A phase II, prospective, randomized, open-label study of defibrotide added to standard-of-care prophylaxis for the prevention of acute graft-*versus*-host disease after allogeneic hematopoietic cell transplantation

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Abstract

Acute graft-*versus*-host disease (aGvHD) is a life-threatening complication typically occurring within 100 days after allogeneic hematopoietic cell transplantation (allo-HCT). This hypothesis-generating, phase II, prospective, open-label, randomized study (*clinicaltrials gov. Identifier*: *NCT03339297*) compared defibrotide added to standard-of-care (SOC) GvHD prophylaxis (defibrotide prophylaxis arm) *versus* SOC alone (SOC arm) to prevent aGvHD post-transplant. This study estimated incidences of aGvHD and was not statistically powered to assess differences among treatment arms. Patients were randomized 1:1 to defibrotide prophylaxis arm (n=79; median age 57 years; range, 2-69 years) or SOC arm (n=73; median age 56 years; range, 2-72 years). Patient demographics in the two arms were similar except for conditioning regimen type (myeloablative: defibrotide, 76% *vs*. SOC, 61%) and stem cell source for allo-HCT (bone marrow: defibrotide, 34% *vs*. SOC, 26%). In the intent-to-treat primary endpoint analysis, the cumulative incidence of grade B-D aGvHD at day 100 post-transplant was 38.4% in the defibrotide prophylaxis arm *versus* 47.1% in the SOC arm (difference: –8.8%, 90% confidence interval [CI]: –22.5 to 4.9). The difference noted at day 100 became more pronounced in a subgroup analysis of patients who received antithymocyte globulin (defibrotide: 30.4%, SOC: 47.6%; difference: –17.2%; 90% CI: –41.8 to 7.5). Overall survival rates at day 180 post-transplant were similar between arms, as were the rates of serious treatment-emergent adverse events (defibrotide: 42%, SOC: 44%). While the observed differences in endpoints between the two arms were not substantial, these results suggest defibrotide prophylaxis may add a benefit to currently available SOC to prevent aGvHD following allo-HCT without adding significant toxicities.

Introduction

Graft-*versus*-host disease (GvHD), the most important life-threatening complication after allogeneic hematopoietic cell transplantation (allo-HCT), occurs when donor T cells are activated in response to major or minor histocompatibility mismatch or gene polymorphisms from the recipient, causing a cytotoxic effect in healthy tissues and organs.[1,2] Acute GvHD (aGvHD) typically occurs within the first 100 days after allo-HCT.[3,4] The pathophysiology of aGvHD broadly follows a three-stage process whereby tissue damage from the conditioning regimen activates the host antigen-presenting cells, which in turn activate donor T cells to initiate GvHD. Subsequently, T-cell–induced cellular and inflammatory factors cause damage to organs,[5] namely the skin, gastrointestinal tract, and liver.[6] Patients who develop aGvHD exhibit a greater degree of endothelial damage and dysfunction compared to patients without this complication,[7,8] as well as elevated biomarkers associated with endothelial cell damage (endothelial microparticles, E-selectin, intercellular adhesion molecule–1 [ICAM-1], and von Willebrand factor).[9-12] Furthermore, factors in serum from patients with aGvHD have been shown to promote endothelial cell activation.[7]

Prophylactic regimens used to prevent aGvHD usually include a calcineurin inhibitor (e.g., cyclosporine A [CSA], ta-

crolimus) and methotrexate or mycophenolate mofetil.[2,14] Despite the use of these immunosuppressive regimens, approximately 39% to 59% of patients receiving allo-HCT develop grade B-D aGvHD.[15] Antithymocyte globulin (ATG) has been shown to lower the incidence of aGvHD after allo-HCT from an unrelated or sibling donor.[16-18] Furthermore, cyclophosphamide taken post-HCT (PTCy) is widely used in both haploidentical and matched unrelated donor transplants.[19,20] Although PTCy is on the path to becoming the new standard-of-care (SOC) for post-HCT aGvHD prophylaxis, it has been associated with graft dysfunction and infection.[21] The mechanism of action of ATG and presumably of PTCy in the prevention of aGvHD involves T-cell depletion in blood and peripheral lymphatic tissues.[20,22-24] Additionally, the selective T-cell co-stimulation modulator abatacept was recently approved by the US Food and Drug Administration for aGvHD prophylaxis when in combination with a calcineurin inhibitor and methotrexate.[25] However, as abatacept is also a cytotoxic T-cell immunoglobulin, its primary mechanism of action involves immune suppression.[25] The effectiveness of current aGvHD prophylactic regimens remains unsatisfactory, resulting in a need for safe and more effective therapies for the prevention of aGvHD.[26]

Defibrotide is a polydisperse mixture of predominantly single-stranded polydeoxyribonucleotide sodium salts.[27] It reduces endothelial cell activation and enhances protection and stabilization of endothelial cells through anti-inflammatory and anti-adhesive mechanisms and has been shown to protect the endothelium from toxic, inflammatory, and ischemic damage.[27-29] *In vitro* evidence suggests that defibrotide protects endothelial cells, restores the thrombotic-fibrinolytic balance, and has immunosuppressive effects by inducing synthesis of prostaglandins that inhibit T-cell proliferation.[30,31] Defibrotide has also been shown to suppress heparanase gene expression, and high levels of heparanase have been postulated as a risk factor for aGvHD development.[32,33] Defibrotide has been approved for the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS),[34,35] a disease characterized by endothelial cell dysfunction.

The current SOC for prophylaxis of aGvHD works to suppress the immune system through either inhibition or depletion of T-cell lymphocytes or induction of tolerance to overcome the immune response from donor T-cell recognition that induces aGvHD; however, this can attenuate the beneficial graft-*versus*-tumor effect and increase the risk of opportunistic infection and disease relapse.[2,36,37] Due to high morbidity and mortality associated with GvHD and the limitations of current therapies, prevention of aGvHD remains an area with significant unmet need. New treatment strategies for aGvHD prophylaxis are needed to improve clinical outcomes. Defibrotide is postulated to reduce the incidence of aGvHD without an increase in opportunistic infections and relapse by (i) protecting endothelial cells in GvHD target organs from donor alloreactive T-cell infiltration and damage, (ii) not directly depleting T cells involved in the graft-*versus*-tumor effect, and (iii) ameliorating the inflammatory response and tissue damage associated with this immunopathological disease, reducing its incidence and severity.[26]

Several clinical studies have examined whether defibrotide can reduce the incidence of aGvHD.[39-42] We designed the present hypothesis-generating, phase II, prospective, open-label, randomized study (*clinicaltrials gov. Identifier: NCT03339297*) to evaluate defibrotide added to SOC GvHD prophylaxis compared with SOC GvHD prophylaxis alone for the prevention of aGvHD following allo-HCT.

