RAPID COMMUNICATION

Treatment of Severe Veno-Occlusive Disease With Defibrotide: Compassionate Use Results in Response Without Significant Toxicity in a High-Risk Population

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Hepatic veno-occlusive disease (VOD) is the most common of the regimen-related toxicities accompanying stem cell transplantation (SCT). Despite aggressive therapies, including the combination of tissue plasminogen activator (t-PA) and heparin, severe VOD is almost uniformly fatal. Defibrotide (DF) is a polydeoxyribonucleotide with activity in several vascular disorders and, unlike t-PA and heparin, produces no systemic anticoagulant effects. Nineteen patients who developed severe VOD after SCT were treated with DF on a compassionate-use basis. Patients had clinically established VOD and met risk criteria predicting progression and fatality. At the initiation of DF, all 19 patients had evidence of multiorgan dysfunction; median bilirubin was 22.3 mg/dL, 12 patients had renal insufficiency (5 dialysis dependent), 14 required oxygen supplementation, and encephalopathy was present in 8 patients. Beginning a median of 6 days after diagnosis of VOD, DF was administered intravenously in doses ranging from 5 to 60 mg/kg/d for a planned minimum course of 14 days. In no case was DF discontinued for attributable toxicity. No severe hemorrhage related to DF administration was observed. Resolution of VOD (bilirubin <2 mg/dL with improvement in other symptoms and signs) was seen in 8 patients (42%). Six of 8 responders survived past day +100, contrasted with the 2% predicted survival reported in comparable patients. The observed response rate, survival to day +100, and absence of significant DF treatment-associated toxicity are compelling and warrant further evaluation.

REGIMEN-RELATED TOXICITY (RRT) constitutes a barrier to successful allogeneic (allo) and autologous (auto) hematopoietic stem cell transplantation (SCT).[1] Perhaps the most common life-threatening RRT is hepatic veno-occlusive disease (VOD), a clinical syndrome characterized by painful hepatomegaly, jaundice, ascites, and fluid retention manifested by otherwise unexplained weight gain.[2-6] VOD develops in 10% to 60% of patients after SCT, and ranges in severity from mild, reversible disease to a severe syndrome associated with multiorgan failure and death.[2-4,7,8] Established severe VOD has been estimated as having a mortality rate approaching 100% by day +100 post-SCT.[2,3,6,8] VOD is thought to be caused by injury first to the area surrounding the central veins where damage is seen in sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus.[2,9-11] Early pathologic changes include deposition of fibrinogen and factor VIII within venular walls and liver sinusoids.[9] Progressive venular occlusion contributes to the structural damage in zone 3 of the acinus and ultimately widespread zonal liver disruption becomes manifest as VOD.[2,11] Later pathologic changes include deposition of collagen in the sinusoids, sclerosis of venular walls, and fibrosis of venular lumens.[9] Throughout, a procoagulant state is present with low plasma levels of antithrombin III (AT III) and protein C, consumption of factor VII, and increased levels of plasminogen activator inhibitor 1 (PAI-1).[4,12-15] In addition, increased levels of vWF multimers and refractoriness to platelet transfusions are seen in VOD, suggesting further activation of the coagulation cascade with ongoing endothelial cell injury.[12] Hepatocellular necrosis and vascular occlusion lead to hepatorenal physiology, liver failure, multiorgan dysfunction (MOD), and death.

Although the pathophysiology is complex and remains incompletely understood, antithrombotic and thrombolytic agents, including prostaglandin E1 and t-PA with or without concurrent heparin, have been evaluated for the treatment of VOD.[4,16,17] However, these approaches have been limited by significant toxicity, including fatal hemorrhage.[4,16,18] In addition, efficacy itself has been difficult to establish and as a result no therapies for VOD have been evaluated in a prospective, randomized fashion. A search for an agent having demonstrable antithrombotic properties but with little evidence of increased bleeding associated with its use was therefore undertaken. Defibrotide (DF), a large, single-stranded polydeoxyribonucleotide, has such a profile.[19] It is derived from mammalian tissue (porcine mucosa) by controlled depolymerization and has been found to have antithrombotic, anti-ischemic, anti-inflammatory, and thrombolytic properties without significant systemic anticoagulant effects.[19] DF has a complex mechanism of action.[19,20] It is an adenosine receptor agonist with affinity for receptors A1 and A2, apparently via aptameric activity which results in thrombin antagonism in vitro.[21,22] DF also increases levels of

