen. Notably, the reported incidence and severity of bleeding associated with UFH in SOS prophylaxis are not significantly worse when compared to non-UFH prophylaxis[15,21]. Most of the bleeding events associated with UFH have been reported as mild and in some cases moderate[15,19,21,23]. We therefore analyzed the efficacy and safety of UFH for the prevention of SOS in a large cohort of patients with hematologic malignancies at Memorial Sloan Kettering Cancer Center (MSK). Our evaluation includes recipients of unmodified and CD34+ selected *ex vivo* T-cell depleted (TCD) allogeneic stem cell grafts.

METHODS

Patient and Graft Characteristics

This retrospective analysis included 514 patients who underwent allo-HCT at MSKCC between 01/2003 to 4/2015, follow-up until 10/2021. Patients eligible for this analysis included adults between the ages of 18–75 years, undergoing first allo-HCT for the treatment of hematologic malignancies. Eight-two percent of the patients received CD34+ selected TCD allografts, 13% received unmodified allografts, and only 5% received cord blood grafts. T cell-depletion was the primary graft-versus-host disease (GVHD)

prophylaxis in the first group, whereas unmodified and cord blood transplant groups receive pharmacologic GVHD prophylaxis. Donor-recipient HLA-match was > 8/10, except for cord blood transplants, where patients received either double-unit mismatched cords (one of whom additionally received CD34+ selected, T-cell depleted haploidentical PBSCs on protocol to assess speed of myeloid recovery, NCT01682226). We excluded from the analysis any patient with refractory malignant disease, recipients of reduced intensity or non-myeloablative conditioning[24], patients who received dual prophylaxis with UFH and ursodiol, or patients on therapeutic anticoagulation at the time of allo-HCT admission. All patients provided written informed consent for transplantation according to the principles of the Declaration of Helsinki[25], and transplantation outcome analysis was approved by the MSK Institutional Review and Privacy Board.

Conditioning Regimens, Immunosuppression and SOS Prophylaxis

Pre-transplant conditioning of these patients was exclusively myeloablative[24] and included busulfan-based and hyperfractionated total body irradiation (TBI) regimens. Other regimens less frequently used were clofarabine/thiotepa/melphalan, carmustine/etoposide/cytarabine/melphalan, and thiotepa/fludarabine/melphalan (Table 1). Patients received either an unmodified stem cell graft from an adult donor, double-unit cord blood graft, or *ex-vivo* TCD predominantly using CD34+ cell selection of peripheral blood HSC by Isolex™ or Miltenyi™ columns[26–28]. One patient received double-unit cord blood transplant combined with peripheral blood derived Miltenyi CD34+ selected haplo-identical stem cells[29]. GVHD prophylaxis in unmodified allograft recipients was predominantly with a calcineurin-inhibitor (CNI) and methotrexate[30]. Cord blood transplant recipients received CNI and mycophenolate mofetil[31]. All patients received granulocyte-colony-stimulating factor to promote earlier neutrophil recovery.

All patients received SOS prophylaxis with UFH 100 units/kg/24hrs by continuous intravenous infusion[15] from admission through day +21 or engraftment. The intravenous route was selected over subcutaneous due to practical reasons and to minimize subcutaneous injections in the early post-HCT period. A minority of patients had SOS prophylaxis discontinued at the time of neutrophil engraftment at the discretion of the treating physician. The activated partial thromboplastin time (aPTT) was monitored 3 times per week per institutional standard of care. Thrombocytopenia was not a contraindication for UFH infusion at this low dose. Platelet transfusional threshold was < 10×10^9/l per institutional standard of care.

Study Definitions

Time to neutrophil recovery was the first of three consecutive days with a sustained absolute neutrophil count (ANC) > 0.5×10^9/l and platelet > 20×10^9/l, and at least 7 days without platelet transfusion. GVHD was diagnosed clinically with histologic confirmation when appropriate. Acute GVHD was graded according to International Bone Marrow Transplant Registry (IBMTR) severity index, except grades A-D were labeled grades I-IV[32]. Grading was reviewed by a transplant clinician panel to reach consensus of maximum acute GVHD grade by day +100. Transplant-related mortality (TRM) was defined as death from any cause

in continued remission, and causes of death were assigned according to the algorithm of Copelan et al[33].