Methods

Study design and patients

Overall, 150 patients were planned for enrollment. Patients were stratified by age at screening (<17 years *vs*. ≥17 years), geographic region (North America *vs*. Europe), and use of ATG and were randomized 1:1 to defibrotide prophylaxis plus SOC (defibrotide prophylaxis arm) or SOC alone (SOC arm; *Online Supplementary Figure S1*). ATG type and dose were per the site SOC and varied by region. ATG use was limited to 30% of patients. Eligible patients (age ≥1 year) had to have a diagnosis of acute leukemia (in morphologic complete remission) or myelodysplastic syndrome and, after myeloablative or reduced-intensity conditioning, were scheduled for CD3+ T-cell replete peripheral blood stem cell or non-manipulated bone marrow graft transplantation from a human leukocyte antigen-matched or single-allele mismatched, unrelated donor. Key exclusion criteria were prior autologous or allo-HCT and clinically significant acute bleeding within 24 hours before study treatment initiation.

Institutional Review Boards at participating centers approved the study, which was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients, parents, or legal guardians provided written informed consent.

Treatment

Patients in the defibrotide prophylaxis arm received defibrotide 25 mg/kg/day administered as 2-hour intravenous infusions of 6.25 mg/kg/dose every 6 hours prior to the start of conditioning therapy (1-4 doses) and continued for ≥21 days (ending no later than day 30 post-transplant). SOC GvHD immunoprophylaxis consisted of methotrexate or mycophenolate mofetil plus CSA or tacrolimus with or without ATG starting on the day of the conditioning

regimen. During the study, patients who developed VOD/SOS in either treatment arm could be treated with defibrotide. Per protocol, the use of medications that increased the risk of bleeding was closely monitored, and patients on defibrotide would be discontinued from defibrotide when bleeding developed or when taking medications that increased the risk of bleeding during the study. Thromboprophylaxis with heparin was allowed throughout the study for patients in both arms (maximum of 100 U/kg/day). Patients were followed for up to 180 days after transplantation.

Endpoints and assessments

The primary endpoint was cumulative incidence of grade B-D aGvHD by day 100 post-transplant. Key secondary endpoints included cumulative incidence of grade B-D aGvHD by day 180 post-transplant, grade C-D aGvHD by days 100 and 180 post-transplant, and safety. Grading of aGvHD for assessment of the primary and applicable secondary efficacy endpoints was based on the International Bone Marrow Transplant Registry Severity Index.[43] An exploratory endpoint was overall survival (OS) by day 180 post-transplant. Safety assessments included monitoring treatment-emergent adverse events, serious treatment-emergent adverse events, and treatment-related treatment-emergent adverse events. Investigators classified adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analysis

This study was designed to obtain estimates of the treatment difference of the cumulative incidence rates of aGvHD between the two treatment arms to compare the efficacy of defibrotide added to SOC (defibrotide prophylaxis arm) *versus* SOC alone (SOC arm). The study was for hypothesis generating and was not powered to detect minimal clinically meaningful differences between treatment arms at a significant level of 5%. A sample size of 75 patients per arm was estimated to provide a 90% confidence interval (CI): −0.28 to −0.03 for the treatment difference of the primary endpoint, assuming a cumulative incidence of 28.6% for the defibrotide prophylaxis arm and 44% for the SOC arm.[41]

Data were summarized by treatment arms using descriptive statistics for continuous variables, and numbers and percentages of patients for categorical variables. Computations were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The primary analysis was performed on the intent-to-treat (ITT) population of all randomized patients. The safety population included all patients randomized to the defibrotide prophylaxis arm who received ≥1 dose of defibrotide and all patients randomized to the SOC arm. Analysis of the primary endpoint is detailed in the *Online Supplementary Appendix*.

Results

Patients

From February 21, 2018 to May 12, 2020, 152 patients participated in this study at 43 sites across 11 countries. The ITT population comprised 79 patients randomized to the defibrotide prophylaxis arm and 73 patients randomized to the SOC arm (*Online Supplementary Figure S2*). Five patients randomized to defibrotide prophylaxis did not undergo allo-HCT and did not receive defibrotide; three patients randomized to the SOC did not undergo allo-HCT. The safety population included 74 patients in the defibrotide prophylaxis arm and 70 patients in the SOC arm. Fifty-six patients (71%) in the defibrotide prophylaxis arm and 59 patients (81%) in the SOC arm completed the study (*Online Supplementary Figure S2*).

The two treatment arms had similar baseline demographic characteristics (Table 1); however, the proportion of patients who received myeloablative conditioning prior to allo-HCT was higher in the defibrotide prophylaxis arm than in the SOC arm (56/74 patients [76%] *vs*. 43/70 patients [61%], respectively). Similarly, patients in the defibrotide prophylaxis arm more frequently received bone marrow as the source of stem cells compared to patients in the SOC arm (25/74 [34%] *vs*. 18/70 [26%], respectively). Among patients stratified to ATG use, baseline characteristics between the defibrotide prophylaxis (n=24) and SOC (n=21) arms followed a similar pattern as the total population (Table 2).

Treatment

The same percentage of patients (74%) in both the defibrotide prophylaxis and SOC arms received GvHD prophylaxis with methotrexate-based regimens (*Online Supplementary Table S1*), and 30% of patients received ATG in both study arms, per protocol. The percentage of patients who received CSA (47% *vs*. 47%) or tacrolimus (51% *vs*. 53%) was similar in the defibrotide prophylaxis and SOC arms, respectively. Median duration of exposure to defibrotide and duration of defibrotide treatment were both 25 days (range, 11-40 days) among the 74 patients who received defibrotide prophylaxis. A total of four (5%) patients in the defibrotide prophylaxis arm discontinued defibrotide treatment; three (4%) were due to adverse events and one (1%) was due to patient withdrawal. One patient (1%) in the defibrotide prophylaxis arm and four patients (6%) in the SOC arm received defibrotide for the treatment of VOD/SOS.

Cumulative incidence of acute graft-*versus*-host disease

Per the primary endpoint ITT analysis, where death without experiencing grade B-D aGvHD was treated as a competing risk, the cumulative incidence of grade B-D aGvHD by day 100 post-transplant in the defibrotide prophylaxis arm *versus* the SOC arm was 38.4% *versus* 47.1%, respectively (difference: −8.8%; 90% CI: −22.5 to 4.9; Figure 1A). In a planned

Table 1. Baseline demographic and clinical characteristics (intent-to-treat population).

