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Analysis of Time to Complete Response after Defibrotide Initiation in Patients with Hepatic Veno-Occlusive Disease/ Sinusoidal Obstruction Syndrome after Hematopoietic Cell Transplantation

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Abstract

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication that occurs after hematopoietic cell transplantation (HCT). The mortality associated with untreated VOD/SOS with multiorgan dysfunction (MOD) has been reported to be >80%. The recommended dose of defibrotide is 6.25 mg/kg every 6 hours, administered as a 2-hour i.v. infusion, for a minimum of 21 days or until resolution of VOD/SOS signs and symptoms. The objective of this analysis was to evaluate the time to complete response (CR) in patients with post-HCT VOD/SOS treated with defibrotide. The time to defibrotide discontinuation due to a CR served as a surrogate for time to CR in an expanded access study (T-IND; ClinicalTrials.gov NCT00628498; n = 1000), and was analyzed separately from the time to CR data pooled from a phase 2 randomized dose-finding study (NCT00003966; n = 74 patients who received 25 mg/kg/day) and a phase 3 historically controlled study (NCT00358501; n = 102). For all studies, a CR

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was defined as total serum bilirubin <2 mg/dL with resolution of VOD/SOS-related MOD (renal and/or pulmonary dysfunction); the phase 2 study also required resolution of central nervous system dysfunction. In the T-IND, 390 patients discontinued treatment due to a CR and had sufficient data for analysis. The median time to discontinuation was 22 days (range, 2 to 64 days). Discontinuation due to CR occurred beyond 21 days in 235 patients (60%) and beyond 28 days in 57 patients (15%). The pooled phase 2 and 3 studies included 60 patients who achieved a CR, with a median time to CR of 24.5 days (range, 7 to 123 days). A CR was achieved beyond 21 days in 32 patients (53%) and beyond 28 days in 24 patients (40%). The Kaplan-Meier estimate of day +100 survival rate was substantially higher in patients who discontinued due to a CR compared with those who did not (92.5% versus 37.3%). Treatment-emergent adverse events occurred in 185 of 390 patients (47%) who discontinued due to a CR in the T-IND and in 55 of 60 patients (92%) who achieved a CR in the pooled phase 2 and 3 studies, and rates did not differ according to duration of treatment (≤21 days versus >21 days). Taken together, these results highlight the importance of continued defibrotide therapy until resolution of VOD/SOS signs and symptoms, as currently indicated in the approved product labels, which may occur beyond the recommended minimum of 21 days.

Keywords

Defibrotide; Veno-occlusive; disease/sinusoidal; obstruction syndrome; Hematopoietic cell; transplantation; Complete response

INTRODUCTION

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication following hematopoietic cell transplantation (HCT) [1]. The vascular endothelium is a key mediator of HCT-related complications, including VOD/SOS [2,3]. Endothelial cells can be damaged during HCT via conditioning regimen agents, cytokines produced by damaged tissue, and other transplantation-related factors [3,4]. Damage and activation of endothelial cells results in a procoagulant and hypofibrinolytic state that ultimately develops into VOD/SOS, which may lead to multiorgan dysfunction (MOD) in the most severe cases [5]. Mortality associated with untreated VOD/SOS with MOD has been reported to be >80% [1].

Defibrotide is a sodium salt of predominately single-stranded polydeoxyribonucleotides derived from porcine mucosal DNA [6,7]. It is believed to reduce endothelial cell activation and dysfunction by mechanisms that are antithrombotic, fibrinolytic, antiadhesive, and anti-inflammatory, thereby restoring the thrombotic-fibrinolytic balance and pre-serving endothelial homeostasis [5]. In vitro, defibrotide has been shown to protect the endothelium from cytotoxic and inflammatory damage by reducing activation of endothelial cells [5,8]. Evidence suggests that defibrotide restores the thrombotic-fibrinolytic balance by promoting endothelial cell−mediated activity of fibrinolytic enzymes, including profibrinolytic and thrombolytic pathways [5]. However, the mechanism of action of defibrotide has not been fully elucidated and is an area of continued study.

