Defibrotide for the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome following nontransplant-associated chemotherapy: Final results from a post hoc analysis of data from an expanded-access program

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Abstract

Background: Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially fatal complication of conditioning for hematopoietic stem cell transplantation (HSCT) but can occur after nontransplant-associated chemotherapy. Following HSCT, VOD/SOS with multi-organ dysfunction (MOD) may be associated with >80% mortality. Defibrotide is approved to treat severe hepatic VOD/SOS post-HSCT in patients aged >1 month in the European Union and hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in the United States. Prior to US approval, defibrotide was available to treat VOD/SOS through an expanded-access treatment (T-IND) program. A post hoc analysis of nontransplant-associated VOD/SOS patients treated with defibrotide initiated within 30 days of starting chemotherapy and followed for 70 days is presented.

Procedure: Patients were diagnosed by Baltimore or modified Seattle criteria or biopsy, and received defibrotide 25 mg/kg/day in four divided doses (≥21 days recommended).

Results: Of the 1,154 patients in the T-IND, 137 had nontransplant-associated VOD/SOS. 82 of whom developed VOD/SOS within 30 days of starting chemotherapy. Of them, 66 (80.5%) were aged ≤16 years. Across all the 82 patients, Kaplan–Meier estimated day +70 survival was 74.1%, 65.8% in patients with MOD (n = 38), and 81.3% in patients without MOD (n = 44). By age group,
1 | INTRODUCTION

Hepatic veno-occlusive disease, also called sinusoidal obstruction syndrome (VOD/SOS), is an unpredictable, potentially life-threatening complication associated with conditioning regimens for hematopoietic stem cell transplantation (HSCT), including reduced-intensity regimens. VOD/SOS also can occur as a complication of chemotherapy alone. The reported mean incidence of VOD/SOS following HSCT is 13.7% (range, 0–62.3%). Even among patients undergoing reduced-intensity conditioning for allogeneic HSCT, an incidence of 8.8% has been reported. Following HSCT, VOD/SOS with concomitant multi-organ dysfunction (MOD) has an associated mortality rate that may exceed 80%. The incidence and mortality rate of VOD/SOS following nontransplant-associated chemotherapy are not known. A number of agents have been reported to be associated with an increased risk of VOD/SOS in the non-HSCT setting, including inotuzumab and gemtuzumab ozogamicin, vincristine, and/or actinomycin D.

In the context of HSCT, the primary event in the pathogenesis of VOD/SOS is injury to hepatic sinusoidal endothelial cells and hepatocytes, usually within the first 21 days post-HSCT, resulting in a prothrombotic-hypofibrinolytic state and sinusoid obstruction. Clinically, VOD/SOS is typically characterized by hepatomegaly, hyperbilirubinemia, jaundice, ascites, and weight gain. Hepatocellular necrosis and vascular occlusion can lead to the hepatorenal syndrome, liver failure, MOD, and death. The pathophysiology in the non-HSCT setting has not been well described, but is presumed to be similar.

In the United States, defibrotide is approved for the treatment of hepatic VOD/SOS post HSCT in patients with renal or pulmonary dysfunction, and in the European Union for the treatment of severe hepatic VOD/SOS following HSCT in adults, adolescents, children, and infants aged older than 1 month. A position statement published by the European Society for Blood and Marrow Transplantation recommends defibrotide for VOD/SOS treatment, and guidelines from the Pediatric Acute Lung Injury and Sepsis Investigators and Pediatric Blood and Marrow Transplantation Consortium Joint Working Committee state that defibrotide is the treatment of choice for VOD/SOS and “should be started as early as possible.”

Defibrotide sodium is a polydisperse mixture of predominantly single-stranded polydeoxyribonucleotides derived from porcine mucosal DNA. Preclinical data suggest that defibrotide increases the expression of tissue plasminogen activator and thrombomodulin and decreases the expression of von Willebrand factor and plasminogen activator inhibitor-1 and reduces endothelial-cell activation, promoting the restoration of thrombotic-fibrinolytic balance and protecting the endothelial cells from the continued damage caused by chemotherapy and tumor necrosis factor-α.

