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Defibrotide for the Treatment of Hepatic Veno-Occlusive Disease: Final Results From the International Compassionate-Use Program

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A B S T R A C T

Hepatic veno-occlusive disease, also called *sinusoidal obstruction syndrome* (VOD/SOS), is an unpredictable and potentially fatal complication of hematopoietic cell transplantation (HCT) or nontransplantation-associated chemotherapy/radiotherapy. In cases of severe hepatic VOD/SOS, typically defined by associated multiorgan failure (MOF, also known as *multiorgan dysfunction*), mortality exceeds 80%. Preclinical and early clinical data have provided a rationale for defibrotide treatment in hepatic VOD/SOS. Based on this evidence and in recognition of the dismal prognosis for these patients, defibrotide was made available through an international multicenter compassionate-use program conducted from December 1998 to March 2009. Physicians participating in the program voluntarily provided demographic and outcome data for patients given defibrotide. Efficacy and safety analyses were performed using the data received for 710 treated patients. Defibrotide was given at 10, 25, 40, 60, or 80 mg/kg/day for a median of 15 days (range, 1 to 119 days). By Kaplan-Meier analysis, the estimated overall day +100 survival was 54% (58% in the 25 mg/kg/day dose group). Adverse events (AEs) were reported in 53% of patients. The most common AEs were MOF, progression of hepatic VOD/SOS, sepsis, and graft-versus-host disease, which were consistent with the AEs expected for this patient population. No clinically meaningful trends in AEs were identified by gender, age, or dose group. Safety and efficacy results

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were consistent with prior studies of defibrotide in hepatic VOD/SOS, and subgroup analyses lend support to the use of the 25 mg/kg/day dose.

INTRODUCTION

Hepatic veno-occlusive disease, also called *sinusoidal obstruction syndrome* (VOD/SOS), is an unpredictable, potentially fatal complication of hematopoietic cell transplantation (HCT) or of nontransplantation-associated chemotherapy/radiotherapy [1-4]. In severe hepatic VOD/SOS, typically defined by the presence of multiorgan failure (MOF, also known as *multiorgan dysfunction*), the mortality rate may exceed 80% [3,5]. *MOF* is defined as VOD/SOS along with dysfunction in another major organ system, such as the renal, pulmonary, or central nervous system (CNS) [1-4]. Clinically, hepatic VOD/SOS is diagnosed using Baltimore [6] or modified Seattle [7] criteria in the absence of other disorders that can cause similar signs and symptoms.

The pathophysiologic cascade in hepatic VOD/SOS involves primary injury to sinusoidal endothelial cells and stellate cell activation [3,8,9]. This is associated with increases in von Willebrand factor and plasminogen activator inhibitor type 1, along with decreases in soluble thrombomodulin and tissue plasminogen activator (tPA) [10,11]. The sinusoidal lumen narrows because of the deposition of fibrin and cell debris into the space of Disse and intrasinusoidal coagulation, which causes progressive ischemia, hepatocyte dysfunction, and hepatocellular necrosis [3,8,9]. This narrowing also can lead to postsinusoidal portal hypertension, hepatorenal syndrome, MOF, and death [3,8,9].

The reported incidence of hepatic VOD/SOS varies, in part because of the use of different diagnostic criteria, conditioning regimens, patient populations, types of transplantation, and prior therapies. One analysis of data from 135 studies with a total of 24,920 HCT patients treated between 1979 and 2007 disclosed an overall mean incidence of VOD/SOS of 13.7% [5]. Severe VOD/SOS may develop in approximately 30% to 50% of these cases, with some reports as high as 77% [5,12]. The analysis of 135 studies also found that the mean incidence of VOD/SOS had increased from 11.5% between 1979 and 1994 to 14.6% between 1994 and 2007, an increase that may in part be due to changes in HCT populations (eg, extension of age limits) [5]. Interestingly, the overall increase seen across studies seems to have occurred despite the reduction in incidence observed at certain single centers, such as a large, expert center [12], which reported a decreased incidence (11.5% using Baltimore criteria from 1985 to 1996 compared with 6.5% from 1997 to 2008). In addition, despite the use of reduced-intensity conditioning, incidence of hepatic VOD/SOS was reported to be 2% to 9% in populations receiving allogeneic HCT [12,13].

Because of the dismal outcomes in hepatic VOD/SOS with MOF, effective treatments are clearly needed. Defibrotide is approved in the European Union for the treatment of severe hepatic VOD/SOS in adults and children ages >1 month who have undergone HCT and was recently approved by the US Food and Drug Administration for the treatment of adult and pediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction after HCT [14]. In vitro testing of defibrotide demonstrated increased tPA and thrombomodulin and decreased von Willebrand factor and plasminogen activator inhibitor type 1 expression, thereby reducing endothelial cell activation, protecting endothelial cells from further damage, and augmenting endothelial cell–mediated fibrinolysis [15-18].