The Baltimore criteria were used to make the diagnosis of SOS, characterized by bilirubin > 2 mg/dL and at least two other findings of painful hepatomegaly, ascites, and/or weight gain > 5% from baseline[34]. Severe SOS was defined using Baltimore criteria plus multiorgan failure, defined as creatinine ≥ 2 times the baseline at transplant, creatinine clearance ≤ 50% level at transplant or dialysis; oxygen saturation ≤ 90% or need for positive pressure/ventilator; confusion, lethargy and/or delirium[35,36]. The measurement of bleeding severity was characterized by using the CTCAE v.4 and included grade 0: no bleeding, grade 1: minor mucosal bleeding or petechiae not requiring packed red blood cells (PRBC); grade 2: any bleeding episode requiring transfusion support of 1–2 units of PRBC/episode in 24 hours; grade 3: any bleeding episode requiring transfusion of > 2 units of PBRC/episode but < 4 units or retroperitoneal bleeding; and grade 4: any bleeding causing hemodynamically instability in a 24h period or any central nervous system bleeding.

Statistical Analysis

The MSKCC Adult Bone Marrow Transplant database verified by primary source documents provided patient characteristics and transplant-related outcomes. Cumulative incidence functions estimated neutrophil engraftment, SOS, liver GVHD and NRM. Gray's test estimated the associations between SOS, patient and graft risk factors. Risk factors evaluated include age (< 40 vs. > 40), hepatitis B and/or C serology pre-HCT (positive vs. negative), donor-recipient HLA-match (10/10 HLA-match vs. < 9/10 HLA-match), graft manipulation (unmodified vs. T-cell depleted).

RESULTS

Patient Demographics

We evaluated 514 patients. Table 1 summarizes patients' demographics and graft characteristics. The median age was 52 years (range 21–75). The majority had a diagnosis of acute leukemia or myelodysplastic syndrome (74%), followed by multiple myeloma (11%), lymphoma (9%), and chronic myeloid leukemia/myeloproliferative disorder (6%). A similar number of patients received pre-transplant conditioning with either a busulfan- or TBI-based regimen, and only a minority (3%) had other conditioning regimens. The most common allograft type was *ex vivo* CD34+ selected TCD. Approximately half of the patients were CMV seropositive. Two-thirds received a 10/10 donor-recipient HLA-matched graft (37% related, 35% unrelated) whereas one-third received <9/10 HLA-matched grafts (including CB grafts). The most common GVHD prophylaxis was TCD by CD34+ selection (n = 422; 82%) without other pharmacologic prophylaxis, followed by various CNI based regimens. Only 30 (6%) patients had hepatitis B exposure prior to HSCT, 2 patients had hepatitis B and C exposures, and 7 patients were hepatitis C virus antibody. Most patients had normal liver function test pre-HCT, only 2 patients had a total bilirubin level >2.0 mg/dL.

Low dose unfractionated heparin associated complications

Bleeding complications occurred in 12/514 patients (2.3%). Only 2 (0.4%) patients had significant grade 3 bleeding, and no patient had grade 4 bleeding. One patient developed hemoptysis, requiring admission to the intensive care unit; and another patient had diffuse alveolar hemorrhage. Ten patients had mild, grade 1–2 bleeding complications during UFH prophylaxis. Of those, 5 patients had minor mucosal bleeding or epistaxis, 1 patient had bruising, 3 patients had mild gastrointestinal bleeding, and 1 patient had other minor bleeding.

Sinusoidal Obstructive Syndrome

Strikingly few patients (n = 14, 2.7%,) developed hepatic SOS, at a median time of 30 days (range 5–57) post-transplant. Since low dose UFH was discontinued through day +21 or time of neutrophil engraftment, 9 of the 14 patients had SOS prophylaxis completed at the time of SOS diagnosis. The day 100 cumulative incidence of SOS was 3% (95%CI: 2.0–4.0) (Figure 1). The majority were women (n = 10, 71%) and older than 40 years. The most common malignant disease was acute leukemia (n = 10), followed by myelodysplastic syndrome (n = 2), myeloproliferative disease (n = 1), and non-Hodgkin's lymphoma (n = 1). Eight patients (57%) received myeloablative conditioning with high-dose total body irradiation (TBI), while 5 (36%) had busulfan-based regimen. Only 1 (7%) patient underwent melphalan/fludarabine/thiotepa. Most of the patients who had SOS were recipients of an unrelated donor (n = 11, 79%). Of the 14 pts with SOS, 10 had received an HLA-matched stem cell graft (n = 10), and 4 had received <9/10 HLA-matched grafts. Seven patients received an unmodified adult allograft (6 PBSC, 1 bone marrow), 3 had double-unit CBT grafts, and 4 had TCD grafts. Of the patients who received an unmodified stem cell graft, the most common GVHD prophylaxis regimen was CNI and methotrexate (n = 6, 60%). Eleven of the 14 (78.5%) patients with SOS were CMV seropositive pre-HCT. Two patients (14%) had hepatitis B exposure, and 1 (7%) hepatitis C exposure prior to allo-HCT.