Completed clinical trials of defibrotide are usually restricted to patients with diagnosis of VOD/SOS following HSCT. In a phase 2 dose-finding trial that tested two dosage levels (25 mg/kg/day and 40 mg/kg/day) in a mixed adult and pediatric population with VOD/SOS and MOD following HSCT, the lower dose level was found to be the appropriate dosage for further study, because of similar efficacy and a safety profile that was more favorable. A subsequent phase 3 trial in patients with VOD/SOS and MOD following HSCT reported significant improvement in survival at day +100 post-HSCT and in complete response (i.e., total bilirubin <2 mg/dl and resolution of MOD) among patients who received defibrotide 25 mg/kg/day, compared with historical controls who received standard of care alone. In addition, defibrotide has demonstrated efficacy in VOD/SOS prevention in pediatric HSCT patients in a large phase 3 trial (12% of patients [n = 180] with defibrotide prophylaxis developed VOD/SOS by day +30 after HSCT vs. 4.8% [n = 248] in the control group), and in adults and pediatric patients in a single-center study (0% of patients [n = 248] with defibrotide prophylaxis developed VOD/SOS at day +100 after HSCT vs. 4.8% [n = 248] in the control group).

Defibrotide was prospectively evaluated in an expanded-access treatment-investigational new drug (T-IND) study initiated in 2007 (ClinicalTrials.gov identifier NCT00628498). This was a multicenter, single-arm, open-label, US trial designed to provide defibrotide (25 mg/kg/day) to patients who developed hepatic VOD/SOS with or without MOD following HSCT or nontransplant-associated chemotherapy. The results of the final analysis of this trial presented here focus on defibrotide usage, tolerability, and safety in patients whose VOD/SOS developed following nontransplant-associated chemotherapy.

2 | METHODS

2.1 | Study participants

In the original 2007 version of the protocol for the T-IND study, all patients were required to have a diagnosis of VOD/SOS by Baltimore criteria or by biopsy by day +35, and to have MOD (renal and/or...
respiratory failure) by day +45 post HSCT. The Baltimore criteria call for a serum bilirubin level $\geq 2$ mg/dL, plus at least two of the following three findings: ascites (by radiographic or physical examination), weight gain $\geq 5\%$ from the baseline value, and hepatomegaly. Renal dysfunction was defined by a tripled serum creatinine level, a creatinine clearance level, or glomerular filtration rate $\leq 40\%$ of the baseline value, or dialysis dependence. Respiratory dysfunction was defined by need for oxygen supplementation, an oxygen saturation $\leq 90\%$ on room air, or ventilator dependence.

The study protocol was amended in 2009 to also include patients with VOD/SOS following nontransplant-associated chemotherapy, without MOD, and (in a 2012 amendment) with VOD/SOS diagnosed by modified Seattle criteria, which require two or more of: bilirubin $\geq 2$ mg/dL, hepatomegaly or right upper quadrant pain, and weight gain ($\geq 5\%$ in this study). The requirement to have VOD/SOS diagnosed by day +35 was removed. Exclusion criteria included clinically significant, uncontrolled acute bleeding, medication that increases the risk of hemorrhage, need for more than one vasopressor, and pregnancy.

The post hoc analyses presented here pertain to the subset of enrolled patients who had received nontransplant-associated chemotherapy. Results for the HSCT population were reported previously.  