Defibrotide was initially tested in 19 patients with hepatic VOD/SOS and MOF in 1998; those patients showed a promising day +100 survival rate of 32% [19]. After the publication of those early findings, and in the absence of other effective therapies, defibrotide was made available to patients with hepatic VOD/SOS through an international compassionate-use program (CUP), which was in effect from December 1998 to March 2009. Subsequent to the initiation of the CUP, additional studies showed consistent and promising results for defibrotide treatment of hepatic VOD/SOS with MOF [20-25]. Here, we report the final safety and efficacy results for patients with hepatic VOD/SOS who received defibrotide through the CUP.

METHODS

Study Design

This open-label multicenter program provided defibrotide on a compassionate-use basis or via single-patient emergency investigational new drug in response to requests from physicians for patients who developed hepatic VOD/SOS either after HCT or after nontransplantation-associated chemotherapy/radiotherapy treatment. The CUP was conducted at multiple centers globally (Supplementary Table S1).

There was no official protocol for the CUP; physicians requesting defibrotide through the program were asked to complete an eligibility screening form and provide detailed demographic and outcome information on each patient. Baseline data included age, gender, body weight, primary diagnosis/disease, date of hepatic VOD/SOS diagnosis, presence of MOF, hepatitis B surface antigen and hepatitis C antibody positivity, and aspartate transaminase and alanine transaminase levels, as well as any hepatic VOD/SOS prophylaxis/treatment that had been given (eg, tPA, low-molecular-weight heparin, heparin, ursodiol, prostaglandin E). For patients who underwent HCT, details about the transplantation (type of donor/graft), date of transplantation, conditioning regimen, and graft-versus-host disease (GVHD) prophylaxis (if any) were collected. For patients who did not undergo HCT, information about the nontransplantation-associated chemotherapy/radiotherapy regimen and related start date and the diagnosis date were collected. Requested defibrotide treatment and outcomes data included dosing information, adverse events (AEs), and survival.

Treating physicians were responsible for requesting use of defibrotide as an emergency-use investigational drug from the relevant authority (eg, from the US Food and Drug Administration), securing approval from the appropriate institutional review board, and ensuring that the patient granted informed consent.

Eligibility Criteria

Inclusion criteria

Patients were required to meet the Baltimore criteria [6] or modified Seattle criteria [7] for hepatic VOD/SOS (Table 1). For this study, the Seattle criteria were further modified to use a >5%, rather than >2%, weight gain threshold [4]. Patients were also eligible if they did not meet 2 of the Seattle criteria but, per the report of the treating physician, had hemodynamic (eg, hepatic venous pressure gradient), ultrasound, or histologic evidence of hepatic VOD/SOS.

In the CUP, *severe VOD/SOS* was defined as VOD/SOS with MOF or by ≥30% predicted risk of retrospectively assessed severe hepatic VOD/SOS using the Bearman model [26]. *MOF* was defined by renal dysfunction (at least a doubling of creatinine levels from baseline or reduced creatinine clearance from baseline with or without need for dialysis), respiratory dysfunction (the need for oxygen supplementation with or without assisted ventilation), or CNS dysfunction (ie, cerebral failure).

Table 1
Hepatic VOD/SOS Criteria

Baltimore Criteria [6]	Modified Seattle Criteria [7]
Within 21 days of HCT: Bilirubin >2 mg/dL *plus* 2 or more of the following: Hepatomegaly Ascites Weight gain ≥5% of body weight	Within 20 days after HCT, 2 or more of the following: Bilirubin ≥2 mg/dL Hepatomegaly or upper right abdominal quadrant pain Ascites and/or weight gain >2% of body weight*

* In this study, weight gain was further modified to >5% [4].

Potential factors for exclusion

Physicians requesting defibrotide were asked, at their discretion, to review patients for the following as potential reasons for not initiating treatment with defibrotide: hemodynamic instability (regardless of association with hepatic VOD/SOS and MOF), severe coagulopathy requiring replacement therapy, GVHD grades 3 or 4, the need for assisted ventilation (not associated with hepatic VOD/SOS and MOF), loss of consciousness, or receipt of another investigational drug.

Treatment

When the CUP was initiated, the recommended starting dose of defibrotide was 10 mg/kg/day, administered intravenously in 4 divided doses over 2 hours each, with titration up to a recommended maximum of 60 mg/kg/day based on tolerability and response. However, based on the 2004 presentation of results from a phase 2 study from the United States [27], the recommended dose of defibrotide was amended to a fixed 25 mg/kg/day, in 4 divided doses, each administered over 2 hours. Recommended treatment duration was a minimum of 14 days (with the final decision on duration at discretion of treating physician), and therapy could be continued until the patient had a complete response or was discharged from the hospital.