Defibrotide is approved to treat hepatic VOD/SOS with renal or pulmonary dysfunction post-HCT in adult and pediatric patients in the United States [9] and to treat severe hepatic VOD/SOS post-HCT in adult and pediatric patients aged >1 month in the European Union [10]. The recommended dosage is 6.25 mg/kg every 6 hours (25 mg/kg/day) for a minimum of 21 days, continued until resolution of signs and symptoms of VOD/SOS (or up to a maximum of 60 days in the United States) or severe VOD/SOS (in the European Union) [9,10]. The median duration of treatment in studies of defibrotide in patients with VOD/SOS ranged from 19.0 days to 21.5 days [11–13]. It is of clinical interest to evaluate the time required for patients to achieve a complete response (CR) to defibrotide treatment, defined as total serum bilirubin <2 mg/dL with the resolution of VOD/SOS-related MOD (in patients with MOD), and to explore the relationship between CR and outcomes.

The objective of this post hoc analysis of defibrotide studies was to evaluate the time needed for patients with post-HCT VOD/SOS to achieve a CR.

METHODS

This study analyzed data from 3 studies: an expanded access study (T-IND; ClinicalTrials.gov identifier NCT00628498; n = 1000) [13], a phase 2 randomized dose-finding study (NCT00003966; n = 74 patients who received 25 mg/kg/day) [11], and a phase 3 historically controlled study (NCT00358501; n = 102) [12]. The methodologies of these studies have been described in detail previously [11–13]. Data were included for patients who received ≥1 dose of defibrotide 25 mg/kg/day.

For the T-IND, the time to treatment discontinuation due to a CR (ie, duration of defibrotide treatment in those who discontinued therapy due to CR) was analyzed as a surrogate for the time to CR after start of defibrotide treatment, because the time to CR was not formally recorded. Data from patients who discontinued for reasons other than a CR were not included in this analysis. Complete response and safety data were pooled from the phase 2 and 3 studies of defibrotide (25 mg/kg/day) in patients with post-HCT VOD/SOS and MOD [11,12]. Given the differences in recording CR among the studies, data from the T-IND were not pooled with data from the phase 2 and 3 studies. For the phase 2 and 3 studies, VOD/SOS was diagnosed using the Baltimore criteria (which require hyperbilirubinemia) or biopsy specimen analysis. The T-IND protocol originally required diagnosis of VOD/SOS according to the Baltimore criteria or biopsy, but the protocol was later amended to also include patients diagnosed using the modified Seattle criteria (which do not require hyperbilirubinemia). In addition, initial enrollment criteria for the T-IND included patients with a diagnosis of MOD up to day +45 post-HCT; following the end of enrollment in the phase 3 study, the requirement for MOD by day +45 was removed from the T-IND.

For all studies, CR was defined as total serum bilirubin <2 mg/dL with the resolution of VOD/SOS-related MOD (in patients with MOD). MOD was defined by renal and/or pulmonary dysfunction; the phase 2 study also considered central nervous system dysfunction for a designation of MOD. Definitions of renal and pulmonary dysfunction were similar in the T-IND and phase 3 studies but slightly different in the phase 2 study

(Table 1) [11–13]. Broadly, renal dysfunction was defined as creatinine ≥2 to 3 times the level at admission for conditioning, creatinine clearance or estimated glomerular filtration rate ≤40% to 50% the level at admission, or dialysis dependence. Pulmonary dysfunction was defined as oxygen saturation ≤90% on room air and/or positive-pressure ventilation/ventilator dependence or oxygen supplementation/ventilator dependence. In the phase 2 study, MOD was also defined by central nervous system dysfunction, which included confusion, lethargy, and/or delirium not attributed to another cause.

RESULTS

Patients

Baseline demographic and clinical characteristics of patients with VOD/SOS post-HCT who were enrolled in the T-IND (n = 1000) and the pooled phase 2 and 3 studies (n = 176) are presented in Table 2. The T-IND included patients with MOD (n = 512; 51%) and without MOD (n = 488; 49%); however, the phase 2 and 3 studies included only patients with VOD/SOS with MOD.