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endogenous prostaglandins (PGI2 and E2), reduces levels of leukotriene B4, inhibits monocyte superoxide anion generation, stimulates expression of thrombomodulin in human vascular endothelial cells, modulates platelet activity, and stimulates fibrinolysis by increasing endogenous t-PA function while decreasing activity of PAI-1.[23-27] DF is avidly bound to vascular endothelium, has a relatively short circulating half-life ranging from 10 to 30 minutes with intravenous (IV) administration, and can be given orally or parenterally.[19] It has been studied in a number of vascular disorders, including peripheral vascular disease, microvascular thrombotic states, and chemotherapy-related hemolytic uremic syndrome (HUS).[28-30] An active dose range from 400 mg/d to 5.6 g/d has been described in various clinical settings.[31] DF appears to be well tolerated; adverse events are mild, range in incidence from 1% to 9%, and include flushing, transient mild systolic hypotension, nausea, and abdominal discomfort.[19]

This relative lack of systemic anticoagulant activity coupled with its potential for ameliorating diverse manifestations of vascular injury suggested that DF might have a therapeutic advantage over other available treatments in SCT patients at high risk of hemorrhage. This hypothesis led to the investigation of the feasibility of using DF in the treatment of severe VOD.

MATERIALS AND METHODS

Patient selection. From March 1995 through August 1997, 23 patients with severe VOD were treated with DF (Crinos SpA, Como, Italy) on a compassionate-use basis and assigned sequential unique patient numbers (UPN). On retrospective review, 19 patients were treated and observed in a comparable fashion and are reported here. Insufficiently detailed data were available from the treating centers of 3 patients, rendering them inevaluable. These 3 patients (UPN 10, 13, 20) were treated for 4, 12, and 21 days, respectively, and no attributable toxicity was noted. One patient appeared to respond while 2 patients appeared to have progressive disease. A fourth patient (UPN 11) received concurrent low-dose heparin during the first 6 days of DF, making that patient also inevaluable. Although treatment with two agents makes attribution of both efficacy and toxicity unclear, the patient was neither responsive nor had apparent toxicity attributable to either treatment.

Patients were eligible for consideration if they were undergoing SCT and the referrring physicians had made a clinical diagnosis of VOD based on jaundice (bilirubin > 2.0 mg/dL) and two of the following: hepatomegaly and/or right upper quadrant pain, ascites, or greater than 5% weight gain above admission weight. Patients who did not meet the above criteria but had a liver biopsy confirming the diagnosis were also eligible. In addition, patients within the 16-day window defined by the Bearman model were required to have a predicted risk of 40% or more of severe VOD.[8] Patients not formally addressed by the Bearman model (ie, onset of VOD beyond day + 16) were considered eligible for treatment if VOD constituted their major clinical problem. Patients with concurrent, confounding causes of liver dysfunction such as graft-versus-host disease or inconsistent findings evident on ultrasound imaging required biopsy-proven VOD to be considered eligible. Patients must have failed prior treatment with t-PA and heparin ($n = 7$) based on progressive rise in bilirubin and/or MOD, or they had to be considered inappropriate for such treatment on the basis of risk for excessive bleeding ($n = 12$). Patients with significant uncontrolled bleeding or hemodynamic instability were excluded. Patients who had received t-PA had a minimum 3-day interval before DF was initiated. Heparin was discontinued at least 6 hours before DF initiation. Concurrent therapy with warfarin or nonsteroidal anti-inflammatory drugs was prohibited. Patients or their parents/guardians or designated proxy gave voluntary informed consent and in each case Institutional Review Board approval was obtained per the guidelines of each participating institution. The US Food and Drug Administration approved the use of DF in each case per its compassionate-use guidelines.