### 2.2 Study drug dosing

For all patients, the recommended defibrotide regimen was 25 mg/kg/day, administered as a 2-hour intravenous infusion of 6.25 mg/kg every 6 hr. Dosing was based on each patient's weight prior to chemotherapy, with doses rounded to the nearest 10 mg for patients of any age $>35$ kg, and rounded to the nearest 5 mg for pediatric patients $<35$ kg. The recommended minimum treatment duration was 21 days. After 21 days, treatment was recommended to continue until resolution of symptoms of VOD/SOS (and MOD, if present) or the patient's discharge from the hospital. Blood parameters that were monitored and maintained during treatment were hemoglobin $>8$ mg/dL, platelet count $>30,000$/mm$^3$, international normalized ratio $<1.5$ with fresh frozen plasma, and fibrinogen $>150$ mg/dL, with factor replacement as necessary. The protocol recommended that treatment was to be discontinued or withheld for clinically significant bleeding defined as either $>15$ cc/kg packed red blood cells/24 hr or bleeding from a potentially life-threatening site (pulmonary hemorrhage or central nervous system bleeding) irrespective of amount of blood loss. The cause of bleeding was to be treated, and, after the patient was hemodynamically stable and bleeding had stopped, consideration was to be given to resuming treatment at the same dose and infusion volume. In the event of recurrent severe significant bleeding, defibrotide was to be permanently discontinued.

### 2.3 Efficacy analyses

The original T-IND program followed patients to day +100 after HSCT, and day +100 survival was the primary efficacy endpoint for the analysis, as this is a standard outcome milestone for HSCT studies of patients with VOD/SOS. When the protocol was amended to permit enrollment of patients with VOD/SOS after nontransplant-associated chemotherapy (August 2009), the data were collected for 100 days after the first dose of the most recent course of chemotherapy, and the efficacy endpoint of day +100 was not adjusted for these patients. To obtain a population with a clinically meaningful follow-up time after defibrotide initiation for this post hoc analysis, only patients who initiated defibrotide within 30 days of starting chemotherapy were included in the primary efficacy assessment, and the efficacy endpoint for analysis was survival at day +70 following the start of defibrotide (i.e., for a total of up to 100 days after the start of chemotherapy).

For all patients who initiated defibrotide within 30 days of the start of the most recent chemotherapy course, including the subset with MOD and the subset without MOD, the proportions of patients alive at day +70 post-initiation of defibrotide are presented as point estimates with 95% confidence intervals (CI) calculated using the normal approximation to the binomial distribution. Kaplan-Meier curves are presented to describe the distribution of time to death. The curves are supplemented by numbers of patients at risk at various points along the time axis.

### 2.4 Safety measures

Safety was assessed by adverse events (AEs), as reported by the study's investigators. For this purpose, AEs were defined as any adverse event that began or worsened after a patient's first dose of defibrotide. Symptoms of the disease targeted by a patient's chemotherapy were not to be reported as AEs unless the event was considered serious. Based on the investigator's assessment, each AE was classified as to whether it was at least possibly related to defibrotide. Hemorrhagic events and hypotension were predefined as AEs of special interest. The study collected limited laboratory data, primarily to support VOD/SOS diagnosis and outcome assessment. Accordingly, these data were not employed for study drug safety evaluation.

### 2.5 Ethical conduct

The study protocol was approved by each institution's independent ethics committee or institutional review or privacy board and was conducted in accordance with the principles of the Declaration of Helsinki or with local laws and regulations. All patients or guardians, as appropriate, provided written informed consent and written Health Insurance Portability and Accountability Act authorization.

### 3 RESULTS

#### 3.1 Study participants

From December 14, 2007, through April 4, 2016, 1,154 patients were enrolled in the T-IND study at 101 centers across the United States and received at least 1 defibrotide dose. Among these patients, 1,137 had adequate data for defibrotide efficacy analyses (i.e., a
### TABLE 1  Baseline characteristics of patients treated with defibrotide for VOD/SOS within 30 days of starting nontransplant-associated chemotherapy