Key Outcomes Measures

Physicians reported information to regulatory authorities in the context of their own emergency investigative new drug procedures. Study sites voluntarily reported data on outcome forms without on-site monitoring or query generation or resolution. Treating physicians were asked to provide outcome data that included survival status at day +100 after HCT or after nontransplantation-associated chemotherapy/radiotherapy. Exploratory efficacy analyses on day +100 survival were conducted for pediatric and adult patients and subgroups based on dose received, presence of MOF, and Bearman status (if available), and for the subgroup of patients developing VOD/SOS after nontransplantation-associated chemotherapy.

Because data were reported by study sites without on-site monitoring or query generation or resolution, all AEs were considered to be treatment-emergent, regardless of their temporal relationship to dosing. Exploratory subgroup analyses were conducted to assess AEs by dose, age, and gender.

Statistical Analysis

Baseline patient demographic and clinical characteristics, exposure to defibrotide, survival, and AE data (ie, overall, serious, leading to death, leading to discontinuation) were analyzed for all patients with outcome data who received at least 1 documented dose of defibrotide. All continuous variables were summarized using descriptive statistics; categorical variables were presented as frequencies and percentages for patients with available data. Survival was estimated by Kaplan-Meier analysis with 95% confidence intervals (CIs). Patients who were alive but were lost to follow-up before day +100 were censored for survival analyses.

RESULTS

Patients

A total of 1129 patients from 311 sites were provided with defibrotide. Of these, outcome forms were returned for 710 (63%) who received at least 1 documented dose of defibrotide. These 710 patients are the subject of the present analysis (Tables 2 and 3). Most of these patients were ≥18 years (57%) and acute leukemias were the most common primary diseases (44%) (Table 2). The large majority of patients received HCT (primarily allogeneic, 71%), and in this HCT cohort, cyclophosphamide and busulfan were the most common conditioning regimens (>40%), whereas cyclosporine and methotrexate were the most common prophylactic treatments for GVHD (>40%). Hyperbilirubinemia and weight gain were each observed in >80% of patients. Because the CUP depended on voluntary reporting, not all returned forms included all requested data.

Table 2
Summary of Demographic and Disease Characteristics

Variable	Analysis Population (N = 710)
Gender	
Male	433 (61)
Female	277 (39)
Age at time of HCT or nontransplantation-associated chemotherapy/radiotherapy treatment, yr	
Mean (SD)	26.7 (19.8)
Median (range)	25.0 (.2-70.0)
Age	
<18 yr	303 (43)
≥18 yr	407 (57)
Primary disease*	
Acute myelogenous leukemia	177 (26)
Acute lymphoblastic leukemia	120 (18)
Myelodysplastic syndrome	46 (7)
Non-Hodgkin lymphoma	43 (6)
Chronic myelogeneous leukemia	43 (6)
Neuroblastoma	32 (5)
Thalassemia	22 (3)
Hodgkin lymphoma	15 (2)
Severe combined immunodeficiency	14 (2)

Data presented are n (%), unless otherwise indicated.

* Conditions occurring in ≥2% of patients; data were missing for 25 patients, and percentages were calculated based on 685 patients with data. Primary diseases in 1% to 2% of patients were severe combined immunodeficiency (1.9%), Ewing's sarcoma (1.7%), multiple myeloma (1.6%), hemophagocytic lymphohistiocytosis (1.3%), medulloblastoma (1.2%), lymphoma not otherwise specified (1.1%), and chronic lymphocytic leukemia (1.1%).

Exposure

The median daily dose of defibrotide was 25 (range, 10 to 80) mg/kg/day, given for a median of 15 days (range, 1 to 119). Forty-three percent (272) of patients who had available dosing data received 25 mg/kg/day (Table 4), which is the approved recommended dose in the European Union and in the United States.

Premature treatment discontinuation (before the minimum treatment period) occurred in 197 (28%) patients. The reasons for discontinuation included AEs (9%), clinical improvement/resolution (4%), failure/disease progression (3%), death (3%), consent withdrawn (<1%), other (1%), and reason not reported (9%).

Survival

Across all doses, the Kaplan-Meier estimate of survival at day +100 after HCT or nontransplantation-associated chemotherapy/radiotherapy treatment was 54% (95% CI, 50.2 to 58.0) (Figure 1) for the 701 patients with available data. Of these patients with data, 92 (13%) were alive but lost to follow-up before day +100 (reasons for loss to follow-up were not collected by the treating physicians), and their data were censored in the analysis.