Time to Discontinuation due to a CR in the T-IND

Overall, 392 patients discontinued treatment due to a CR; however, 2 patients were not included in the time to CR analysis because of missing data. Among the 390 patients analyzed for time to CR, the median time to discontinuation due to a CR was 22.0 days (range, 2 to 64 days). Although 101 patients (26%) discontinued due to a CR before day +21, large proportions of patients discontinued due to a CR on day +21 (n = 54; 14%) and day +22 (n = 123; 32%). Discontinuation due to a CR occurred beyond 21 days in 235 patients (60%) and beyond 28 days in 57 patients (15%) (Figure 1). There were no notable differences between the baseline demographic and clinical characteristics of patients who discontinued due to a CR by day +21 and those who did so after day +21 (Table 2).

Time to CR in the Pooled Phase 2 and 3 Studies

In the pooled phase 2 and 3 studies, 60 of 176 patients (34%) achieved a CR (n = 34 and n = 26, respectively). The median time to CR was 24.5 days (range, 7 to 123 days). A CR was achieved beyond 21 days in 32 patients (53%) and beyond 28 days in 24 patients (40%) (Figure 2). The demographic and clinical characteristics were similar in patients who achieved a CR by day +21 and those who did so after day +21, except that those patients achieving a CR by day +21 tended to be younger than those achieving a CR after day +21 (Table 2).

Survival by CR Status

In the T-IND, the Kaplan-Meier–estimated day +100 survival rate was 92.5% (95% confidence interval [CI], 89.3% to 94.8%) in patients who discontinued defibrotide due to a CR (n = 392) and 37.3% (95% CI, 33.4% to 41.2%) in patients who did not (n = 608). The corresponding median overall survival in the 2 groups was 796 days (95% CI, 164 days to not reached) versus 68 days (95% CI, 63 to 76 days). In the pooled phase 2 and 3 studies, the Kaplan-Meier–estimated day +100 survival rate was 90% (95% CI, 79% to 95%) in patients who achieved a CR (n = 60) and 15% (95% CI, 9% to 22%) in patients who did not

achieve a CR (n = 116). The median overall survival in these 2 groups was 1393 days (95% CI, 458 days to not reached) and 44 days (95% CI, 37 to 53 days), respectively.

Safety

In the T-IND, 185 of 390 patients (47%) who discontinued due to a CR experienced a treatment-emergent adverse event (TEAE); 31 of these 390 patients (7.9%) had TEAEs considered treatment-related (Table 3). Serious TEAEs occurred in 83 patients (21%) who discontinued due to a CR, and TEAEs leading to death occurred in 16 patients (4.1%). In the pooled phase 2 and 3 studies, 55 of 60 patients (92%) who achieved a CR experienced a TEAE, including 14 (23%) with TEAEs considered treatment-related (Table 3). Serious TEAEs were reported in 24 patients (40%) who achieved a CR, and TEAEs leading to death occurred in 8 patients (13%). The most common (>5% of patients) individual serious TEAEs are listed in Table 3. In general, in both the T-IND and pooled phase 2 and 3 studies, no clinically meaningful differences were observed between the safety profiles of patients who achieved a CR (or discontinued defibrotide due to a CR) and received defibrotide for ≤21 days and those who received defibrotide for >21 days (Table 3).

DISCUSSION

Among the patients in this analysis with post-HCT VOD/SOS who discontinued defibrotide treatment due to a CR (T-IND) or who reached a CR after defibrotide treatment (pooled phase 2 and 3 studies), more than one-half required continuation of treatment beyond 21 days to achieve a CR (T-IND: 60%; phase 2/3: 53%). In addition, a notable proportion required treatment beyond 28 days to achieve a CR (T-IND: 15%; phase 2/3: 40%). A lower proportion of patients in the T-IND required treatment beyond 28 days compared with the pooled phase 2 and 3 studies; this may be due to the inclusion of patients without MOD (and thus with less severe VOD/SOS) in the T-IND versus the pooled phase 2 and 3 studies. This idea is supported by the higher survival rate in the T-IND compared with the phase 2 and 3 studies. As reported previously, in the T-IND, the Kaplan-Meier−estimated day +100 survival rate was 59% (95% CI, 56% to 62%) in defibrotide-treated post-HCT VOD/SOS patients, including 50% in patients with MOD and 69% in those without MOD [13]. Day +100 survival in VOD/SOS patients treated with 25 mg/kg/day in the phase 2 study was 44% (95% CI, 33% to 55%) [11], and day +100 survival in VOD/SOS patients in the phase 3 study was 38% (95% CI, 28% to 47%) [12].