Characteristics[a]	Defibrotide prophylaxis (N=79)	SOC (N=73)
Sex, N (%)		
Male	41 (52)	36 (49)
Female	38 (48)	37 (51)
Race, N (%)		
Asian	1 (1)	4 (5)
Black or African American	0	1 (1)
White	66 (84)	63 (86)
Not reported	12 (15)	5 (7)
Age in years, median (range)	57 (2-69)	56 (2-72)
Age group, N (%)		
<17 years	4 (5)	3 (4)
≥17 years	75 (95)	70 (96)
Primary disease in >5% of patients, N (%)[b]		
MDS[c]	12 (15)	8 (11)
AML[d]	43 (54)	38 (52)
B-lymphoblastic leukemia	8 (10)	10 (14)
T-lymphoblastic leukemia	4 (5)	2 (3)
Other	4 (5)	11 (15)
Conditioning regimen, N (%)	74	70
Myeloablative conditioning	56 (76)	43 (61)
Reduced-intensity conditioning	18 (24)	27 (39)
Source of stem cells, N (%)[e]	74	70
Bone marrow	25 (34)	18 (26)
Peripheral blood	49 (66)	52 (74)
Degree of HLA matching, N (%)		
Full match of A, B, C, and DRB	67 (85)	62 (85)
One mismatch of A, B, C, and DRB	7 (9)	8 (11)

[a]Percentages may not total 100 due to rounding. [b]In either treatment arm. [c]Includes MDS with single-lineage dysplasia, ringed sideroblasts, multilineage dysplasia, or isolated del5q and unclassifiable MDS. [d]Includes AML with recurrent genetic abnormality, myelodysplasia-related changes, or not otherwise specified AML. [e]Five patients in the defibrotide prophylaxis arm and 3 patients in the SOC arm did not receive HCT. AML: acute myeloid leukemia; HCT: hematopoietic cell transplantation; HLA: human leukocyte antigen; MDS: myelodysplastic syndrome; SOC: standard-of-care.

sensitivity analysis for the primary endpoint using disease relapse as a competing risk in addition to death, the cumulative incidence of grade B-D aGvHD by day 100 post-transplant in the defibrotide prophylaxis arm compared to the SOC arm was 37.0% *versus* 45.7%, respectively (difference: –8.7; 90% CI: –22.4 to 4.9; Figure 1B). Both treatment arms had similar cumulative incidences of grade B-D aGvHD by day 180 post-transplant (49.0% *vs*. 50.2%, respectively).

In patients who received ATG, the cumulative incidence of grade B-D aGvHD by day 100 was consistent with the ITT population; however, the incidence was numerically lower in the defibrotide prophylaxis arm compared with the SOC arm. The cumulative incidence of grade B-D aGvHD by day 100 post-transplant in the defibrotide prophylaxis arm compared to the SOC arm was 30.4% *versus* 47.6%, respectively (difference: –17.2%; 90% CI: –41.8 to 7.5; Figure 2A). In patients who did not receive ATG, the cumulative incidence rates of grade B-D aGvHD by day 100 were similar between the defibrotide prophylaxis and SOC arms (42.0% *vs*. 46.9%, respectively; difference: –4.9%; 90% CI: –21.6 to 11.7; Figure 2B). Results of the cumulative incidence of grade C-D aGvHD in ATG subgroups (Figure 3; Table 3) followed a similar pattern as the grade B-D aGvHD ATG subgroup analysis but with a more pronounced lowering of the cumulative incidence of grade C-D aGvHD by day 100 post-transplant with defibrotide prophylaxis *versus* SOC (4.3% *vs*. 28.9%, respectively; difference: –24.5%; 90% CI: –42.9 to –6.2). As shown in Table 2, in the ATG use subgroup, there was a slightly higher proportion of mismatched donors in the SOC arm (24% [5/21]) *vs*. the defibrotide prophylaxis arm (13% [3/24]); these proportions are somewhat higher than those seen in the non-ATG groups (DP: 7%; SOC 6%).

As in the subgroup of patients who received ATG, decreases in the cumulative incidence of grade B-D aGvHD at day 100 post-transplant were noted with defibrotide prophylaxis (n=56) compared with SOC alone (n=43) in patients who received myeloablative conditioning (41.8% *vs*. 55.8%, respectively; difference: –14.0%; 90% CI: –30.8 to 2.9; Table 3). In patients who did not receive myeloablative conditioning, the cumulative incidence of grade B-D aGvHD by day 100 was 27.8% in the defibrotide prophylaxis arm (n=18) *versus* 33.3% in the SOC arm (n=27; difference: –5.6%; 90% CI: –29.1 to

Table 2. Baseline demographic and clinical characteristics by antithymocyte globulin subgroup.[a]

Characteristic[b]	ATG use		No ATG use	
	Defibrotide prophylaxis (N=24)	SOC (N=21)	Defibrotide prophylaxis (N=55)	SOC (N=52)
Sex, N (%)				
Male	10 (42)	11 (52)	31 (56)	25 (48)
Female	14 (58)	10 (48)	24 (44)	27 (52)
Race, N (%)				
Asian	0	2 (10)	1 (2)	2 (4)
Black or African American	0	1 (5)	0	0
White	19 (79)	15 (71)	47 (85)	48 (92)
Not reported	5 (21)	3 (14)	7 (13)	2 (4)
Age in years, median (range)	54.5 (1.6-68.0)	56.0 (1.5-67.0)	58.0 (14-69)	58.5 (20-72)
Age group, N (%)				
<17 years	3 (13)	3 (14)	1 (2)	0
≥17 years	21 (88)	18 (86)	54 (98)	52 (100)
Primary disease in >5% of patients, N (%)[c]				
MDS[d]	3 (13)	5 (24)	9 (16)	3 (6)
AML[e]	15 (63)	9 (43)	28 (51)	29 (56)
B-lymphoblastic leukemia	5 (21)	5 (24)	3 (5)	5 (10)
T-lymphoblastic leukemia	0	0	4 (7)	2 (4)
Other	0	2 (10)	4 (7)	9 (17)
Conditioning regimen, N (%)				
Myeloablative conditioning	20 (83)	13 (62)	36 (65)	30 (58)
Reduced-intensity conditioning	3 (13)	8 (38)	15 (27)	19 (37)
Source of stem cells, N (%)[f]				
Bone marrow	7 (29)	3 (14)	18 (33)	15 (29)
Peripheral blood	16 (67)	18 (86)	33 (60)	34 (65)
Degree of HLA matching, N (%)				
Full match of A, B, C, and DRB	20 (83)	16 (76)	47 (85)	46 (88)
One mismatch of A, B, C, and DRB	3 (13)	5 (24)	4 (7)	3 (6)

[a]Two patients in the defibrotide prophylaxis arm were randomized and stratified as receiving ATG per the interactive response technology but were verified as not receiving ATG. [b]Percentages may not total 100 due to rounding. [c]In any treatment subgroup. [d]Includes MDS with single-lineage dysplasia, ringed sideroblasts, multilineage dysplasia, or isolated del5q and unclassifiable MDS. [e]Includes AML with recurrent genetic abnormality, myelodysplasia-related changes, or not otherwise specified AML. [f]Among patients stratified to ATG use, 1 patient in the defibrotide prophylaxis arm did not receive HCT. Among patients stratified to no ATG use, 4 patients in the defibrotide prophylaxis arm and 3 patients in the SOC arm did not receive HCT. AML: acute myeloid leukemia; ATG: antithymocyte globulin; HCT: hematopoietic cell transplantation; HLA: human leukocyte antigen; MDS: myelodysplastic syndrome; SOC: standard-of-care.