Laboratory and clinical evaluation. In addition to history and physical examination, each patient was followed with abdominal ultrasound scans and serial laboratory studies including bilirubin, serum chemistries, complete blood count, and differential, platelet count, prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen. Time of onset of VOD was defined as the first day that retrospective chart review could confirm that the patient fulfilled the diagnostic criteria detailed above. Retrospective chart review was also used to determine if there was evidence of MOD at the time of treatment initiation. Patients were said to have MOD if there was documentation of dysfunction of one other system in addition to the liver.[3,32] Renal dysfunction was defined as a doubling of the admission creatinine or dialysis dependence; pulmonary dysfunction was defined by the need for supplemental oxygen and/or documentation of hypoxemia by arterial blood gas determination or oxygen saturation by oximetry, or the need for mechanical ventilation, and central nervous system dysfunction was defined by the attending physician's documentation of confusion, lethargy, delirium, and/or coma.

Treatment design. DF was administered IV in normal saline (NS) in four divided doses each infused over 2 hours, starting at an initial daily dose of 10 mg/kg. Where possible, doses were rounded to the nearest 10 or 100 mg in children and adults, respectively, to facilitate efficient drug administration. Drug was mixed with a minimum of 100 mL of NS to a maximum concentration of 400 mg/dL. DF was increased incrementally by 10 mg/kg every 24 to 48 hours to a maximum potential daily dose of 60 mg/kg depending on tolerance and response. In one patient (UPN 07), DF was administered as a 200-mg bolus in NS followed by continuous infusion at the same daily doses. For purposes of continuation and dose escalation, tolerance was defined as the ability to administer drug without adverse events attributable to DF, while response was defined as clinical improvement with fluid mobilization, decrease in bilirubin, reduction in hepatomegaly and/or right upper quadrant (RUQ) pain, improvement in coagulopathy, and/or reduction in other end-organ dysfunction. DF was discontinued or dose reduced if significant toxicity potentially attributable to the drug was encountered. The planned treatment course was for a minimum of 14 days. Treatment was discontinued before 14 days only for death (7 patients) or patient request (1 patient). In 4 patients DF administration was interrupted for the performance of diagnostic or therapeutic surgical procedures. One patient discontinued DF at the end of the initial 14-day course while 10 patients continued treatment. During therapy, wherever possible, platelets were kept $\geq$20,000/μL, hematocrit (HCT) greater than 30% with transfusion, PT less than 15 seconds, and fibrinogen greater than 150 mg/dL with factor replacement including fresh-frozen plasma and cryoprecipitate. One patient (UPN 05) also received antithrombin III (ATIII) concentrates for documented low ATIII levels ($\approx$25%) during the last 7 days of her 15-day DF course. Treating physicians and care providers were made aware of known adverse effects of DF, and patients were followed prospectively per institutional practice for evidence of both potential adverse events and response. Toxicities were graded according to the National Cancer Institute common toxicity criteria. For purposes of evaluating efficacy in this series, response was defined as evidence of improvement in VOD-related symptoms and a concomitant or subsequent decrease in bilirubin to less than 2 mg/dL.

Statistical analysis. Association of patient characteristics with response to therapy was assessed using the exact Wilcoxon signed rank test for continuous variables and the Fisher exact test for categorical variables. Exact binomial confidence intervals are provided for binary variables.

RESULTS

Retrospective review of the medical charts and laboratory values of 19 patients who received DF for treatment of VOD occurring after SCT was undertaken. This review confirmed that all patients met the diagnostic criteria for VOD and had evidence of severe disease as defined by the model of Bearman et al[8] for patients diagnosed before day 16 or by clinical course for those falling outside the bounds of this model. The presence or absence of MOD, and designation of response or nonresponse were determined according to the definitions in Materials and Methods.

Patient characteristics. Of the 19 patients, only 1 had a nonmalignant disorder, thalassemia (Table 1). Thirteen had underlying hematologic malignancies and 5 had solid tumors. Eleven patients underwent autoSCT and 8 received allografts. All but 1 patient received cyclophosphamide (CY) in the preparative regimen. In addition to CY, 4 of the alloSCT group received total body irradiation (TBI) while the other four, including two patients who had previously undergone autoSCT, received busulfan (BU). None received additional agents. Conditioning regimens were more diverse for the autoSCT recipients. Most (9 of 11) received three agents in combination. In 6 patients the regimen included carmustine (BCNU). In the remainder, the regimen included BU (n = 2), TBI (n = 2), and melphalan (n = 1). All except the patient with thalassemia had received prior chemotherapy. Fourteen patients had normal aspartate aminotransferase (AST) on admission to the hospital.