Eight of these 14 patients with SOS received defibrotide therapy, while the remaining 6 received best supportive care. Patients received defibrotide under a clinical trial for VOD/SOS (NCT00628498, NCT00358501, and NCT00003966)[37–40]. Two patients treated with defibrotide and 5 patients with best supportive care died due to progression to severe hepatic SOS, resulting in multiorgan failure and death. Additionally, 2 patients died due to graft failure, 1 had GVHD, and 1 had malignant disease relapse. Only 3 of the 14 survived SOS.

Analysis of Risk Factors for Day 100 SOS

Univariate analysis was performed to study risk factors of SOS (Table 2). Age, HLA-match, and conditioning regimen were not significant in the univariable analysis. In contrast, patients who received unmodified allografts had a significantly higher incidence of SOS when compared to TCD recipients (11% vs. 1%, $p \leq 0.001$). Similarly, positive hepatitis B and/or C serologies pre-HCT was associated with higher day +100 SOS risk (9% vs. 2%, $p = 0.028$). Due to the overall few SOS events, adjusted multivariable analysis was not performed.

Hepatic GVHD, Transplant-Related Mortality, and Causes of Death

The day 100 grade II-IV and III-IV liver acute GVHD were 2% (95%CI: 1.0–3.0) and 1% (95%CI: <1.0–2.0), respectively. The incidence of day 100 TRM was 9% (95%CI: 7.0–12.0) whereas 1-year TRM was 16% (95%CI: 13.0–2.0). During the first year post-HCT, 95 patients died of TRM, including infection (n = 37), organ toxicity (n = 27), GVHD (n = 20), graft failure (n = 7), and other (n = 4).

With a median follow-up was 8 years 1 month (range 1–15.5 years), we evaluated long-term outcomes and found that 153 had died of TRM causes at a median of 216 days (range 1 day – 14.3 years). The most common cause of death was infection (n = 58, 38%), followed by GVHD (n = 41, 27%), organ toxicity (n = 31, 20%), graft failure (n = 10, 7%), other/unknown (n = 8, 5%), and secondary malignancies (n = 5, 3%). Causes of death according to stem cell graft were similar, except that infection was more common in TCD recipients whereas GVHD was more common after unmodified allo-HCT.

One hundred and three patients died due to malignant disease relapse or progression at a median time to diagnosis of 239 days (range 30 days – 9.9 years). Patients who relapsed or progressed had acute leukemia (n = 53), multiple myeloma (n = 25), lymphoma (n = 14), and chronic leukemia/myelodysplastic syndrome (n = 12). Of those, 47 patients died between the first year post-HCT.

DISCUSSION

Prevention of hepatic SOS is routinely recommended in allo-HCT[4,14]. In the absence of positive prospective randomized clinical trials in adult patients, there is no consensus regarding the length of prophylaxis or drug of choice[41]. Currently, ursodeoxycholic acid or ursodiol is widely use given its safety profile, easy route of administration and association with decreased incidence of SOS in several clinical trials[9,10]. Additionally, treatment until 90 days post-HCT is associated with reduced proportion of patients with elevated bilirubin levels, severe acute GVHD and liver GVHD[12,42]. In our study, we evaluated an alternative SOS prophylaxis using low dose UFH which compared favorably with historical reports using different strategies[43]. Hepatic SOS prophylaxis was overall well tolerated and associated with minimal complications despite concurrent thrombocytopenia in the early post allo-HCT period. Hemostasis was routinely monitored by aPTT measurement, and UFH did not affect coagulation time. In fact, if standard clinical tests of coagulation became abnormal, this was an indication to identify a cause other than the low-dose UFH. Bleeding events during UFH prophylaxis occurred in a small number of patients, in the majority of whom it was mild, transient, and self-limited. The few patients who had serious bleeding events were non-fatal and due to causes other than the low dose UFH infusion. Most patients completed UFH prophylaxis as planned and without complications. However, UFH infusion required continuous intravenous access which may limit a wider use of this approach.

We found in this analysis with predominant TCD graft recipients, that age and donor-recipient HLA match had no association with SOS whereas prior hepatitis B or C exposure was associated with increased risk. Recipients of TCD grafts also had a low risk of developing SOS supporting previously reported findings from small series[44,45].

We hypothesize that in the absence of donor derived T-cells, there is less donor-host alloreactivity that may reduce endothelial damage and inflammation to the liver sinusoids. Notably, we observed a late median onset of SOS at day +30 post-HCT. Thus, two third of patients had already completed UFH at the time of SOS diagnosis. This observation suggest that prolonged exposure to SOS prophylaxis beyond day +21 may be consider in select patients including those with high-risk features pre-HCT.