| Variable                        | All patients (N = 82) | VOD/SOS without MOD (n = 44) | VOD/SOS with MOD (n = 38) |
|---------------------------------|-----------------------|-----------------------------|---------------------------|
| **Sex, n (%)**                  |                       |                             |                           |
| Male                            | 40 (49)               | 21 (48)                     | 19 (50)                   |
| Female                          | 42 (51)               | 23 (52)                     | 19 (50)                   |
| **Race, n (%)**                 |                       |                             |                           |
| White                           | 55 (67)               | 31 (71)                     | 24 (63)                   |
| Non-White                       | 27 (33)               | 13 (30)                     | 14 (37)                   |
| **Age at time of chemotherapy, years** |                   |                             |                           |
| Mean (SD)                       | 10.5 (12.5)           | 9.44 (11.935)               | 11.82 (13.161)            |
| Median [range]                  | 7.5 [0.0–68.0]        | 5.0 ([0.30–68.0]          | 8.00 [0.0–67.0]           |
| **Age class, n (%)**            |                       |                             |                           |
| Adult (>16 years)               | 16 (20)               | 8 (18)                      | 8 (21)                    |
| Pediatric (≤16 years)           | 66 (81)               | 36 (82)                     | 30 (79)                   |
| 0–23 months                     | 10 (12)               | 7 (16)                      | 3 (7.9)                   |
| 2–11 years                      | 49 (60)               | 26 (59)                     | 23 (61)                   |
| 12–16 years                     | 7 (11)                | 3 (6.8)                     | 4 (11)                    |
| **Primary disease, n (%)**      |                       |                             |                           |
| ALL                             | 42 (51)               | 27 (61)                     | 15 (40)                   |
| AML                             | 11 (13)               | 4 (9.1)                     | 7 (18)                    |
| Neuroblastoma                   | 5 (6.1)               | 3 (6.8)                     | 2 (5.3)                   |
| Non-Hodgkin lymphoma            | 2 (2.4)               | 1 (2.3)                     | 1 (2.6)                   |
| Other                           | 22 (27)               | 9 (21)                      | 13 (34)                   |
| **Use of chemotherapeutic agents, n (%)** |       |                             |                           |
| Cyclophosphamide                | 44 (54)               | 22 (50)                     | 22 (58)                   |
| Cytarabine                      | 42 (51)               | 24 (55)                     | 18 (47)                   |
| Vincristine                     | 39 (48)               | 22 (50)                     | 17 (45)                   |
| Methotrexate                    | 28 (34)               | 16 (36)                     | 12 (32)                   |
| Thioguanine                     | 25 (31)               | 17 (39)                     | 8 (21)                    |
| Pegasparagase                   | 24 (29)               | 15 (34)                     | 9 (24)                    |
| Doxorubicin                     | 16 (20)               | 9 (21)                      | 7 (18)                    |
| Etoposide                       | 15 (18)               | 8 (18)                      | 7 (18)                    |
| Dexamethasone                   | 11 (13)               | 5 (11)                      | 6 (16)                    |
| Daunorubicin                    | 9 (11)                | 5 (11)                      | 4 (11)                    |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; HSCT, hematopoietic stem cell transplantation; MOD, multi-organ dysfunction; SD, standard deviation; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

In patients who underwent both nontransplant-related chemotherapy and HSCT (n = 3), chemotherapy was closer to onset of VOD/SOS than HSCT.

Overall patient population, usage >10.0%.

Overall patient population, usage >10.0%.

diagnosis of VOD/SOS plus documented evidence of receiving the drug). Of these 1,137 patients, 137 (12.0%) had VOD/SOS following nontransplant-associated chemotherapy, including 82 who initiated defibrotide treatment within 30 days of first chemotherapy dose. Of these 82 patients, 38 (46.3%) had MOD and 44 patients (53.7%) did not have MOD. Demographic and clinical characteristics are summarized in Table 1. A large majority of the patients (80.5%) were aged 16 years or younger (“pediatric”). The most common primary diseases were acute lymphoblastic leukemia (ALL; 51.2%) and acute myelogenous leukemia (AML; 13.4%). Overall, the most commonly administered chemotherapeutic agents for the 82 patients with VOD/SOS following nontransplant-associated chemotherapy were cyclophosphamide (53.7%), cytarabine (51.2%), vincristine (47.6%), methotrexate (34.1%), and thioguanine (30.5%). Of note, gemtuzumab is a known risk factor of VOD/SOS, and it was received by one patient with and one without MOD.
### TABLE 2  Survival at day +70 after defibrotide initiation among patients treated with defibrotide for VOD/SOS within 30 days of starting nontransplant-associated chemotherapy