Characterization of VOD. The median day to onset of VOD was 12 days (range, 5 to 32) (Table 2). Although the median time to onset was equivalent in autoSCT and alloSCT recipients, all patients with allogeneic donors had VOD diagnosed within the first 3 weeks while 3 of 11 autograft recipients had later onset ($P = .23$). The most consistent clinical features were RUQ pain and ascites, which were present in 17 and 18 patients, respectively. In 9 patients, ultrasound reports before DF initiation commented on hepatomegaly and abnormal portal flow by Doppler was noted in five. On the day that the patients first fulfilled the clinical criteria for diagnosis of VOD, bilirubin ranged from 2.3 to 28.1 mg/dL (median, 8.3 mg/dL). Weight gain, on that same day, ranged from −2.9% to 24.5% (median, 6.8%) of the admission baseline weight. Histologic confirmation of the diagnosis was made in 7 patients (UPNs 07, 15, 16, 17, 21, 22, 23) by needle biopsy (1 percutaneous, 6 transjugular).

Patient status at the time of DF initiation. Seven of the 19 patients had received a therapeutic trial of t-PA and heparin (Table 3). None of these patients had evidence of clinical response nor did they respond by the 50% reduction in bilirubin criterion used in published trials of t-PA and heparin.[16,18] Patients began treatment with DF at a median of 25 days after BMT (range, 10 to 58 days) and a median of 6 days after the diagnosis of VOD was established (range, 0 to 47 days). At the time that DF was initiated, the patients had a median bilirubin of 22.3 mg/dL (range, 11.7 to 54.4 mg/dL). Autograft recipients had a slightly higher median bilirubin at 24.3 mg/dL (range, 11.7 to 54.4 mg/dL) while allograft recipients had a median bilirubin of 18.5 mg/dL (range, 14.4 to 39 mg/dL), although the difference was not statistically significant. In all cases except one where treatment with DF was initiated on the day VOD was

Table 1. Patient Characteristics

ID	Age/Sex	Diagnosis	Graft	Conditioning Regimen	AST Elevated Pretransplant
UPN01	28F	Hodgkin's	Auto	Cy/BCNU/VP-16	Y
UPN02	46M	AML	Auto	Cy/Bu	N
UPN03	20F	MDS	Allo	Cy/TBI	N
UPN04	16F	AML	Allo	Cy/TBI	N
UPN05	40F	Hodgkin's	Auto	Cy/BCNU/VP-16	N
UPN06	27M	Hodgkin's*	Allo	Cy/Bu	Y
UPN07	41F	Hodgkin's	Auto	Cy/BU/VP-16	N
UPN08	43M	ALL	Allo	Cy/TBI	Y
UPN09	41M	NHL	Allo	Cy/TBI	N
UPN12	35F	NHL	Auto	Cy/TBI	N
UPN14	17F	Thalassemia	Allo	Cy/Bu	N
UPN15	7M	Medulloblastoma	Auto	Cy/Carbo/L-PAM	Y
UPN16	41F	NHL	Auto	Cy/BCNU/Cisplat	N
UPN17	47F	AML*	Allo	Cy/Bu	N
UPN18	18F	MDS	Allo	Cy/Bu	N
UPN19	45F	Breast (S2)	Auto	Cy/BCNU/Cisplat	Y
UPN21	58F	Breast (S2)	Auto	Cy/BCNU/Cisplat	N
UPN22	42F	Breast (S4)	Auto	Cy/BCNU/Cisplat/Taxol	N
UPN23	4M	Neuroblastoma	Auto	TBI/VP-16/Thiotepa	N

Abbreviations: AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; S2, stage 2 (high risk); S4, stage 4 (metastatic); Cy, cyclophosphamide; BCNU, carmustine; VP-16, etoposide; Bu, busulfan; Cisplat, cisplatin; Carbo, carboplatin; L-PAM, melphalan; Y, yes; N, no.