Patients who received UFH had a low incidence of day 100 hepatic GVHD and TRM. The most common cause of death was infection, followed by GVHD. While the incidence of hepatic SOS was low, patients with SOS commonly had multiorgan failure and died. These findings highlight the critical role of optimizing hepatic SOS prophylaxis.

This study is the largest single-center analysis of UFH for the prevention of SOS in allo-HCT, and our results support the use of this parenteral strategy early after allo-HCT. However, our findings may be limited due to the studied population with predominant TCD graft recipients. A prospective multicenter clinical trial exploring the use of defibrotide for the prevention of hepatic SOS in adult and pediatric patients (NCT02851407) have been closed recently due to futility. Which highlights the difficulty of finding an optimal strategy in hepatic SOS prophylaxis. While prospective studies comparing UFH to other prophylaxis methods are warranted, UFH prophylaxis can be prioritized in recipients of conditioning agents that cause severe mucositis, emesis, and/or high-volume diarrhea.

Acknowledgements

This work was supported in part by the National Institutes of Health award number P01 CA23766 and NIH/NCI Cancer Center Support Grant P30 CA008748 by the NCI Core Grant Core Grant (P30 CA008748). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. M.S. was supported by a grant Innovacion tecnologica 2016 from the Sociedad Española de Hematologia y Hemoterapia. We would like to acknowledge the nursing staff, transplant coordinators and Laboratory Medicine staff who greatly contributed to this work.

Data Availability Statement:

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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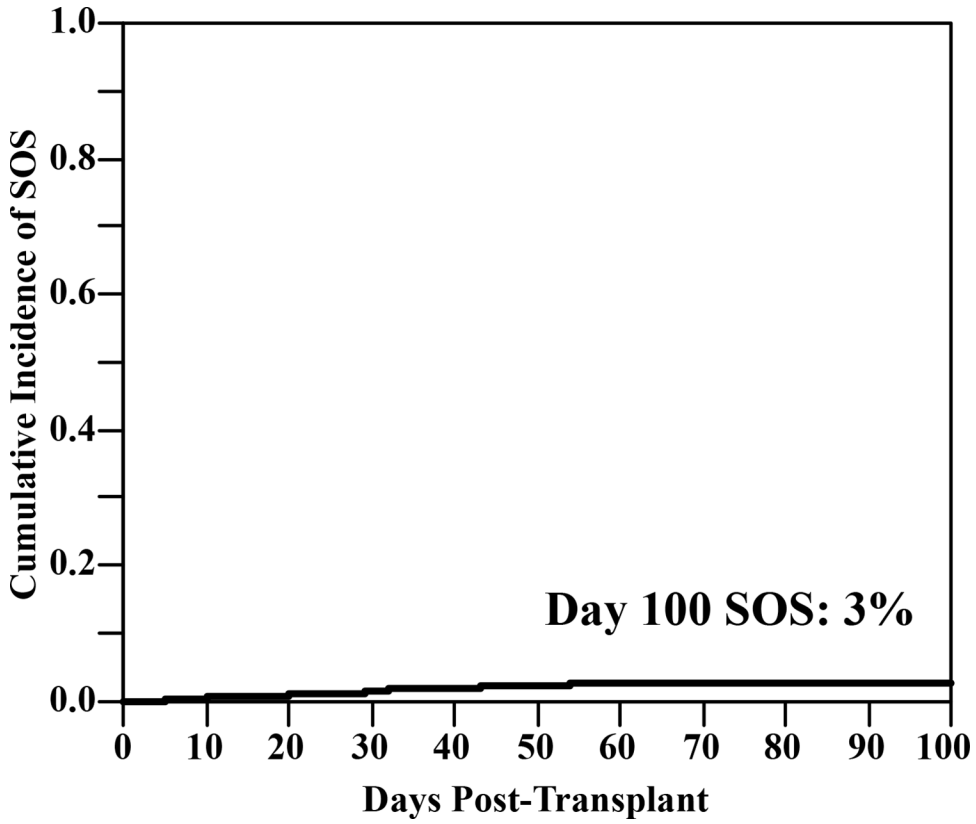

Figure 1. Cumulative incidence of hepatic sinusoidal obstruction syndrome.

Fourteen patients were diagnosed with hepatic SOS, at a median time of 30 days (range 5–57) post-transplant, day +100 incidence of 3% (95%CI: 2.0–4.0).

Table 1.

Patients Demographics (n = 514).