The importance of achieving a CR is demonstrated by the observation that patients whose VOD resolved (or who had a proxy for resolution) had a substantial survival benefit over those whose disease remained unresolved after defibrotide treatment. In both analyses, ≥90% of patients who achieved a CR (or proxy for CR) were still alive at 100 days post-HCT, compared with <40% of those patients who did not. These data strongly support continuing defibrotide treatment until resolution of the signs and symptoms of VOD/SOS.

Evidence from several studies also suggests that patient outcomes may be improved with earlier initiation of defibrotide treatment. In a retrospective study of pediatric patients with post-HCT VOD/SOS treated with defibrotide (n = 45), patients who achieved a CR had a shorter average number of days to defibrotide initiation [14]. In the T-IND, day +100

survival was higher with earlier versus later initiation of defibrotide treatment in patients with post-HCT VOD/SOS with or without MOD [13].

Adverse event reporting was consistent with the known safety profile for defibrotide and with what would be expected in the critically ill patient population evaluated in this analysis, as observed from historical controls [12]. This analysis showed a higher proportion of TEAEs and serious TEAEs in patients who achieved a CR in the pooled phase 2 and 3 studies (92% and 40%, respectively) than in patients who discontinued due to a CR in the T-IND (47% and 21%, respectively). This difference was likely due to the higher proportion of patients with more advanced disease (all patients had MOD) in the phase 2 and 3 studies. The proportion of TEAEs in patients who discontinued due to a CR in the T-IND (47%) was lower than that observed in the overall T-IND population (71%) [13]; however, in the pooled phase 2 and 3 studies, the proportion of patients who achieved a CR and who experienced TEAEs (92%) was similar to the 97% and 99% reported in the overall phase 2 and 3 study populations, respectively [11,12]. Notably, there was no marked difference in safety profile between patients who achieved a CR (or discontinued due to a CR) and had a duration of defibrotide treatment ≤21 days and those with a longer duration of treatment.

Strengths of this analysis included the large number of patients; in particular, the T-IND is the largest prospective analysis of defibrotide treatment of patients with post-HCT VOD/SOS reported to date [13]. The study population comprised a diverse patient population with various primary diseases and HCT types, and included patients with MOD and patients without MOD. Data from the T-IND also provide a real-world perspective on time to CR. Limitations of the analysis include the varying definitions of MOD across studies and the use of a surrogate endpoint for time to CR in the T-IND. In addition, this study did not examine factors associated with a CR beyond 21 days or any effect of treatment duration on outcomes. Finally, a minimum treatment period of 21 days was recommended in the T-IND and phase 3 study protocols (minimum of 14 days in the phase 2 study), which likely influenced the duration of treatment. Of note, 13% of patients in the T-IND and 25% of those in the phase 2 and 3 studies had achieved a CR (or discontinued due to a CR, in the T-IND) by day +14.

In conclusion, this analysis highlights the importance of administering defibrotide therapy until the signs and symptoms of VOD/SOS have resolved (or to a maximum of 60 days in the United States), as currently indicated in the approved product labels, and continuing defibrotide beyond the recommended minimum of 21 days if necessary [9,10]. There were no new safety signals identified in this analysis.