18.0; Table 3). Similarly, in patients who received bone marrow as the source of stem cells, decreases in the cumulative incidence of grade B-D and grade C-D aGvHD at day 100 post-transplant were noted with defibrotide prophylaxis (n=25) compared with SOC alone (n=18; Table 3).

Overall survival

OS rates were similar in the defibrotide prophylaxis and SOC arms by day 180 post-transplant (86.0% *vs*. 86.9%, respectively; Figure 4).

Safety

All patients experienced ≥1 treatment-emergent adverse event (Table 4). Fewer patients in the defibrotide prophylaxis arm experienced bleeding events compared to patients in the SOC arm (34% *vs*. 41%, respectively). Nausea (78% *vs*. 70%), diarrhea (65% *vs*. 76%), stomatitis (57% *vs*. 51%), and vomiting (53% *vs*. 54%) were the most common treatment-emergent adverse events reported in patients in both the defibrotide prophylaxis and SOC arms, respectively. In the defibrotide prophylaxis arm, 12 patients (16%) had treatment-related adverse events (*Online Supplementary Table S2*). No patients discontinued defibrotide due to treatment-related treatment-emergent adverse events.

Serious treatment-emergent adverse events were reported in 42% of patients in the defibrotide prophylaxis arm and 44% of patients in the SOC arm; none of the serious events were deemed to be related to defibrotide. Five patients in the defibrotide prophylaxis arm and three patients in the SOC arm had treatment-emergent adverse events leading

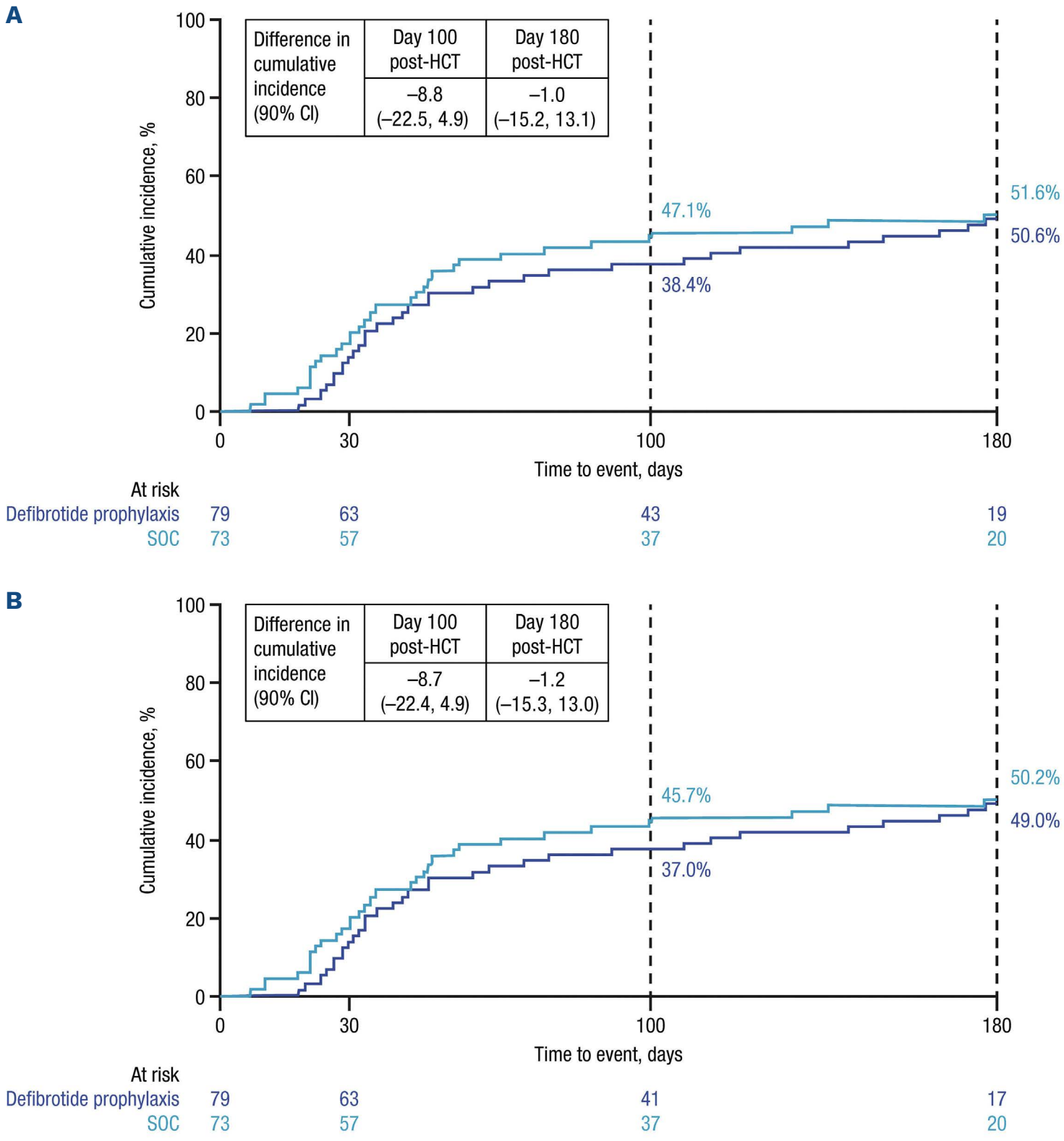

Figure 1. Cumulative incidence of grade B-D acute graft-*versus*-host disease by (A) day 100 and day 180 after allogeneic hematopoietic cell transplantation and (B) with disease relapse as a competing risk. The International Bone Marrow Transplant Registry (IBMTR) Severity Index was used to grade acute graft-*versus*-host disease. HCT: hematopoietic cell transplantation; CI: confidence interval; SOC: standard-of-care.

to death. The events leading to death were aGvHD (n=2), bacterial sepsis (n=1), respiratory failure (n=1), and VOD/SOS (n=1) in the defibrotide prophylaxis arm and multiple organ failure (n=1), lung disorder (n=1), and shock (n=1) in the SOC arm. None of these events were related to defibrotide.