| Category                  | All patients (N = 82) | VOD/SOS without MOD (n = 44) | VOD/SOS with MOD (n = 38) |
|---------------------------|-----------------------|------------------------------|---------------------------|
| Alive, n (%)              | 58 (71)               | 33 (75)                      | 25 (66)                   |
| Dead, n (%)               | 21 (26)               | 8 (18)                       | 13 (34)                   |
| Unknown, n (%)            | 3 (3.7)               | 3 (6.8)                      | -                         |
| Kaplan–Meier\(^a\) Survival, % | 74.1                  | 81.3                         | 65.8                      |
| 95% CI                    | 63.0–82.3             | 65.9–90.2                    | 48.5–78.5                 |

#### Age-stratified survival category

| Age-stratified survival category | Age ≤16 (n = 66) | Age >16 (n = 16) | Age ≤16 (n = 36) | Age >16 (n = 8) | Age ≤16 (n = 30) | Age >16 (n = 8) |
|---------------------------------|------------------|------------------|------------------|----------------|------------------|----------------|
| Alive, n (%)                    | 50 (76)          | 8 (50)           | 29 (81)          | 4 (50)         | 21 (70)          | 4 (50)         |
| Dead, n (%)                     | 13 (20)          | 8 (50)           | 4 (11)           | 4 (50)         | 9 (30)           | 4 (50)         |
| Unknown, n (%)                  | 3 (4.5)          | –                | 3 (8.3)          | –              | –                | –              |
| Kaplan–Meier\(^a\) Survival, % | 80.1             | 50.0             | 88.6             | 50.0           | 70.0             | 50.0           |
| 95% CI                          | 68.2–87.9        | 24.5–71.0        | 72.4–95.6        | 15.2–77.5      | 50.3–83.1        | 15.2–77.5      |

Abbreviations: CI, confidence interval; MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome. \(^a\)Estimated survival at day +70 after defibrotide initiation.

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**FIGURE 1**  Kaplan–Meier survival plot to day +70 after defibrotide initiation for patients undergoing defibrotide treatment of VOD/SOS by day 30 following start of nontransplant-associated chemotherapy, stratified by presence versus absence of MOD.

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### 3.2 Survival

Point estimate and Kaplan–Meier estimated survival at day +70 after defibrotide initiation for the 82 patients with VOD/SOS following nontransplant-associated chemotherapy are summarized in Table 2. At day +70 after defibrotide was started, the overall Kaplan–Meier estimated survival was 74.1% (95% CI, 63.0–82.3). Estimated survival was higher for patients without MOD (81.3%; 95% CI, 65.9–90.2) than for patients with MOD (65.8%; 95% CI, 48.5–78.5) (Figure 1). Kaplan–Meier estimated day +70 survival after defibrotide initiation for the 66 post-chemotherapy pediatric patients was 80.1% and was 50% for the 16 adult patients. Estimated survival was higher in the 36 pediatric patients without MOD (88.6%) than in the 30 pediatric patients with MOD (70.0%). Day +70 survival was identical for the eight adult patients with or without MOD (50.0% each).