Kaplan-Meier estimates of survival at day +100 were assessed by defibrotide dose group (Figure 2). The day +100 survival estimates by dosage ranged from 43% to 61%. The survival estimate for patients receiving 25 mg/kg/day, the approved recommended dose in the European Union and

Table 3
Initial Treatment and Hepatic VOD/SOS and MOF Characteristics

Characteristic	Analysis Population (N = 710)
Transplantation*	628 (89)
Allograft	499 (71)
Autograft	112 (16)
Other/not specified	17 (2)
Nontransplantation*: chemotherapy/radiotherapy treatment†	79 (11)
Conditioning regimen (>10% of patients)	
Cyclophosphamide	369 (52.0)
Busulfan	300 (42.3)
Total body irradiation	209 (29.4)
Antithymocyte globulin	141 (19.9)
Melphalan	134 (18.9)
Fludarabine	124 (17.5)
GVHD prophylaxis	
Cyclosporine	403 (57)
Methotrexate	287 (40)
Antithymocyte globulin‡	105 (15)
Tacrolimus	71 (10)
Mycophenolate mofetil	61 (9)
Prednisone	58 (8)
Other§	22 (3)
Median time to hepatic VOD/SOS onset,‖ d	13
Hepatic VOD/SOS criteria met	
Bilirubin >2 mg/dL	623 (88)
Weight gain >5%	584 (82)
Hepatomegaly	548 (77)
Ascites	477 (67)
Right upper quadrant pain	455 (64)
Liver histology	22 (3)
Bearman criteria [26]¶	
Severe	337 (48)
Not severe	217 (31)
Not assessed	147 (21)
Missing	9
MOF	292 (41)
Renal#	229 (32)
Dialysis#	41 (6)
Respiratory#	162 (23)
Assisted/mechanical ventilation (associated with hepatic VOD/SOS)#	37 (5)
Cerebral#	37 (5)
Other**	4 (<1)
No MOF	418 (59)

Data presented are n (%), unless otherwise indicated.
* Transplantation status was missing for 3 patients, with percentages calculated based on patients with data only.
† The most common regimens (in >1% of patients) were vincristine, cytarabine, gemtuzumab ozogamicin, cyclophosphamide, thioguanine, etoposide, and actinomycin-B.
‡ Specified as GVHD prophylaxis only, 141 patients received antithymocyte globulin as conditioning therapy.
§ Includes T cell depletion, alemtuzumab, and rituximab.
‖ After HCT or start of nontransplantation-associated chemotherapy/radiotherapy treatment, data missing for 15 patients.
¶ Bearman criteria (≥30% risk of retrospectively assessed severe hepatic VOD/SOS) not assessed for all patients, percentages calculated for patients with data.
# This criterion meets the definition of MOF and severe hepatic VOD/SOS.
** Includes oxygen requirement and intermittent supplemental oxygen.

United States [14,28], was 58% (95% CI, 51.1 to 63.5) at day +100.

Day +100 survival was higher among the subgroups of pediatric patients (Figure 3), patients without MOF (Supplementary Figure S1), and in nontransplantation-associated chemotherapy/radiotherapy patients, compared with day +100 survival among the overall population (Table 5).

Table 4
Exposure to Defibrotide in Patients with Dosing Data

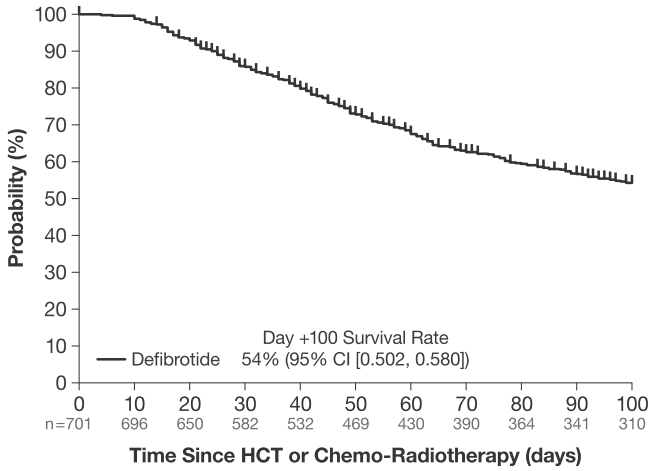
Dose (mg/kg/day)	Age <18 yr n = 267*	Age ≥18 yr n = 371*	Total Population N = 638†
10	22 (8)	63 (17)	85 (13)
25‡	131 (49)	141 (38)	272 (43)
40	78 (29)	148 (40)	226 (35)
60/80	36 (13)	19 (5)	55 (9)

Data presented are n (%), unless otherwise indicated.
* This number does not include 36 patients for whom dose was not reported.
† This number does not include the 72 total patients for whom dose was not reported.
‡ Approved recommended dose in the European Union and in the United States.