Discussion

This hypothesis-generating, phase II, prospective, open-label, randomized study is the first multi-national prevention study to use a novel approach directed towards endothelial injury. Here, defibrotide plus SOC GvHD prophylaxis *versus* SOC alone was evaluated for the prevention of aGvHD after allo-HCT in 152 patients with acute leukemia or myelodysplastic syndrome. Patient baseline demographic and clinical characteristics were mostly similar between the two arms of the study and were consistent with those of a population at risk for aGvHD. There were differences between treatment arms in the type of conditioning regimen (myeloablative: defibrotide, 76% *vs*. SOC, 61%) and source of stem cells (bone marrow: defibrotide, 34% *vs*. SOC, 26%). While the data from this study many only suggest a modest treatment effect of defibrotide, the findings add to the relatively small body of literature of randomized assessments for GvHD prevention.

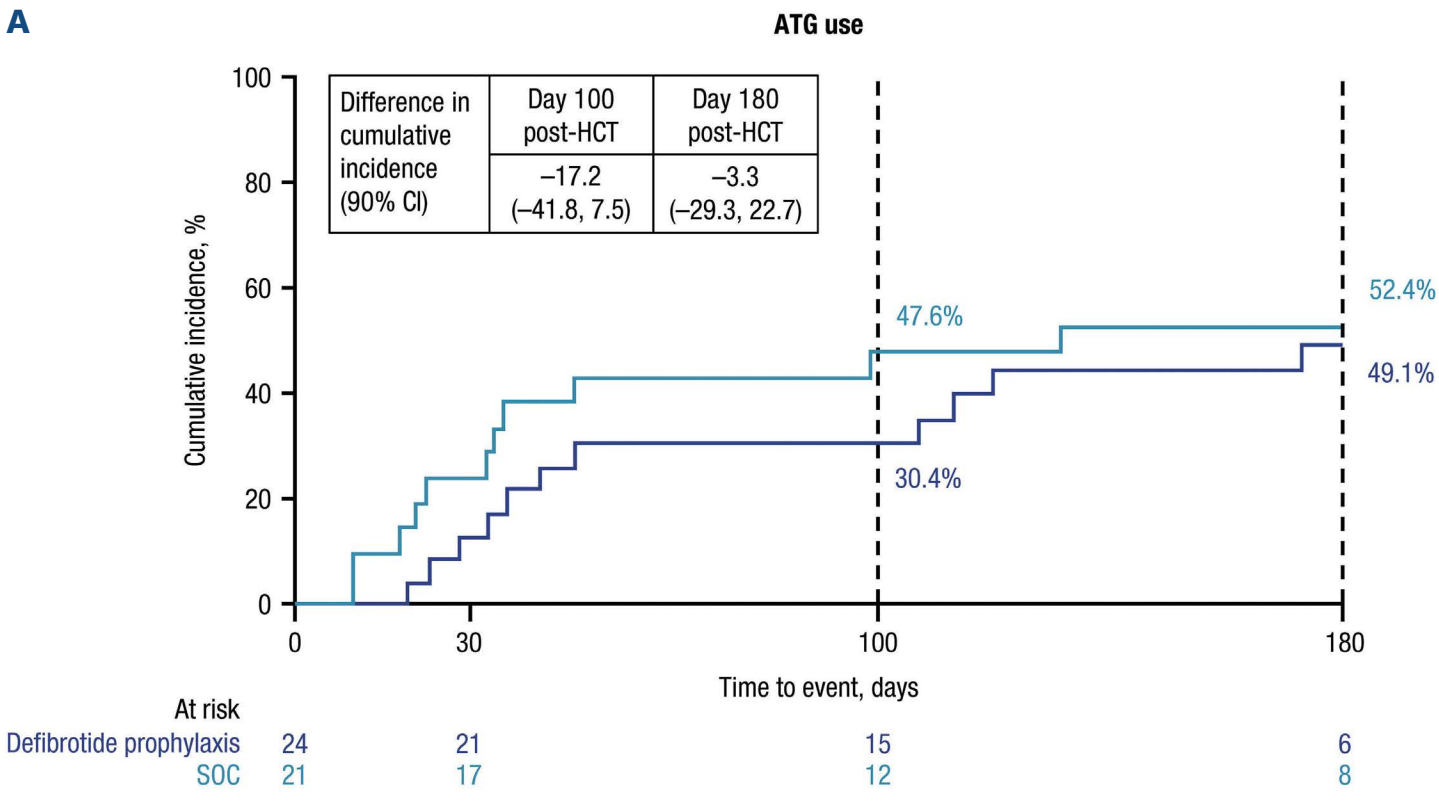

Figure 2. Cumulative incidence of grade B-D acute graft-*versus*-host disease by day 100 and day 180 after allogeneic hematopoietic cell transplantation by (A) antithymocyte globulin use and (B) no antithymocyte globulin use. The International Bone Marrow Transplant Registry (IBMTR) Severity Index was used to grade acute graft-*versus*-host disease. HCT: hematopoietic cell transplantation; ATG: antithymocyte globulin; CI: confidence interval; SOC: standard-of-care.

ITT analysis of the primary endpoint revealed that the cumulative incidence of grade B-D aGvHD by day 100 post-transplant was numerically lower in the defibrotide prophylaxis arm (38.4%) compared with the SOC arm (47.1%). By day 180 post-transplant, patients in the two treatment arms had similar cumulative incidences of grade B-D aGvHD. Similar results were reported in a study by Corbacioglu *et al.*[41,42] in which patients who received defibrotide prophylaxis for VOD/SOS had a lower incidence of aGvHD by day 100 post-transplant *versus* control (no defibrotide; 47% *vs*. 65%, respectively; *P*=0.0046), and the incidence of chronic GvHD by day 180 did not differ between study arms (defibrotide prophylaxis, 9%; control, 10%; *P*=0.8022). The absence of a noted effect of defibrotide on the incidence of chronic GvHD by day 180 may be explained by the different pathophysiologies of acute and chronic forms of this disease. Another study by Strouse *et al.*[44] found notable differences in the cumulative incidence of grade B-D acute GvHD at day 100 post-HCT in patients who received defibrotide *versus* those who did not (23.1% *vs*. 37.7%; difference, –14.6; 95% CI: –33.1 to 3.9]). Furthermore, a study by Tekgündüz *et al.*[39] demonstrated that