### 3.3 Safety

Among the 82 patients with VOD/SOS following nontransplant-associated chemotherapy who initiated defibrotide treatment within 30 days of first chemotherapy dose, 54 patients (65.9%) reported one or more AE, including 33 patients (40.2% of 82) with AEs rated as serious and 22 patients (26.8% of 82) with AEs considered by the investigators to be at least possibly related to defibrotide (Table 3). The most common serious AEs were new or worsening MOD (in seven patients; 8.5%), veno-occlusive liver disease, hypoxia, and respiratory failure (each in five patients; 6.1%), and pulmonary hemorrhage (in four patients; 4.9%), followed by febrile neutropenia, encephalopathy, renal failure, and hypotension (each in three patients; 3.7%) and hepatic failure and sepsis (each in two patients; 2.4%). The most common AEs possibly related to defibrotide were mouth and pulmonary hemorrhage (each in three patients; 3.7%), followed by hematochezia, nausea, encephalopathy, epistaxis, and hypotension (each in two patients; 2.4%).

The incidence of AEs and of serious AEs was notably higher among patients with MOD (84.2% and 57.9%, respectively) than among patients without MOD (50.0% and 25.0%, respectively). Six patients (7.3%) withdrew from the study due to an AE considered by the investigator to be at least possibly related to defibrotide; except for one case each of hypopotension and intraventricular hemorrhage, these AEs were primarily gastrointestinal disorders (3.7%; gastric, gastrointestinal and mouth hemorrhage, each in one patient with MOD [2.6%]), followed by respiratory, thoracic, and mediastinal disorders (2.4%; epistaxis...
TABLE 3  AEs among patients treated with defibrotide for VOD/SOS following nontransplant-associated chemotherapy

| AE, n (%) | All patients (N = 82) | VOD/SOS without MOD (n = 44) | VOD/SOS with MOD (n = 38) |
|-----------|-----------------------|-------------------------------|---------------------------|
| Any AE    | 54 (66)               | 22 (50)                       | 32 (84)                   |
| Any serious AE | 33 (40)     | 11 (25)                       | 22 (58)                   |
| Hemorrhagic AEs<sup>a</sup> |                 |                               |                           |
| Pulmonary hemorrhage | 5 (6.1)   |                               | 5 (13)                    |
| Epistaxis   | 3 (3.7)               |                               | 3 (7.9)                   |
| Mouth       | 3 (3.7)               | 1 (2.3)                       | 2 (5.3)                   |
| Hematochezia | 2 (2.4)  | 2 (4.5)                       |                           |
| Any defibrotide-related<sup>b</sup> AE<sup>a</sup> | 22 (27) | 9 (21)                       | 13 (34)                   |
| Mouth hemorrhage | 3 (3.7)  | 1 (2.3)                       | 2 (5.3)                   |
| Pulmonary hemorrhage | 3 (3.7)  |                               | 3 (7.9)                   |
| Hematochezia | 2 (2.4)  | 2 (4.5)                       | 2 (5.3)                   |
| Nausea      | 2 (2.4)               | 2 (4.5)                       |                           |
| Epistaxis   | 2 (2.4)               |                               | 2 (5.3)                   |
| Hypotension | 2 (2.4)               |                               |                           |
| Any defibrotide-related<sup>b</sup> AE leading to discontinuation | 6 (7.3) |                               | 6 (16)                    |
| Gastric hemorrhage | 1 (1.2)  |                               | 1 (2.6)                   |
| Gastrointestinal hemorrhage | 1 (1.2)  |                               | 1 (2.6)                   |
| Mouth hemorrhage | 1 (1.2)  |                               | 1 (2.6)                   |
| Intraventricular hemorrhage | 1 (1.2) |                               | 1 (2.6)                   |
| Epistaxis   | 1 (1.2)               |                               | 1 (2.6)                   |
| Pulmonary hemorrhage | 1 (1.2)  |                               | 1 (2.6)                   |
| Hypotension | 1 (1.2)               |                               | 1 (2.6)                   |
| Any defibrotide-related<sup>b</sup> AE leading to death | 1 (1.2) |                               | 1 (2.6)                   |
| Pulmonary hemorrhage | 1 (1.2)  |                               | 1 (2.6)                   |
| Hypotension | 1 (1.2)               |                               | 1 (2.6)                   |

Abbreviations: AE, adverse event; MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.
<sup>a</sup>The listed events were each reported in >one patient.
<sup>b</sup>At least possibly related, in the judgment of the investigator.

and pulmonary hemorrhage, each in one patient with MOD (2.6%).