Safety

A total of 378 of 710 (53%) patients reported AEs. Details regarding relationship to defibrotide and severity were not available for the majority of the reported AEs; however, causes of death were frequently reported as AEs and were primarily due to progressive hepatic VOD/SOS with MOF. Therefore, the vast majority of serious adverse events (SAEs) included in tabulations were those leading to death, because, by definition, such events met the criteria of seriousness. The majority of AEs were serious. A total of 364 of 710 (51%) patients experienced an SAE and 350 of 710 (49%) patients had a fatal SAE. Withdrawals due to an AE (n = 63 [9%] patients) were mostly due to hemorrhage (n = 50 [7%] patients), with gastrointestinal disorders system organ class (SOC) being the most common (n = 22 [3%]). Of 85 (12%) patients with a reported AE consistent with hemorrhage, the most commonly affected SOCs were gastrointestinal disorders (n = 33 [5%]); respiratory, thoracic, and mediastinal disorders (n = 24 [3%]); vascular disorders (unspecified site, n = 15 [2%]); and nervous system disorders (n = 10 [1%]). Serious hemorrhagic AEs occurred in 55 (8%) patients and were fatal in 37 (5%) of these. The most common fatal hemorrhagic events by SOCs were respiratory, thoracic, and mediastinal disorders (n = 11 [2%]); gastrointestinal disorders (n = 9 [1%]); and nervous system disorders (n = 7 [1%]). Hypotension occurred in 2 (.3%) patients, both with MOF, and both events were fatal.

There were no clinically meaningful differences observed in overall incidence of AEs or AEs leading to discontinuation among the defibrotide doses (Table 6). A slight increase in the incidence of hemorrhagic events was reported with increasing doses, with rates of 11% (10 mg/kg/day group), 11% (25 mg/kg/day group), 14% (40 mg/kg/day group), and 15% (60/80 mg/kg/day group). Respiratory-tract hemorrhage was highest in the 60/80 mg/kg/day dose group (9%) versus in those on lower doses (<5% each), but gastrointestinal and CNS hemorrhages were similar across doses (4% to 6% and 0 to 2%, respectively). Rates of hemorrhage were similar in pediatric (13%) and adult (12%) patients. Gastrointestinal-tract hemorrhage was more common in adults (6%) than in pediatric patients (3%), and respiratory-tract hemorrhage was more common in pediatric patients (5%) than in adults (2%). The rate of hemorrhagic AEs in patients with VOD/SOS and MOF was slightly higher (14%) than in patients without MOF only (11%), and these were predominantly gastrointestinal (5% for each subgroup). There were no clinically meaningful trends identified with respect to AEs (ie, the overall incidence of AEs, SAEs, AEs leading to death, or discontinuations due to AEs) by gender or age.



Vertical lines signify censored data.
*Excludes 9 patients with missing HCT or nontransplantation–associated chemo-radiotherapy dates.
CI, confidence interval; HCT, hematopoietic cell transplantation.

Figure 1. Survival to day +100 (n = 701).*

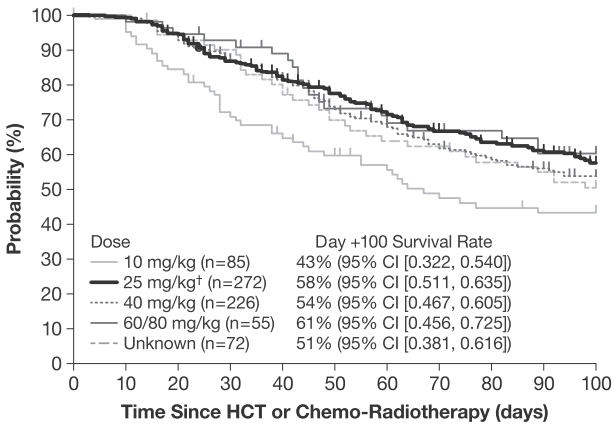
Consistent with the patient population under study, the most common AEs were MOF, progression of hepatic VOD/SOS, sepsis, and GVHD (Table 7).

DISCUSSION

This CUP provided access to defibrotide for patients with hepatic VOD/SOS with or without MOF after HCT or nontransplantation-associated chemotherapy/radiotherapy treatment. The day +100 survival and safety profiles in this study are notably consistent with those reported in other defibrotide studies [21,23,29].