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REFERENCES

1. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 2010;16:157–168. [PubMed: 19766729]
2. Eissner G, Multhoff G, Gerbitz A, et al. Fludarabine induces apoptosis, activation, and allogenicity in human endothelial and epithelial cells: protective effect of defibrotide. Blood 2002;100:334–340. [PubMed: 12070045]
3. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. Bone Marrow Transplant 2011;46:1495–1502. [PubMed: 21460864]
4. Carreras E. Early complications after HSCT. In: Carreras E, Gluckman E, Masszi T, eds. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies 6th ed. Paris: European School of Haematology; 2012:177–195.
5. Richardson PG, Corbacioglu S, Ho VT, et al. Drug safety evaluation of defibrotide. Expert Opin Drug Saf 2013;12:123–136. [PubMed: 23228043]
6. Palmer KJ, Goa KL. Defibrotide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in vascular disorders. Drugs 1993;45:259–294. [PubMed: 7681375]
7. Kornblum N, Ayyanar K, Benimetskaya L, Richardson P, Iacobelli M, Stein CA. Defibrotide, a polydisperse mixture of single-stranded phosphodiester oligonucleotides with lifesaving activity in severe hepatic veno-occlusive disease: clinical outcomes and potential mechanisms of action. Oligonucleotides 2006;16:105–114. [PubMed: 16584299]
8. Pescador R, Capuzzi L, Mantovani M, Fulgenzi A, Ferrero ME. Defibrotide: properties and clinical use of an old/new drug. Vascul Pharmacol 2013;59:1–10. [PubMed: 23680861]
9. Jazz Pharmaceuticals, Inc. Defitelio (defibrotide sodium) injection [packet insert] Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2016.
10. Jazz Pharmaceuticals, Inc. Defitelio. Summary of product characteristics Available at: https://pp.jazzpharma.com/pi/defitelio.en.SPC.pdf. Accessed April 2, 2019.
11. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant 2010;16:1005–1017. [PubMed: 20167278]
12. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood 2016;127:1656–1665. [PubMed: 26825712]
13. Kernan NA, Grupp S, Smith AR, et al. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Br J Haematol 2018;181:816–827. [PubMed: 29767845]
14. Corbacioglu S, Greil J, Peters C, et al. Defibrotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multicentre study demonstrates therapeutic efficacy upon early intervention. Bone Marrow Transplant 2004;33:189–195. [PubMed: 14661036]

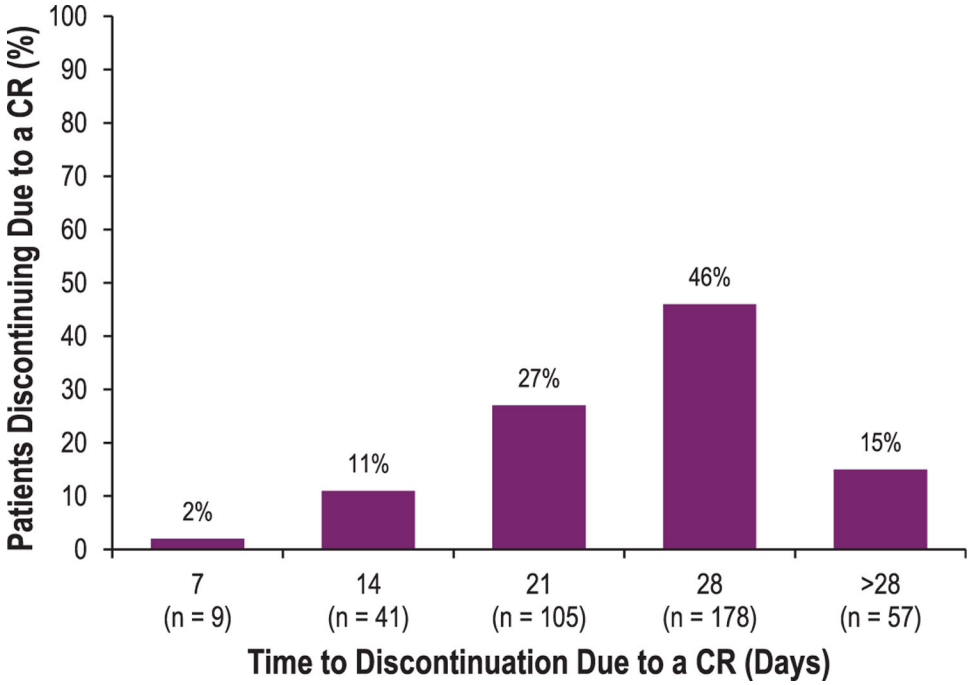

Figure 1.