Characteristic	Patients
Median Age (range)	52 (21–73)
Male gender, n (%)	278 (54%)
Diagnosis, n (%)	
Acute leukemia/MDS	378 (74%)
Lymphoma	44 (9%)
Multiple myeloma	5 (11%)
CML/MPD	33 (6%)
Conditioning regimen, n (%)	
Busulfan-based	259 (50%)
Bu/Mel/Flu	*231*
Bu/Mel	*22*
Bu/Mel/Thio	*2*
Bu/Flu	*3*
Bu/Cy	*1*
TBI-Based (1320–1375 cGy)	239 (46.4%)
Flu/Thio/TBI	*92*
Flu/Cy/TBI	*24*
Cy/Thio/TBI	*119*
VP-16/Thio/TBI	*2*
VP-16/TBI	*1*
Cy/TBI	*1*
Clo/Thio/Mel	9 (1.75%)
Thio/Flu/Mel	3 (0.6%)
Carmustine/VP-16/Cy/Mel	3 (0.6%)
Melphalan	1 (0.2%)
Graft type, n (%)	
T-cell depletion	422 (82%)
Unmodified	65 (13%)
Cord blood *	27 (5%)
Donor-recipient HLA-match, n (%)	
MRD	189 (37%)
MMRD	11 (2%)
MUD	181 (35%)
MMUD	106 (21%)
Cord blood *	27 (5%)

Characteristic	Patients
Recipient CMV serostatus, n (%)	
Negative	233 (45%)
Positive	281 (55%)
GVHD prophylaxis, n (%)	
T-cell depletion **	422 (82%)
CNI/MTX +/− MMF	46 (9%)
CNI/MMF	27 (5%)
CNI/+/− MTX +/− sirolimus	13 (3%)
No prophylaxis ***	6 (1%)
History of hepatitis exposure, n (%)	
Hepatitis B core antibody + or undetermined	30 (6%)
Hepatitis B core antibody −	484 (94%)
Hepatitis C virus antibody + ****	7 (1%)
Hep C virus antibody −	507 (99%)
Liver function test pre-HCT, n (%)	
Total bilirubin, mg/dL	
≤ 12	497 (96.6%)
1.3–2.0	15 (3%)
2.1–2.5	2 (0.4%)
Aspartate aminotransferase, Units/L	460 (89%)
≤ 37	50 (10%)
ULN – 2.5x ULN	4 (1%)
> 2.5 ULN	
Alanine aminotransferase, Units/L	484 (94%)
≤ 55	26 (5%)
ULN – 2.5x ULN	4 (1%)
> 2.5	

N indicates number; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; MPD, myeloproliferative disorder; Bu, busulfan, Mel, melphalan; Thio, thiotepa; Flu, fludarabine; Cy, cyclophosphamide; TBI, total body irradiation; TCD, T-cell depleted; MRD, matched related donor; MMRD, mismatched related donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; CMV, cytomegalovirus; GVHD, graft-versus-host disease; CNI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolate mofetil; HCT, hematopoietic cell transplant; ULN, upper limit of normal.

* includes 1 recipient of double cord plus haploidentical PBSCs

** Seven T-cell depleted graft recipients required additional GVHD prophylaxis

*** includes 6 patients who received syngeneic allo-HSCT without GVHD prophylaxis

**** includes 2 patients positive for both hepatitis B core antibody and hepatitis C virus antibody

Table 2.

Univariable analysis of variables potentially associated with the 100-day cumulative incidence of SOS.

Variable	100-day Estimate (95% CI)	p-value
Age (years)		0.6
< 40 (n = 117)	3.0 (1.0–6.0)	
≥ 40 (n = 397)	3.0 (1.0–4.0)	
Donor-recipient HLA-match		0.973
10/10 (n = 370)	3.0 (1.0–5.0)	
≤ 9/10 (n = 144)	3.0 (1.0–6.0)	
Graft		<0.001
TCD (n = 422)	1.0 (<1.0–2.0)	
Unmodified (n = 92)	11.0 (6.0–18.0)	
Conditioning regimen		0.414
Busulfan-based (n = 259)	2.0 (1.0–4.0)	
TBI-based (n = 239)	3.0 (2.0–6.0)	
Other (n = 16)		
Recipient hepatitis B and/or C serologies (pre HCT)		0.028
Negative (n = 479)	2.0 (1.0–4.0)	
Positive (n = 35)	9.0 (2.0–21.0)	

HLA indicates human leukocyte antigen; TCD, T-cell depleted; TBI, total body irradiation; allo-HSCT, allogeneic hematopoietic stem cell transplantation.