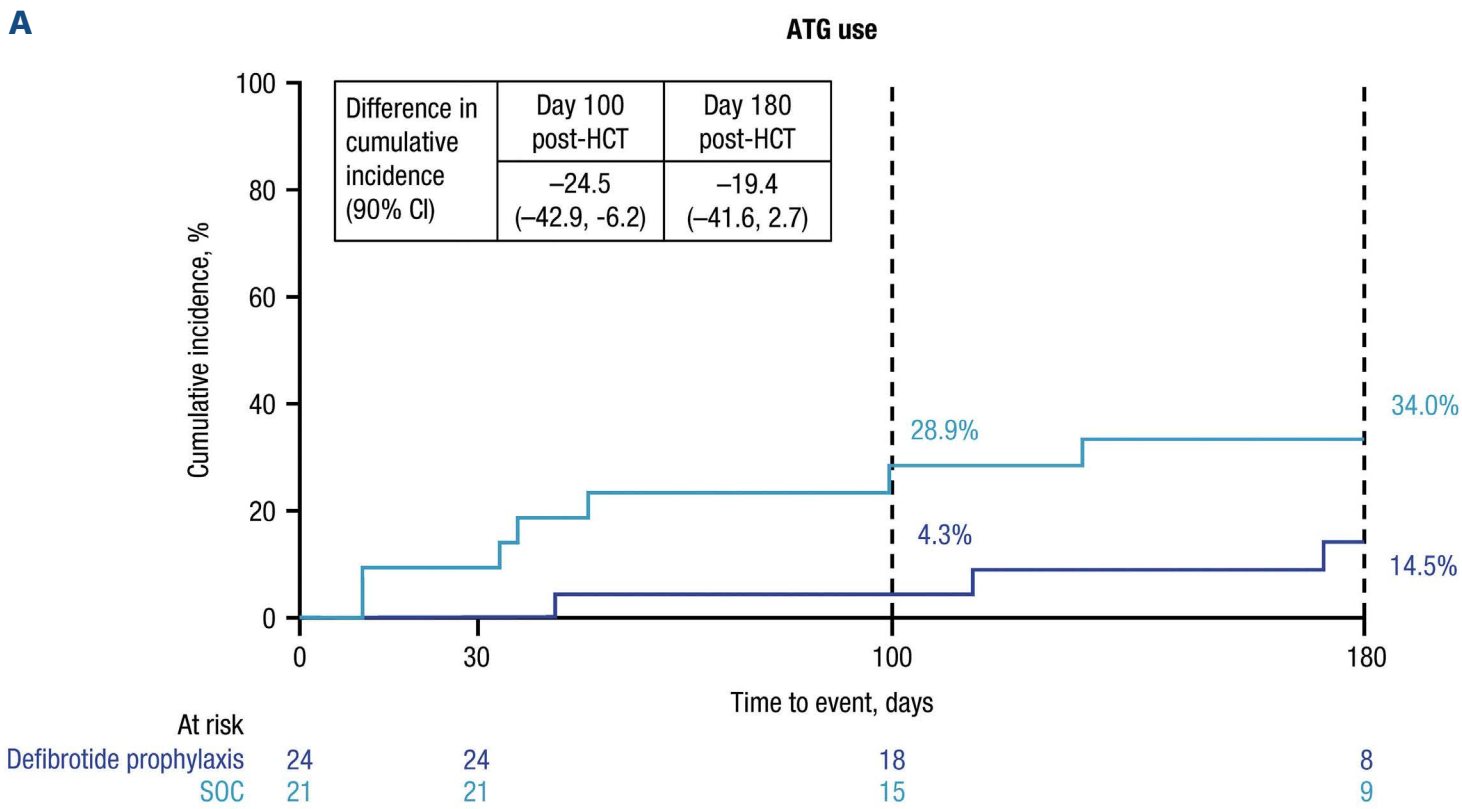

Figure 3. Cumulative incidence of grade C-D acute graft-*versus*-host disease by day 100 and day 180 after allogeneic hematopoietic cell transplantation by (A) antithymocyte globulin use and (B) no antithymocyte globulin use. The International Bone Marrow Transplant Registry (IBMTR) Severity Index was used to grade acute graft-*versus*-host disease. HCT: hematopoietic cell transplantation; ATG: antithymocyte globulin; CI: confidence interval; SOC: standard-of-care.

use of defibrotide prior to transplantation and concurrently with the conditioning regimen may decrease the incidence of aGvHD, and a separate study by Chalandon *et al.*[40] indicated that defibrotide prophylaxis significantly reduced 1-year cumulative incidence of aGvHD. Interestingly, a retrospective study by Tilmont *et al.*[45] showed no protective effect of defibrotide on the development or severity of aGvHD *versus* control (no defibrotide) in patients undergoing allo-HCT. However, in contrast to the current study, this was a retrospective observational study that included a small number of patients who received defibrotide, the majority of whom received defibrotide for the treatment of VOD/SOS, and only a small number who received defibrotide as prophylaxis. Furthermore, more patients in the defibrotide group had progressive disease, which may have contributed to poorer outcomes.

In our study, the numerical difference noted by day 100 post-transplant in the ITT population became more pronounced in subgroup analyses of patients stratified by ATG use. T-cell depletion with ATG in addition to standard

GvHD prophylaxis has been shown to significantly reduce the occurrence and severity of GvHD in patients undergoing allo-HCT; ATG is also associated with impaired immune reconstitution and increased risk of infections.[46,47] In patients receiving ATG in the current study, the cumulative incidence of the more severe grade C-D aGvHD by day 100 was lower with defibrotide prophylaxis compared to SOC alone; this difference was maintained through day 180 post-transplant. There was a slightly higher proportion of mismatched donors with grade C-D aGvHD in the SOC arm (24%) *versus* the defibrotide prophylaxis arm (13%). Although the small patient numbers in each group precludes the ability to draw solid conclusions, this could have led to the somewhat higher incidence of grade C-D aGvHD in the ATG SOC group. These results are consistent with those of Corbacioglu *et al.*,[41] in which prophylaxis with defibrotide significantly reduced the occurrence and severity of aGvHD *versus* control; adjusting for ATG as a covariate confirmed the significant effects of defibrotide (adjusted risk difference for aGvHD grade B-D: −0.1470; 95% CI: −0.2618 to −0.0322; *P*=0.0121).[42] Furthermore, the authors noted that defibrotide did not seem to interfere with the graft-*versus*-leukemia effect.[42] In the current study, the two treatment arms had similar OS by day 180 post-transplant.