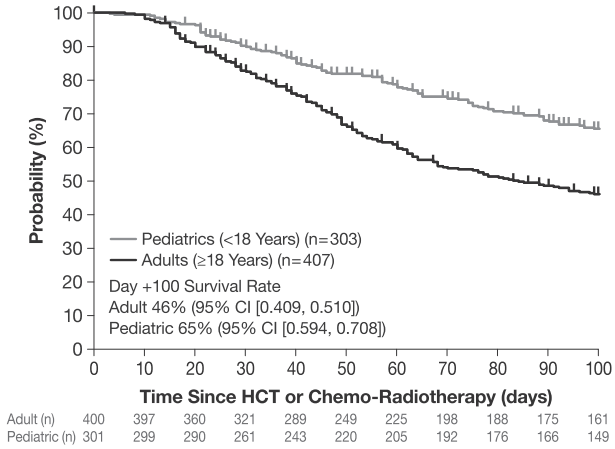
Consistent with the results of a phase 2 defibrotide dose-finding study presented in 2004 and published in 2010 [21] and also a phase 3 study for efficacy and safety [23], the current study supports usage of the 25 mg/kg/day dose of defibrotide (in 4 divided doses, each infused intravenously over 2 hours). That dose is now approved as the recommended dose in the European Union for the treatment of severe hepatic VOD/SOS in adults and in children ages >1 month who undergo HCT [28] and in the United States for the treatment of adult and pediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction after HCT [14].

The median duration of treatment in the CUP was 15 days. Evidence from other trials suggests there is a benefit of longer duration of treatment. In the phase 2 study [21], although the recommended minimum duration of dosing was 14 days, the actual median length of treatment was 19 days in the 25 mg/kg/day arm and 20 days in the 40 mg/kg/day arm. Based on the data from that study, the phase 3 study of defibrotide recommended that defibrotide be administered for a minimum of 21 days at a dose of 25 mg/kg/day (median duration of treatment: 21.5 days) [23]. The duration of therapy that was recommended in the phase 3 study was ≥21 days, which also was the median duration that was observed. This shared recommended duration and median value was similar to the observed difference between median time to diagnosis (13 days) and median time to onset of complete response (34.5 days; ie, 34.5 less 13 equals 21.5), as well as the median



Vertical lines signify censored data.
*Excludes 9 patients with missing HCT or nontransplantation–associated chemo-radiotherapy dates; †Approved recommended dose in the European Union and in the United States.
CI, confidence interval; HCT, hematopoietic cell transplantation.

Figure 2. Survival to day +100 by dose (n = 701).*



Vertical lines signify censored data.
*Excludes 9 patients with missing HCT or nontransplantation–associated chemo-radiotherapy dates.
CI, confidence interval; HCT, hematopoietic cell transplantation.

Figure 3. Survival at day +100 pediatric patients (n = 303) and adults (n = 407).*