Across all patients, one death (1.2%) from pulmonary hemorrhage and hypotension in a patient with MOD was considered to be related to defibrotide.

AEs by System Organ Class and Preferred Term consistent with hemorrhage were reported in 18 of 82 patients (22.0%). The events in more than one patient were pulmonary hemorrhage (in five patients; 6.1%), epistaxis and mouth hemorrhage (each in three patients; 3.7%), and hematochezia (in two patients; 2.4%). The organ systems most commonly affected in these events were the gastrointestinal and respiratory systems (each in nine patients; 11.0%). Hemorrhagic AEs were more common among patients with MOD (34.2%) than among patients without MOD (11.4%).

4 | DISCUSSION

Most published studies of defibrotide for VOD/SOS have been restricted to post-HSCT patients. However, VOD/SOS can occur following nontransplant-associated chemotherapy. Here we report defibrotide usage, tolerability, and safety data that were collected from a post hoc analysis subgroup of T-IND patients whose VOD/SOS developed after chemotherapy alone. Of 1,154 patients in the T-IND, 137 (12%) patients had nontransplant-associated VOD/SOS. Similarly, in the international defibrotide compassionate use program (CUP) 79/710 (11.1%) patients had nontransplant-associated VOD/SOS. In another study of gemtuzumab and chemotherapy as first-line therapy for AML patients, 7/72 (10%) developed VOD/SOS.

As patients typically receive multi-agent chemotherapy, it is difficult to implicate specific drugs as causing VOD/SOS. Moreover, the incidence of VOD/SOS and survival outcomes associated with a specific agent or combinations of agents have not been routinely reported, and thus, are not known for this population of patients. However, it is notable that individual reports in the literature have demonstrated risk of VOD/SOS associated with certain chemotherapy treatments. For example, the incidence of VOD/SOS in ALL patients treated with inotuzumab ozogamicin was shown to be significantly higher than in patients receiving standard chemotherapy (13% vs.
1%, respectively); however, these data included all VOD/SOS events within two years of randomization, the majority of which were after follow-up HSCT. An increased risk for development of VOD/SOS, with or without HSCT, also has been recognized in patients with AML treated with gemtuzumab ozogamicin. Thioguanine, vincristine, and high-dose actinomycin-D also have been reported to be associated with the development of VOD/SOS. The present analysis was not powered to investigate any possible associations with specific agents or regimens, and no inferences can be made from the results.

Although the design of the present study did not permit either a concomitant or historical control group, the analysis encompassed 82 patients with nontransplant-associated chemotherapy and suggests that defibrotide may be efficacious in VOD/SOS in this setting. Patients who had nontransplant-associated chemotherapy and developed VOD/SOS without MOD demonstrated superior survival (81.3%) compared with patients with MOD (65.8%) by Kaplan–Meier estimates. Similarly, in the international defibrotide CUP study, day +100 Kaplan–Meier survival among patients with VOD/SOS following nontransplantation-associated chemotherapy was 74.2% (41 patients) without MOD, which was higher than the 67.5% (38 patients) for patients with MOD. These data suggest the potential benefit of defibrotide treatment at an earlier stage of VOD/SOS—before MOD develops in patients with VOD/SOS following chemotherapy—as has been demonstrated in patients with VOD/SOS who were recipients of HSCT. In the study of gemtuzumab and chemotherapy as first-line therapy for AML, 6/7 patients with VOD/SOS were treated with defibrotide (dosing was not reported), and five (83.3%) of those patients recovered and received further chemotherapy. In another study, 4/414 (1%) of patients with acute lymphoblastic leukemia treated with vincristine, daunorubicin, and steroid and 2/113 (1.7%) with Wilms tumor treated with vincristine and actinomycin-D developed VOD/SOS and were treated with defibrotide. Clinical and laboratory remission were obtained in all six patients. In another study of treatment of acute lymphoblastic leukemia with a brief course of 6-thioguanine, 10/680 (1.5%) children developed VOD/SOS; none of the patients were treated with defibrotide. Eight patients with moderate disease made a full recovery; two patients with severe disease died during hospitalization.