The effect of defibrotide on the cumulative incidence of aGvHD also appeared more pronounced in patients who had received bone marrow as the source of the stem cells. However, other studies have shown no difference in the incidence of aGvHD with these sources of progenitor cells.[48,49] Similarly, in patients who received myeloablative conditioning, the cumulative incidence of aGvHD was also lower in the defibrotide prophylaxis arm *versus* the SOC arm. HCT recipients are exposed to insults that can stem from stressors such as conditioning regimen, engraftment, and infections that can cause endothelial cell activation and direct endothelial damage.[50] Endothelial cells may be an important target for prophylaxis and therapeutic intervention for complications like GvHD, especially due to the role of endothelium in the pathophysiology of the condition. Despite the potential higher risk of developing aGvHD associated with myeloablative conditioning,[15] defibrotide prophylaxis showed some benefit, which we hypothesize could be due to the known protective effect of defibrotide on the acute endothelial damage inflicted on these patients during conditioning.[51] We speculate that the more intense the conditioning, the higher the endothelial damage. Preclinical studies suggest that defibrotide downregulates expression of key endothelial adhesion molecules (e.g., E-selectin, vascular cell adhesion molecule–1) involved in trafficking alloreactive immune cells to aGvHD target tissues.[26] In a mouse model of allo-HCT, defibrotide prophylaxis prevented T cell and neutrophil tissue infiltration and aGvHD-associated tissue damage, resulting in reduced incidence of aGvHD and significantly improved survival *versus* untreated controls.[26] Additionally, defibrotide may be acting synergis-

Table 3. Cumulative incidence of acute graft-*versus*-host disease by day 100 by subgroups.

Subgroup	Grade B-D		Grade C-D	
	Defibrotide prophylaxis	SOC	Defibrotide prophylaxis	SOC
ATG use	N=24	N=21	N=24	N=21
Cumulative incidence rate (%)	30.4	47.6	4.3	28.9
Difference (90% CI)	-17.2 (-41.8 to 7.5)		-24.5 (-42.9 to -6.2)	
No ATG use	N=55	N=52	N=55	N=52
Cumulative incidence rate grade (%)	42.0	46.9	22.0	18.4
Difference (90% CI)	-4.9 (-21.6 to 11.7)		3.6 (-9.8 to 17.0)	
Myeloablative conditioning	N=56	N=43	N=56	N=43
Cumulative incidence rate (%)	41.8	55.8	16.4	21.1
Difference (90% CI)	-14.0 (-30.8 to 2.9)		-4.7 (-18.0 to 8.7)	
No myeloablative conditioning	N=18	N=27	N=18	N=27
Cumulative incidence rate (%)	27.8	33.3	17.0	22.2
Difference (90% CI)	-5.6 (-29.1 to 18.0)		-5.2 (-25.5 to 15.1)	
Peripheral blood transplant	N=49	N=52	N=49	N=52
Cumulative incidence rate (%)	39.6	42.3	18.8	19.3
Difference (90% CI)	-2.7 (-19.1 to 13.7)		-0.6 (-13.7 to 12.5)	
Bone marrow transplant	N=25	N=18	N=25	N=18
Cumulative incidence rate (%)	36.0	61.1	12.2	27.8
Difference (90% CI)	-25.1 (-50.8 to 0.6)		-15.6 (-36.7 to 5.5)	

aGvHD: acute graft-*versus*-host disease; ATG: antithymocyte globulin; CI: confidence interval; SOC: standard-of-care.

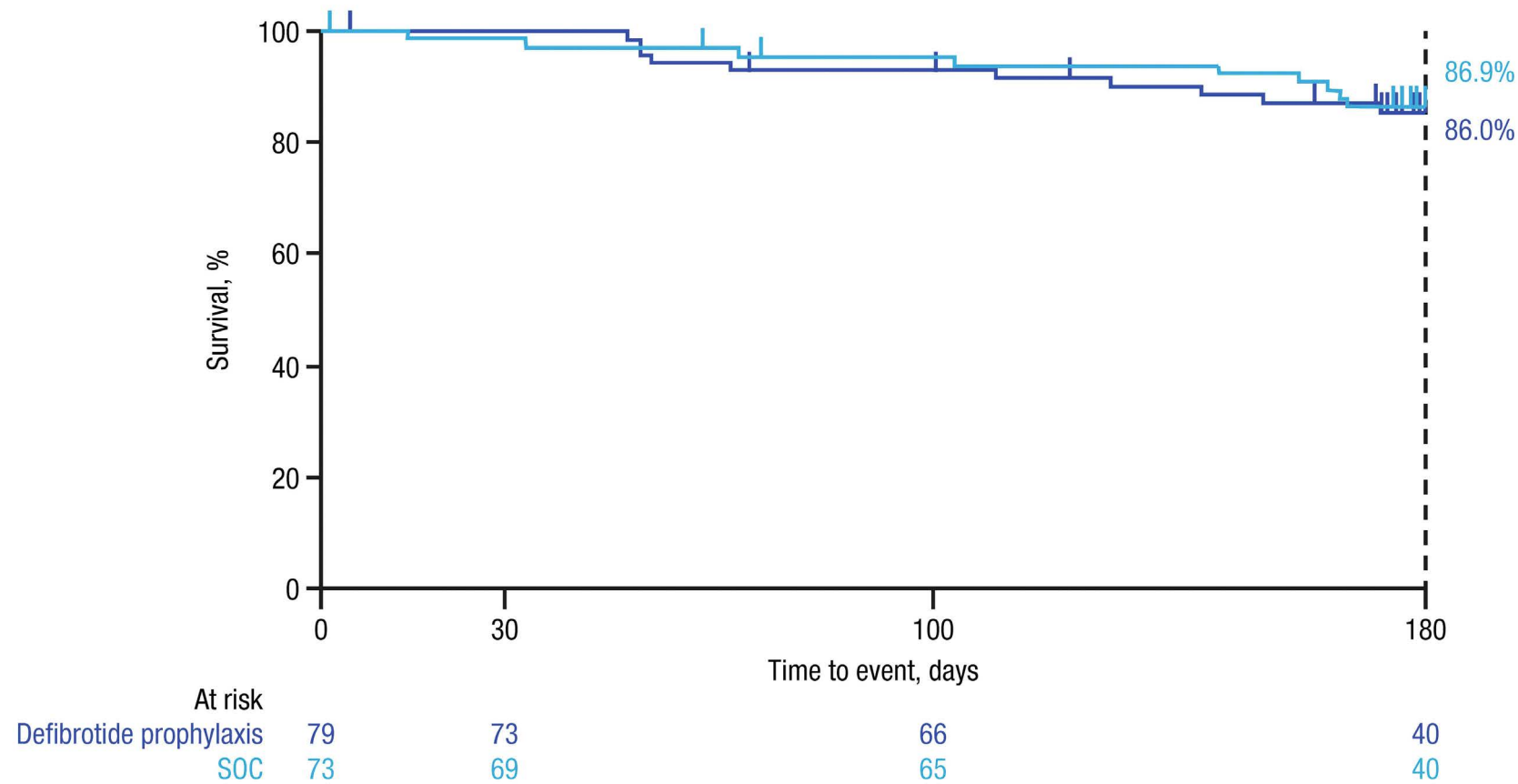

Figure 4. Kaplan-Meier–estimated overall survival by day 180 after allogeneic hematopoietic cell transplantation. SOC: standard-of-care.