Time to treatment discontinuation due to a CR in the T-IND grouped by week. Discontinuation due to a CR served as a surrogate for time to CR in the T-IND.

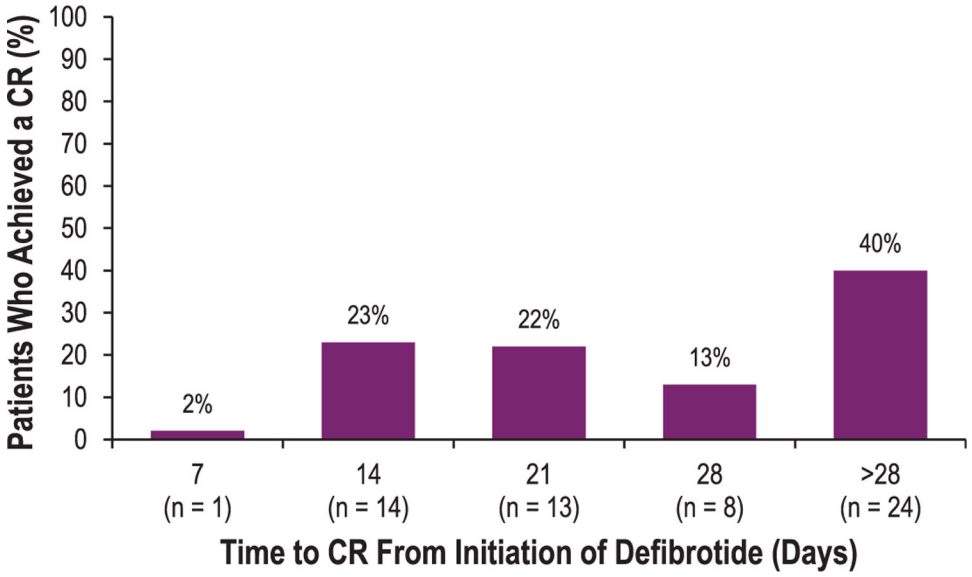

Figure 2.
Time to CR in the pooled phase 2 and 3 studies grouped by week.

Table 1

Definitions of MOD

Study	Renal Dysfunction	Pulmonary Dysfunction
T-IND	Creatinine ≥3 × baseline ***or*** CrCl or eGFR ≤40% of baseline ***or*** dialysis dependence	Oxygen saturation ≤90% on room air ***or*** oxygen supplementation/ventilator dependence
Phase 2 *	Creatinine ≥2 × baseline ***or*** CrCl or eGFR ≤50% of baseline ***or*** dialysis dependence	Oxygen saturation ≤90% on room air ***and/or*** positive-pressure ventilation/ventilator dependence
Phase 3	Creatinine ≥3 × baseline ***or*** CrCl or eGFR ≤40% of baseline ***or*** dialysis dependence	Oxygen saturation ≤90% on room air ***or*** oxygen supplementation/ventilator dependence

CrCl indicates creatinine clearance; eGFR, estimated glomerular filtration rate.

* In the phase 2 study, MOD also was defined by central nervous system dysfunction, which included confusion, lethargy, and/or delirium not attributed to another cause.