*Second transplant.

Table 2. Characterization of VOD

ID	Day Onset VOD Post SCT	RUQ Pain	Ascites	Hepato-megaly	Portal Flow	Bili at Onset VOD (mg/dL)	% WT Gain at Onset VOD*
UPN01	5	Y	Y	Y	NL	5.3	2.1
UPN02	19	Y	Y	N	NL	9.8	7.9
UPN03	7	Y	Y	N	NL	2.3	5.9
UPN04	12	Y	Y	Y	NL	3.2	6.8
UPN05	11	Y	Y	Y	A	5.2	33.9
UPN06	12	Y	Y	N	NL	10.9	24.5
UPN07	23	Y	N	N	NL	28.1	0.8
UPN08	11	Y	Y	N	A	4.5	5.5
UPN09	21	Y	Y	N	A	3.1	9.1
UPN12	24	N	Y	Y	NL	9.0	23.7
UPN14	7	Y	Y	N	NL	2.7	4.4
UPN15	10	Y	Y	Y	NL	24.3	21.3
UPN16	32	Y	Y	Y	NL	31.5	−8.5
UPN17	9	N	Y	N	NL	18.5	11.1
UPN18	12	Y	Y	N	NL	26.2	−2.9
UPN19	11	Y	Y	N	A	6.8	14.6
UPN21	13	Y	Y	Y	NL	2.7	4.5
UPN22	11	Y	Y	Y	A	8.6	1.5
UPN23	21	Y	Y	Y	NL	8.3	15.6

Abbreviations: Y, yes; N, no; A, abnormal; NL, normal; WT, weight.

*% weight gain calculated using the weight on admission as baseline weight.

diagnosed, there had been a significant increase in bilirubin (median, 3.7-fold; range, 1.1 to 17) since initial diagnosis. The weight of patients at DF initiation was influenced by their interim fluid management, including dialysis, aggressive attempts at diuresis, fluid restriction, and volume expansion. In half the patients, the weight was greater than that at the time at which VOD was diagnosed while the remaining half weighed less. At the time that DF was initiated, all patients had MOD. Renal insufficiency was observed in 12 patients, of whom 5 were dialysis dependent. Requirement for supplemental oxygen was documented in 14 patients, including 2 who required mechanical ventilation. Central nervous system dysfunction was documented in 8 patients.

Table 3. Patient Status at Initiation of Defibrotide

ID	Prior t-PA/ Heparin: Response	Day Post SCT DF Start	Bili at DF Start (mg/dL)	Creat at DF Start (mg/dL)	O_2 Require-ment	Encephalo-pathy
UPN01	Y:NR	10	30.3	1.0	Y	Y
UPN02	N	22	24.3	3.6	Y	Y
UPN03	N	21	39.0	1.7	Y	N
UPN04	Y:NR	26	15.2	4.1	Y	N
UPN05	N	12	20.5	0.8	Y	N
UPN06	N	13	14.4	1.4	N	Y
UPN07	N	36	34.8	1.7	N	N
UPN08	Y:NR	26	21.8	DD	Y	Y
UPN09	Y:NR	27	14.9	1.0	Y	Y
UPN12	N	25	11.7	DD	Y/I	N
UPN14	N	11	14.6	DD	N	N
UPN15	N	16	26.0	DD	Y/I	N
UPN16	N	53	54.4	2.9	N	N
UPN17	Y:NR	28	22.3	1.1	Y	Y
UPN18	N	12	26.2	DD	Y	N
UPN19	Y:NR	58	23.5	0.7	N	Y
UPN21	N	38	14.2	1.6	Y	Y
UPN22	N	12	11.9	1.3	Y	N
UPN23	Y:NR	35	31.3	0.8	Y	N

Abbreviations: Y, yes; N, no; NR, no response; DD, dialysis dependent; I, intubated.