Table 5
Day +100 Survival by Subgroup

Status	Alive, n (%) [95% CI]	Alive When Lost to Follow-Up, n (%) [95% CI]	Not Alive, n (%) [95% CI]	With Data Missing*, n	Kaplan-Meier Estimated Survival [95% CI]
Analysis population	310 (44)	92 (13)	299 (43)	9	.542
N = 710	[40.6-47.9]	[10.6-15.6]	[39.0-46.3]		[.502-0.580]
Pediatric (<18 yr)	149 (50)	58 (19)	94 (31)	2	.654
n = 303	[43.9-55.1]	[14.8-23.7]	[26.0-36.4]		[.594-0.708]
10 mg/kg/day (n = 22)	9 (41)	3 (14)	10 (45)	0	.511
	[20.4-61.5]	[–.07-28.0]	[24.6-66.3]		[.278-0.704]
25 mg/kg/day (n = 131)	68 (52)	28 (21)	35 (27)	0	.702
	[43.4-60.5]	[14.4-28.4]	[19.1-34.3]		[.609-0.777]
40 mg/kg/day (n = 78)	36 (47)	16 (21)	24 (32)	2	.653
	[36.3-58.4]	[12.0-30.1]	[21.3-41.9]		[.527-0.753]
60/80 mg/kg/day (n = 36)	19 (53)	8 (22)	9 (25)	0	.709
	[36.5-69.1]	[8.6-35.8]	[10.9-39.1]		[.513-0.838]
Dose not reported (n = 36)	17 (47)	3 (8)	16 (44)	0	.537
	[30.9-63.5]	[–.7-17.4]	[28.2-60.7]		[.359-0.686]
Adult (≥18 yr)	161 (40)	34 (9)	205 (51)	7	.461
n = 407	[35.5-45.0]	[5.8-11.2]	[46.4-56.1]		[.409-0.510]
10 mg/kg/day (n = 63)	22 (36)	4 (7)	35 (57)	2	.406
	[24.2-47.9]	[.4-12.7]	[45.2-69.6]		[.279-0.528]
25 mg/kg/day (n = 141)	54 (39)	15 (11)	70 (50)	2	.463
	[30.8-46.9]	[5.7-15.9]	[42.1-58.6]		[.375-0.547]
40 mg/kg/day (n = 148)	61 (42)	13 (9)	71 (49)	3	.483
	[34.1-50.0]	[4.4-13.6]	[40.9-57.0]		[.396-0.564]
60/80 mg/kg/day (n = 19)	8 (42)	0	11 (58)	0	.421
	[19.9-64.3]		[35.7-80.1]		[.204-0.625]
Dose not reported (n = 36)	16 (44)	2 (6)	18 (50)	0	.471
	[28.2-60.7]	[–1.9-13.0]	[33.7-66.3]		[.299-0.626]
Severity by MOF					
MOF (n = 292)	95 (33)	27 (9)	166 (58)	4	.397
	[27.6-38.4]	[6.0-12.7]	[52.0-63.3]		[.338-0.455]
No MOF (n = 418)	215 (52)	65 (16)	133 (32)	5	.647
	[47.3-56.8]	[12.2-19.2]	[27.7-36.7]		[.596-0.693]
Bearman criteria					
Severe (n = 337)	125 (38)	28 (8.5)	178 (54)	6	.438
	[32.6-42.9]	[5.5-11.4]	[48.5-59.1]		[.382-0.493]
Nonsevere (n = 217)	113 (52)	39 (18)	57 (37)	1	.669
	[45.7-59.0]	[12.9-23.2]	[29.4-44.6]		[.597-0.731]
Nontransplantation-associated chemotherapy/radiotherapy					
MOF (n = 38)	18 (51)	6 (17)	11 (31)	3	.675
	[35.5-67.3]	[5.2-29.1]	[16.7-46.2]		[.489-.806]
No MOF (n = 41)	22 (56)	8 (21)	9 (23)	2	.742
	[41.2-71.6]	[8.2-32.9]	[10.2-36.0]		[.560-.858]

* Patients with missing data not included in percentages.

Table 6
Summary of AEs by Dose of Defibrotide

Category of AE	Total Population (N = 710)	Dose (mg/kg/day)				
		10 (n = 85)	25 (n = 272)	40 (n = 226)	60/80 (n = 55)	Unknown (n = 72)
Any AE (≥1)	378 (53)	59 (69)	129 (47)	124 (55)	27 (49)	39 (54)
AE leading to death	350 (49)	56 (66)	120 (44)	113 (50)	24 (44)	37 (51)
SAE	364 (51)	58 (68)	123 (45)	119 (53)	26 (47)	38 (53)
AE leading to discontinuation	63 (9)	7 (8)	23 (8)	25 (11)	4 (7)	4 (6)
AEs of special interest						
Hemorrhage event	85 (12)	9 (11)	31 (11)	31 (14)	8 (15)	6 (8)
Hypotension event	2 (<1)	1 (1)	1 (<1)	0	0	0

Data presented are n (%), unless otherwise indicated.

length of treatment in the phase 2 dose-finding study [21,23]. Data from an ongoing expanded-access study enrolling patients with VOD/SOS with and without MOF after HCT or after nontransplantation-associated chemotherapy have similarly shown a 21-day median duration of treatment (analysis population) [29], which also was the recommended minimum duration of treatment in that study.

The Kaplan-Meier estimated survival rate of 40% in the CUP for the subgroup of patients with MOF (after HCT or after nontransplantation-associated chemotherapy/radiotherapy) is generally consistent with outcomes of other defibrotide studies in populations with MOF (after HCT), including the historically controlled phase 3 trial: the observed day +100 survival in post-HCT patients was 38% in the defibrotide group (n = 102) versus 25% in the historical control group (n = 32) [23]; the estimated between-group difference in survival was 23% (95.1% CI, 5.2 to 40.8; $P = .0109$), using propensity-adjusted analysis. Outcomes were also similar to the phase 2 dose-finding trial [21].

Similarly, survival results from the CUP in patients with hepatic VOD/SOS without MOF are comparable to those seen in the interim analysis of an ongoing expanded-access study in a similar patient population (dosed at 25 mg/kg/day for a recommended ≥21 days) [29]. For all 255 patients without MOF in the expanded-access study interim analysis (enrolled from 2007 through 2013), the Kaplan-Meier estimated survival rate at day +100 was 65% [29], which is consistent with the CUP Kaplan-Meier estimated survival rate of 65%.