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Table 2

Baseline Demographic and Clinical Characteristics

Characteristic	T-IND				Pooled Phase 2 and 3 Studies			
	Overall (n = 1000)	**Patients Who Discontinued due to a CR (n = 392)**	**Patients Who Discontinued due to a CR at ≤21 d (n = 239)**	**Patients Who Discontinued due to a CR at >21 d (n = 152)**	**Overall (n = 176)**	**Patients Who Achieved a CR (n = 60)**	**Patients Who Achieved a CR at ≤21 d (n = 28)**	**Patients Who Achieved a CR at >21 d (n = 32)**
Age at HCT, yr, median (range)	14 (0–77)	7 (0–71)	7 (0–71)	6 (0–70)	25 (0–72)	17 (1–64)	13 (1–58)	23 (1–64)
Age category, n (%)								
≤16 yr	570 (57)	260 (66)	160 (67)	100 (66)	65 (37)	30 (50)	18 (64)	12 (38)
>16 yr	430 (43)	132 (34)	79 (33)	52 (34)	111 (63)	30 (50)	10 (36)	20 (63)
Sex, n (%)								
Male	568 (57)	226 (58)	130 (54)	96 (63)	105 (60)	36 (60)	19 (68)	17 (53)
Female	432 (43)	166 (42)	109 (46)	56 (37)	71 (40)	24 (40)	9 (32)	15 (47)
HCT type, n (%) *								
Allogeneic HCT	843 (84)	296 (76)	178 (75)	117 (77)	156 (89)	46 (77)	21 (75)	25 (78)
Autologous HCT	155 (16)	95 (24)	60 (25)	35 (23)	20 (11)	14 (23)	7 (25)	7 (22)
Most common (>10%) primary disease, n (%)								
Acute lymphoblastic leukemia	201 (20)	58 (15)	33 (14)	25 (16)	27 (15)	7 (12)	4 (14)	3 (9)
Acute myelogenous leukemia	261 (26)	93 (24)	53 (22)	40 (26)	47 (27)	13 (22)	4 (14)	9 (28)
Myelodysplastic syndrome	52 (5)	19 (5)	15 (6)	4 (3)	17 (10)	7 (12)	3 (11)	4 (13)
Neuroblastoma	105 (11)	72 (18)	43 (18)	29 (19)	8 (5)	7 (12)	4 (14)	3 (9)
Most common (>15%) GVHD prophylaxis, n (%)								
Cyclosporine	282 (28)	107 (27)	61 (26)	45 (30)	76 (43)	24 (40)	11 (39)	13 (41)
Methotrexate	332 (33)	128 (33)	83 (35)	45 (30)	85 (48)	29 (48)	13 (46)	16 (50)
Tacrolimus	483 (48)	161 (41)	97 (41)	64 (42)	50 (28)	11 (18)	5 (18)	6 (19)

* HCT type was unknown in 1 patient in the T-IND who discontinued due to a CR at ≤21 days.

Table 3

Summary of TEAEs in Patients Who Discontinued Due to a CR (T-IND) or Who Achieved a CR (Pooled Phase 2 and 3 Studies) by Duration of Defibrotide Treatment

	T-IND			Pooled Phase 2 and 3 Studies		
TEAEs, n (%)	**Patients Who Discontinued due to a CR (n = 390)**	**Patients Who Discontinued due to a CR and Received Defibrotide for ≤21 d (n = 155)**	**Patients Who Discontinued due to a CR and Received Defibrotide for >21 d (n = 235)**	**Patients Who Achieved a CR (n = 60)**	**Patients Who Achieved a CR and Received Defibrotide for ≤21 d (n = 23)**	**Patients Who Achieved a CR and Received Defibrotide for >21 d (n = 37)**
Any TEAE	185 (47)	72 (47)	113 (48)	55 (92)	20 (87)	35 (95)
Any treatment-related TEAE *	31 (7.9)	10 (6.5)	21 (8.9)	14 (23)	7 (30)	7 (19)
Serious TEAEs	83 (21)	29 (19)	54 (23)	24 (40)	10 (44)	14 (38)
Most common (>5% of patients) serious TEAEs						
Gastrointestinal hemorrhage	2 (.5)	1 (.6)	1 (.4)	2 (3.3)	2 (8.7)	0
Mental status changes	0	0	0	2 (3.3)	0	2 (5.4)
Multiorgan failure	2 (.5)	1 (.6)	1 (.4)	2 (3.3)	0	2 (5.4)
Pulmonary hemorrhage	3 (.8)	1 (.6)	2 (.9)	0	0	0
Respiratory failure	10 (2.6)	3 (1.9)	7 (3.0)	2 (3.3)	0	2 (5.4)
TEAEs leading to death	16 (4.1)	6 (3.9)	10 (4.3)	8 (13)	3 (13)	5 (14)

* Treatment-related TEAEs are events with a relationship to study medication of definitely, probably, or possibly related.