Toxicity. Mild or moderate (grade 1 or 2) toxicities documented during the course of DF administration included nausea (n = 6), transient mild systolic hypotension (n = 5), fever (n = 5), abdominal cramping (n = 3), and vasomotor symptoms [eg, hot flashes] (n = 1). All patients were thrombocytopenic, platelet transfusion and plasma product dependent, and uremic at the time of DF initiation. Seventeen had evidence of mild to moderate bleeding consisting principally of mucosal hemorrhage before initiation of DF. With the initiation and administration of DF, there was no worsening of clinical bleeding as measured by hemodynamic instability, acute transfusion requirement, or end-organ compromise. Most patients thus had evidence of persistent or intermittent grade 1 or 2 bleeding while on treatment (n = 17). Grade 3-4 adverse events during therapy consisted of sepsis, n = 7; pulmonary edema, n = 5; cytomegalovirus (CMV) infection, n = 2; hypotension, n = 2; respiratory failure, n = 2; and single observations of diarrhea, bronchospasm, alveolar hemorrhage, renal failure, gastrointestinal (GI) bleeding from an open rectal ulcer, supraventricular arrhythmia, and encephalopathy. The episode of alveolar hemorrhage was observed in a patient with established CMV pneumonitis. This patient (UPN 16) also had the bleeding rectal ulcer. Other than these events, no significant hemorrhage in any other patient was seen. Because of their complex medical status as described above, the etiology of their adverse events was inherently difficult to characterize. In the 8 patients in whom DF was withheld per DF treatment guidelines and subsequently restarted at the equivalent or decreased dose, a causative temporal relationship to any grade 3 or 4 toxicity with DF could not be shown.

Response. Complete responses (CR) were observed in 8 patients (42%, 90% confidence interval of 23% to 63%; Table 4). Neither the pretreatment variables of patient sex, source of stem cells, conditioning regimen, and abnormal liver function tests (LFTs) on admission nor the immediate VOD-related characteristics of prior therapy with t-PA/heparin, time of onset, presence of RUQ pain, ascites, hepatomegaly, bilirubin at onset, weight gain, and abnormal portal flow were associated with response to treatment at the 0.05 significance level. A higher proportion of younger patients (age < 20 years) responded (4 of 6 *v* 4 of 13), but this also did not reach statistical significance ($P = .32$). Neither patient undergoing second SCT (UPNs 06 and 17) responded.

Of the 8 responders, 6 not only had a decrease in bilirubin to less than 2 mg/dL but also had complete resolution of any other significant end-organ dysfunction. The remaining 2 responders resolved their VOD but had persistence or occurrence of other end-organ toxicity during or after treatment. In 1 (UPN 18) renal failure and uremic coagulopathy persisted and contributed to death on day +68. In the other (UPN 14) a *Candida krusei* and CMV pneumonia supervened, resulting in intubation during DF administration and death on day +47. Because escalating

Table 4. Outcome

ID	Duration DF (d)	Dose Range (DF) mg/kg/d	Long-Term Outcome*
Responders†			
UPN01	61	10-20	Alive: NED, D + 1046 [976 d]
UPN04	26	15-5-15	Alive: NED, D + 833 [782 d]
UPN08	36	10-20	Death: relapsed ALL, D + 191 [130 d]
UPN14	35	10-25	Death: fungal sepsis, CMV pneumonitis, D + 47 [2 d]
UPN18	14	10-20	Death: respiratory failure, intracranial hemorrhage, D + 68 [43 d]
UPN19	26	10-60	Alive: NED, D + 324 [241 d]
UPN22	34	10-60	Alive: NED, D + 224 [179 d]
UPN23	45	10-40	Alive: NED, D + 217 [138 d]
Nonresponders			
UPN02	4	10-15	Death: ARF, D + 26 [1 d]
UPN03	5	15	Death: fungal sepsis, D + 25 [0 d]
UPN05	15	10-25	Death: progressive VOD, ARF, D + 27 [1 d]
UPN06	2	10	Death: fungal sepsis, D + 15 [0 d]
UPN07	7	10-15	Death: CMV pneumonitis, enterobacter, fungal sepsis, D + 45 [3 d]
UPN09	11	10-40	Death: progressive VOD, D + 40 [3 d]
UPN12	11	10	Death: DAH, D + 37 [2 d]
UPN15	10	10-35	Death: progressive VOD, D + 29 [4 d]
UPN16	35	10-60	Death: CMV pneumonitis, fungal sepsis, D + 89 [2 d]
UPN17	11	10-20	Death: CMV pneumonitis, D + 56 [18 d]
UPN21	18	10-60	Death: progressive VOD, D + 55 [0 d]

Abbreviations: NED, no evaluable disease; DAH, diffuse alveolar hemorrhage; ARF, acute renal failure; CMV, cytomegalovirus.