Table 4. Treatment-emergent adverse events and serious treatment-emergent adverse events.

Number of patients, N (%)[a]	**Defibrotide prophylaxis (N=74)**	**SOC (N=70)**
Treatment-emergent adverse events[b]		
≥1	74 (100)	70 (100)
Related to defibrotide	12 (16)	-
Treatment-emergent adverse events of special interest: bleeding	25 (34)	29 (41)
Treatment-emergent adverse events occurring in >40% of patients[c]		
Nausea	58 (78)	49 (70)
Diarrhea	48 (65)	53 (76)
Stomatitis	42 (57)	36 (51)
Vomiting	39 (53)	38 (54)
Febrile neutropenia	31 (42)	20 (29)
Headache	31 (42)	23 (33)
Decreased appetite	30 (41)	30 (43)
Hypomagnesemia	30 (41)	35 (50)
Constipation	28 (38)	29 (41)
Anemia	27 (36)	30 (43)
Hypertension	25 (34)	29 (41)
Hypokalemia	24 (32)	28 (40)
Serious treatment-emergent adverse events[b]		
≥1	31 (42)	31 (44)
Related to defibrotide	0	-
Serious treatment-emergent adverse events in >2 patients[c]		
aGvHD	4 (5)	1 (1)
aGvHD in skin	1 (1)	4 (6)
Acute kidney injury	3 (4)	2 (3)
Diarrhea	3 (4)	2 (3)
Dyspnea	3 (4)	0

aGvHD: acute graft-*versus*-host disease; SOC: standard-of-care. [a]Incidence was based on the number of patients, not the number of events. Percentages were calculated using the number of patients in each arm from the safety population as the denominator. [b]Coding was based on MedDRA version 21.1. [c]In either treatment arm.

tically with ATG's polyclonal nature to produce a better response in patients who had received ATG. In support of a synergistic effect of defibrotide with other immunosuppressive agents, results from a preliminary study suggest that defibrotide prophylaxis combined with ATG, post-transplant cyclophosphamide, and CSA may be an effective strategy for preventing aGvHD.[52] Furthermore, the role of cell subsets other than T cells, such as endothelial cells, in the pathophysiology of GvHD might be more pronounced in the absence of T lymphocytes, as it occurs with natural killer cell and killer Ig–like receptor disparities in the haploidentical transplant setting.[53]

The potential benefits of defibrotide in lowering the incidence of aGvHD, most commonly occurring in the first 100 days following HCT, may reflect defibrotide's mechanism of action, especially its anti-inflammatory and endothelial protective properties, along with the suppression of heparanase gene expression. Additional studies are needed to further evaluate the effect of defibrotide in preventing aGvHD.

Safety results in this study were consistent with the safety profile of defibrotide reported in other randomized studies.[41,54] Importantly, there was no increased incidence of bleeding events with defibrotide prophylaxis compared to SOC, and there were no defibrotide-related serious treatment-emergent adverse events or deaths.

The main limitation of this study is the small sample size, which offered a low statistical power to detect differences between arms, particularly for the ATG and myeloablative conditioning subgroups. The study was intended to be hypothesis generating, with a goal of providing estimates of the cumulative incidence of aGvHD for defibrotide prophylaxis compared with SOC. The greater reductions in the incidence and severity of aGvHD with defibrotide prophylaxis *versus* SOC reported by Corbacioglu *et al.*[41] in the phase III VOD/SOS prevention study may have been the result of a larger number of patients. Furthermore, the study by Corbacioglu *et al.*[41] was performed in pediatric patients while this study included only a few pediatric patients. Another limitation of our study is the potential variability in SOC among patients, given that it was primarily defined by institutional guidelines that may vary among sites and regions. ATG type and dose were not specified in the protocol to be collected in the trial but rather were administered per the site SOC. In addition, although this study included many global HCT centers to include as many diverse populations as possible, the trial ended up with limited enrollment of minority populations and pediatric patients by nature. In order to extend the relevance of our findings to a broader patient population, future studies should have more stringent management of enrollment to ensure patient diversity. While not conclusive, the results of our study suggest that there may be a benefit to addition of defibrotide prophylaxis to SOC for the prevention of aGvHD after allo-HCT; however, further work is needed in the context of recently adopted therapeutic approaches. Future studies are needed to determine which subgroups of patients might derive the most clinical benefit from defibrotide prophylaxis added to standard GvHD prophylaxis.

Disclosures

MH has participated on a Data Safety Monitoring Board or Advisory Board for Jazz Pharmaceuticals, Mesoblast, and Novartis. SM has received payment for speaker bureaus from Incyte Pharmaceuticals. JAP-S has received the following from Novartis, Jazz Pharmaceuticals, Janssen, Gilead, BMS, Amgen, Takeda, MSD, Alexion, and Abvvie: grants or contracts; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; payment for expert testimony; and support for attending meetings and/or travel. FS has served on advisory boards and received honoraria from Jazz Pharmaceuticals, and has received support for attending meetings and/or travel from Jazz Pharmaceuticals. MR is a member of a Data Safety Monitoring Committee for Gamida Cell, is chair of the IT committee for the American Society of Transplantation and Cellular Therapy, is an employee of IQVIA Biotech, and her institution has received research funding and grants/contracts from Atara Biotherapeutics and Jazz Pharmaceuticals. WW, PZ, and SA are employees of Jazz Pharmaceuticals and hold stock and/or stock options in Jazz Pharmaceuticals. IY-A has received grants or contracts and consulting fees from Jazz Pharmaceuticals. DN has no other conflicts of interest to disclose. All authors received medical writing and editorial assistance for the development of this manuscript that was funded by Jazz Pharmaceuticals.

Contributions

MH, SM, MR, WW, SA, and IY-A performed the research, participated in the acquistion, analysis, or interpretation of the data, and critically revised the manuscript; DN, JAP-S, FS, and PZ participated in the acquisition, analysis, or interpretation of the data and critically revised the manuscript.

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Data-sharing statement

All relevant data are provided within the manuscript and supporting files.

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