In the CUP, 11% (79 of 710) of patients with VOD/SOS had received chemotherapy without HSCT. Of those nontransplantation-associated chemotherapy patients, the Kaplan-Meier survival rate by day +100 was similar to the Kaplan-Meier–estimated day +100 survival rates for this subgroup in the expanded-access study: [30] 71% (95% CI, 58.6 to 80.3) (68% for patients with MOF [n = 38] and 74% for patients without MOF [n = 41]). In that study, patients in the nontransplantation-associated chemotherapy subgroup were mostly pediatric (80%, compared with 58% in the overall study), and the most prevalent primary disease was acute lymphocytic leukemia (44%, compared with acute myeloid leukemia [27%] overall), which may be contributing factors to increased survival [29,30].

In both the CUP and expanded-access studies, the higher survival rate in patients without MOF indicates that further studies are warranted to determine the impact of initiating treatment earlier in the course of hepatic VOD/SOS.

The incidence of AEs reported in the CUP was generally consistent with prior trials [21,23,28]. Because of the nature of the CUP, mild-to-moderate AEs not leading to discontinuation were anticipated to be under-reported and deaths were likely to be reported. Indeed, the vast majority of reported AEs were those leading to death. The overall incidence of serious and fatal events was consistent with published findings on VOD/SOS and defibrotide in the treatment of VOD/SOS, and is as expected for this very ill patient population [21,23,28]. No clinically meaningful differences were observed for AEs, SAEs, or fatal events by gender, age, or dose group in this CUP.

Historically, risk of bleeding has been a concern for patients with VOD/SOS [31]. Other forms of treatment, such as tPA and heparin, have been associated with hemorrhage and extensive patient withdrawals from treatment (~50%) [32]. By contrast, the recently published defibrotide phase 3 trial results show that the incidence of common hemorrhagic AEs was similar in the defibrotide and control groups (64% versus 75%, respectively) [23], and an earlier phase 3 prophylaxis trial found cumulative rates of hemorrhage of 22% and 21%, respectively ($P = .8176$) [33].

This study had some limitations. There was no protocol for this program and all reporting of patient data and outcomes was voluntary, without on-site monitoring. As such, in some cases, outcome forms were either not returned or not fully completed for all patients, which may have resulted in under-reporting of AEs that did not lead to death. In addition, the relatively shorter recommended duration of treatment in this program, compared with more recent studies also may have influenced efficacy and safety outcomes.

This CUP includes data on defibrotide use across a long period of time in a large number of patients (n = 710). The study included a heterogeneous population of patients with VOD/SOS, in part because of the real-world nature of the program and in part because of differences in inclusion

Table 7
AEs Reported in ≥2% of Patients

AE*	Analysis Population (N = 710)		
	All	Serious	Leading to Death
MOF, new or worsening	144 (20)	144 (20)	144 (20)
Progression of VOD/SOS	79 (11)	78 (11)	78 (11)
Sepsis	49 (7)	48 (7)	48 (7)
GVHD	28 (4)	28 (4)	28 (4)
Gastrointestinal hemorrhage	19 (3)	10 (1)	7 (1)
Recurrent cancer	15 (2)	15 (2)	15 (2)
Hemorrhage	14 (2)	8 (1)	7 (1)
Pulmonary hemorrhage	14 (2)	12 (2)	9 (1)
Acute myelogenous leukemia, recurrent	12 (2)	12 (2)	12 (2)
Pneumonia	12 (2)	12 (2)	12 (2)
Septic shock	11 (2)	11 (2)	10 (1)

Data presented are n (%).
* Classified by Medical Dictionary for Regulatory Activities 16.0; preferred term by the treating physician.

criteria in different regions. The safety data are consistent with reports from controlled trials of defibrotide [21,23,33]. The CUP also provides valuable information about a range of defibrotide doses and captures the experience of real-world defibrotide usage, demonstrating that the benefits shown in research trials can be achieved in the clinical setting.

CONCLUSIONS

When only supportive care is available, hepatic VOD/SOS with evidence of MOF has been associated with a fatality rate of more than 80% by day +100 after HCT [5]. For patients in this CUP, the Kaplan-Meier estimated day +100 survival rate of 54% in the broad patient population and 40% in the subgroup with MOF is supportive of a beneficial treatment effect for these critically ill patients and is consistent with prior studies of defibrotide in VOD/SOS. AEs were likely under-reported because of the nature of this CUP. Nonetheless, the overall profile of serious and fatal events in this large study population of more than 700 patients was consistent with what has been observed in other studies of defibrotide for the treatment of VOD/SOS and was consistent with the manageable toxicities seen with defibrotide use in this setting. Additionally, safety and efficacy subgroup analyses in this study lend support to the use of 25 mg/kg/day as recommended dosing for defibrotide in VOD/SOS patients.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2016.07.001.

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