*Follow-up at day post SCT [number of days post discontinuation of DF].

†Responders: Bilirubin decrease <2.0 mg/dL with resolution of VOD − associated symptoms and signs.

doses of DF were used on a compassionate basis and the cases analyzed retrospectively, it is difficult to be definitive on the timing and dose dependence of response. Response was noted in the first 4 days in 7 patients who went on to CR, with 1 where response was noted more definitively at day 7. Evidence of responsiveness was seen at doses less than 25 mg/kg/d in all 8 patients. The dose was subsequently escalated in 3 patients to 40 to 60 mg/kg/d, but a dose-response relationship was not obvious. Moreover, 3 of the 8 responders were dialysis dependent at the initiation of DF. The requirement for dialysis resolved in 2 patients during treatment.

Eleven patients failed to meet the definition of response. One of these patients (UPN 17) had apparent improvement after 11 days of DF but subsequently elected to discontinue therapy. She subsequently died of progressive VOD and MOD. The remaining patients were treated until they had clear progression despite 14 days of therapy, had overwhelming infectious complications, or died of progressive VOD with MOD. The median survival of the nonresponding patients was 19 days (range, 4 to 59) from the diagnosis of VOD with deaths occurring a median of 36 days (range, 15 to 89) after SCT. In contrast, only 3 responders have died (Table 4) while 5 are alive, in remission, and remain well without any known hepatic dysfunction at a median of 324 days (range, 217 to 1,046).

Pathology reports of pretreatment biopsy samples or autopsy materials were available in 12 patients. Biopsy speciments obtained on 7 patients before treatment were believed to be confirmatory of the diagnosis of VOD by the pathologists of the treating institutions. Two of these 7 went on to have CR with DF therapy. The remaining 5, including UPN 17 who voluntarily discontinued DF, did not respond after receiving DF for 7 to 35 days (median, 11). Causes of death in this group of nonresponders are listed in Table 4 and occurred on DF in 1 patient and 3 to 22 days after DF discontinuation in the remainder. Autopsies were obtained in 6 patients, including UPN 18 who died of complications related to her renal failure after demonstrating a clinical CR of her VOD. She died 43 days after discontinuation of DF and no evidence of established or active VOD was reported on autopsy. Postmortem pathology on the 5 remaining patients, none of whom had clinical response to DF, was reported to show active, ongoing VOD in 3 (UPNs 05, 06, 07) while no definitive evidence of VOD was noted in the other 2 (UPNs 03 and 12). UPN 03, who died of fungal sepsis, was reported to show evidence of bile-duct epithelial damage and surrounding lymphocytes, interpreted as possibly representing GVHD. A reticulin stain showed mild fibrosis around central veins with mild septal fibrosis. In UPN 12, examination of the liver disclosed hepatomegaly with centrilobular congestion and sinusoidal damage, although the reported interpretation was that pathognomonic findings of VOD were not present.

DISCUSSION

In this report we describe the outcome of administering DF to 19 patients with the clinical diagnosis of severe hepatic VOD occurring after SCT. DF was obtained for compassionate use and administered in escalating doses via IV infusion in doses

ranging from 5 to 60 mg/kg/d. Previously described toxicities of DF such as transient hypotension during infusion were observed in some patients but were mild and did not require interruption or discontinuation of treatment. The severe adverse events experienced by patients receiving DF appeared to be those commonly observed in patients in this clinical context and were not directly attributable to DF administration. No life-threatening hemorrhage during treatment was observed in this very high-risk population. Eight (42%) patients had clinical resolution of their severe VOD and improvement of other organ dysfunction. Six (32%) survived past day +100, with five currently remaining alive and well 217 to 1,046 days post-SCT.