The AE profile observed in the present cohort was consistent with that seen in the VOD/SOS population in the post-HSCT setting, and with the known safety profile of defibrotide in such patients. In the T-IND overall, defibrotide tolerability was better than in other VOD/SOS patient populations, presumably due in part to the inclusion of patients without MOD. Indeed, within the present analysis, patients without MOD had fewer AEs and fewer severe AEs than patients with MOD, and patients without MOD had no AEs leading to withdrawal from the T-IND study. However, the presence of fewer AEs in patients without MOD also might reflect a differing distribution of primary diseases. Hemorrhagic AEs have been associated with defibrotide; however, because hemorrhage can be secondary to the pathophysiologic processes associated with VOD/SOS, namely, thrombocytopenia and coagulopathy, attributing hemorrhagic AEs to the use of defibrotide can be problematic. For example, in the phase 3 defibrotide prophylaxis study, hemorrhage was the most commonly reported treatment-related AE; however, cumulative hemorrhage incidence was the same between the defibrotide group (22%) and the control group (21%). Also, thrombocytopenia and coagulopathy have been observed irrespective of defibrotide treatment, which makes it difficult to attribute causality for these events. In the subgroup of nontransplant-associated chemotherapy patients with MOD in this study, 13 (34%) had a hemorrhagic AE, and 6 (16%) patients with MOD discontinued defibrotide due to a treatment-related AE, mostly hemorrhagic events.

Interpretation of the present analysis is limited by the source of the data, a study designed to provide access to therapy without randomization, which lacked an appropriate control group or formal onsite monitoring. On the other hand, the analysis provides a substantial dataset to support the feasibility of using defibrotide for treatment of patients with nontransplant-associated VOD/SOS, particularly in the larger group of pediatric patients. Because only 12.0% of patients in the T-IND study received treatment for nontransplant-associated VOD/SOS, it is unlikely that a sufficient number of patients could ever be accrued to a randomized controlled study of defibrotide versus best supportive care. Moreover, in the same way that ethical concern prevented withholding a potentially therapeutic modality with an acceptable safety profile from patients with VOD/SOS following HSCT, ethical concern makes it highly unlikely that a randomized study of defibrotide versus best supportive care would ever be undertaken in a nontransplant population.

In summary, this post hoc analysis associates defibrotide use with 74.1% day +70 survival in patients with nontransplant-associated VOD/SOS, including higher survival among patients with less serious disease, suggesting that treatment may be most beneficial before MOD develops. The safety profile of this subgroup shows AEs of the types to be expected in patients with VOD/SOS and underlying coagulation disorders. Although most cases of VOD/SOS develop in post-HSCT patients, there is a non-negligible percentage of patients who develop VOD/SOS post chemotherapy without HSCT. For these patients, the data presented herein demonstrate that defibrotide is a feasible therapeutic option.

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**AUTHOR CONTRIBUTION**

Nancy A. Kernan, Paul G. Richardson, Stephan A. Grupp, Robin Hume, and Robert J. Soiffer were responsible for the study analysis conception and design. All authors contributed to the provision of study materials or patients. All authors were involved in the collection...
and assembly of data. Wei Liang performed statistical analysis. All authors participated in the study data analysis and interpretation and manuscript writing, and provided their final approval of this manuscript.

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