While up to half of patients undergoing SCT meet one of the current definitions of VOD, there is a broad spectrum of clinical illness.[2,3,6,7] This has made the interpretation of prophylactic and therapeutic studies problematic. However, analyses of symptom onset, symptom severity, and outcome have begun to define populations that are likely to do particularly poorly.[3,8] In addition, time to VOD diagnosis with concomitant degree of hyperbilirubinemia and weight gain have been used to generate a model that predicts probable severity and the likelihood of fatal outcome.[8] Overall, patients with mild or moderate disease most often do well without any particular treatment and have a predicted survival of 91% (mild VOD) and 77% (moderate VOD) at day +100.[3] In contrast, those with severe disease have an expected survival of only 2% at day +100.[3] All of the patients in this case series meet the definition of severe VOD used to generate this survival data. In addition, there has been considerable interest in the area of MOD and survival after SCT.[32,33] Patients with evidence of dysfunction in more than one organ have been reported to have a much higher mortality rate than others.[1,3,32,33] Again, all of the patients receiving DF had evidence of failure in at least one other system than the liver at the time of DF initiation. Dialysis dependence alone, seen at DF initiation in 5 of our patients (including 3 responders), has been reported to be associated with an 84% mortality rate, whereas doubling of the serum creatinine, seen in an additional 7 patients including 2 responders, has been associated with a 37% mortality rate.[34]

The selection of DF as a novel approach was based on its unique pharmacologic characteristics. DF represents one of a new class of agents derived from nucleic acids with polyelectrolyte effects through the presence of multiple phosphate groups and adenosine receptor agonist properties from the stearic arrangement of its base sequences.[21] This polyfunctional pharmacology makes the evaluation of measurable parameters of the drug's activity complex. For example, as well as increasing the release of PGI2,[35] PGE2,[36] and decreasing levels of leukotriene B4 in whole blood,[37] it also appears to reduce the the production of superoxide anions by neutrophils and monocytes through the inhibition of calcium ion movement,[25,38] it prevents neutrophil-induced platelet activation via an effect on cathepsin G,[23] and corollary studies in solid organ transplantation have shown improved graft survival with DF and synergy with cyclosporine.[39] Although DF does not produce systemic anticoagulation or significant in vitro anticoagulant effects on blood, both preclinical and clinical studies show profibrinolytic action, decreased levels of endothelin and tissue factor with blunted vascular smooth muscle contractile response, and increased levels of tissue factor pathway inhibitor.[20,24,40] Primate studies confirm t-PA antigen increase and PAI-1 decrease in DF-treated animals.[41] Although the pathogenesis of VOD remains incompletely understood, in vitro, clinical and pathologic data support the concept that damage to sinusoidal endothelium is at least a major contributor to the development of VOD.[4,9,42] DF as a modulator of endothelial cell injury may interrupt the progression of the endothelial-based processes which contribute to the syndrome and therefore impact favorably on the course of the disease.

Current therapeutic approaches to established VOD occurring after SCT are limited both in number and efficacy, and fraught with toxicity. Patients are typically severely ill with confounding causes of their MOD, making diagnosis, evaluation, and attribution of drug effects problematic. Nonetheless, despite both advanced supportive care and a variety of interventions, outcomes have uniformly resulted in high death rates by day +100, usually from MOD and, frequently, hemorrhage.[18] Recognizing that the same difficulties in attributing both response and toxicity exist in the series reported here, the observed survival to beyond day +100 of a significant fraction of patients with severe VOD and MOD is encouraging. In this small, retrospectively analyzed experience of extremely sick patients, it is not possible to be definitive about the attribution of toxicities. However, the absence of significant hemorrhagic or unexpected toxicity is compelling. The patient subgroups in this report are too small to analyze for factors predicting response to DF, but it is noteworthy that approximately equivalent rates of response were observed in alloSCT and autoSCT recipients and in those conditioned for SCT with either TBI, BU, or BCNU. We are conducting a larger, prospective evaluation of DF in severe VOD. This study will better define toxicity, efficacy, and patient characteristics predictive of response or failure. Although this report does not address any potential role of DF in prophylaxis, this area may also merit investigation.

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