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Defibrotide Shows Efficacy in the Prevention of Sinusoidal Obstruction Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective Study

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A B S T R A C T

Sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), is a well-known complication of allogeneic hematopoietic stem cell transplantation (HSCT) associated with a mortality rate of up to 85%. Defibrotide has shown efficacy in treatment of SOS/VOD. Moreover, evidence exists supporting the efficacy of defibrotide as SOS/VOD prophylaxis. We have previously reported our single center experience on 52 HSCT recipients receiving defibrotide as SOS/VOD prophylaxis, which has shown that the patients did not develop any SOS/VOD under this prophylaxis. The aim of the present study was to see if we can confirm the previous results, mainly on the decrease incidence of SOS/VOD, as well as improve event-free survival (EFS) on a larger study population. We extended our previous study in a single-center retrospective analysis to include 237 consecutive patients (248 transplantations) who underwent transplantation between 1999 and 2009 for hematological diseases and receiving intravenous defibrotide as prophylaxis. This cohort was compared to 241 patients (248 transplantations) treated before 1999 or after 2009 when defibrotide prophylaxis was not routinely used in our center. Median follow-up for the study group was 10 (range 2-16) years and for the control group 2.7 (range 1-18) years. None of the 237 patients in the defibrotide group developed SOS/VOD. The cumulative incidence (CI) of SOS/VOD was 0% in the defibrotide group as compared to 4.8% (95% confidence interval [CI], 2.6-8%; *P*= .00046) in the control group. There was also a better 1-year EFS with 38% (95% CI, 32%-44%) in the defibrotide group versus 28% (95% CI, 22%-34%) (*P*= .00969) and decreased cumulative incidence of acute graft-versus-host disease (GvHD) in the defibrotide group 31% (95% CI, 25%-37%) versus 42% (95% CI, 36%-48%) (*P*= .026). The 1-year overall survival, relapse incidence, and non-relapse mortality were not statistically different. Multivariable analysis, performed taking into account clinical factors known to influence the risk of SOS/VOD, confirmed the favorable impact of defibrotide on SOS/VOD (HR 1.38e-08 [95% CI, 3.28e-09-5.80e-08]; *P*< .00001). Conversely, multivariable analysis failed to confirm the impact of defibrotide on 1-year EFS or acute GvHD. This large retrospective study on SOS/VOD-prophylaxis with defibrotide suggests that this approach may be of benefit. These results need to be confirmed in a prospective randomized trial.

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Sinusoidal obstructive syndrome (SOS) of the liver, formerly known as veno-occlusive disease (VOD) of the liver is one of the complications that can occur after hematopoietic stem cell transplantation (HSCT) and can negatively impact non-relapse mortality (NRM) [1–3]. This appears to

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be in relationship with the conditioning regimen which generates toxic metabolites impacting the sinusoid endothelium and hepatocytes in zone 3 of hepatic acini [4]. Clinical manifestations of SOS/VOD are jaundice, weight gain caused by fluid retention, ascites, and painful hepatomegaly [5], but it may also appear without jaundice, as well as with a thrombocyte transfusion refractory state particularly in the pediatric population [6,7]. This plus the fact that this complication may appear after day 21 after HSCT, which was previously defined as a criteria for the diagnosis of SOS/VOD [8], has led to redefine the diagnosis criteria of SOS/VOD by the European Society for Blood and Marrow Transplantation [9].

The reported incidence after HSCT varies widely between 0% to 70% depending on the series [2,10], with the mean incidence being estimated at 14% [10]. This disparity is probably due to heterogeneity in the definition of SOS/VOD, various risk factors identified and small numbers of patients studied, as well as changes in conditioning regimen, with lower incidence with the reduced-intensity conditioning regimen. The condition ranges in severity from a mild, reversible form to a severe syndrome associated with multiple organ failure and death, mostly related to multi-organ dysfunction (MOD) [2,10]. The mortality rate of SOS/VOD can be quite high (20%-50%) [10,11], and in established severe SOS/VOD the death rate was previously shown to be close to 100% by day 100 after HSCT [12], with some improvement more recently with a death rate ranging from 27% to 84% [10,11,13].

The pathophysiology of SOS/VOD remains incompletely defined and is believed to be caused by damage to sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus surrounding the central veins induced by the conditioning regimen toxicity and associated to chemokines and cytokines released by those damaged tissues [4,5,14-16]. The damage of the endothelial cells leads to the formation of gap between them, allowing blood cells and debris to fill the space of Disse and generate the dissection of the endothelium inducing a narrowing of venular lumen with a reduced flow to the sinusoids and post-sinusoidal portal hypertension [4,17,18]. Thus, with sinusoidal endothelial cells being the primary site of the toxic injury, the clinical and physiological findings are more consistent with sinusoidal rather than venular obstruction [19]. This has led to naming this type of liver injury SOS instead of VOD [20]. During this period of toxic injury, 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-I) [21]. In addition, increased levels of von Willebrand factor (VWF) multimers and refractoriness to platelet transfusion suggest ongoing endothelial injury [22]. Finally, hepatocellular necrosis and vascular occlusion lead to hepatorenal pathology, MOD, and death [2].

Defibrotide, which is a mixture of single- and double-stranded oligonucleotides derived from porcine intestinal mucosal DNA has anti-thrombotic, anti-ischemic, anti-inflammatory, and thrombolytic properties [23]. The mechanism of action is not well understood but seems related, at least in vitro, to defibrotide binding to various sites on vascular endothelium, including adenosine receptors, and protecting endothelial cells, as well as restoring the thrombo-fibrinolytic balance [23]. This drug has shown some efficacy in the treatment of moderate to severe SOS/VOD. A 55% rate of complete resolution after defibrotide treatment without significant toxicity has been reported in European studies in patients treated for moderate or severe disease [24] and 35% to 40% of patients with multiorgan failure in American studies focusing on patients with severe SOS/VOD [25,26].

Recently, the defibrotide registration trial, a phase 3, multicenter, open-label study which assessed the efficacy and safety of defibrotide 25 mg/kg/d, in patients with hepatic SOS/VOD with advanced MOD showed a day 100 observed survival rate of 38.2% versus 25% in the historical matched control arm (P= .0109) [27]. The toxicity profile of defibrotide compared to the historical control did not show differences regarding severe hemorrhages such as pulmonary alveolar and gastrointestinal hemorrhages, which occurred in 11.8% versus 15.6% and 7.8% versus 9.4%, respectively [27]. This favorable profile was confirmed in a large, expanded access program in over 1000 patients, which also demonstrated efficacy across various settings, including severe disease and advanced multiorgan failure [28].

Because the outcome of this liver complication can be very severe, there has also been an interest in SOS/VOD prophylaxis with defibrotide for allogeneic HSCT. We previously published promising results on a small subset of 52 adults patients compared to historical controls. In the defibrotide group, we reported no SOS/VOD (0%) compared to 19% in the control group (P= .001) and a significant increased event-free survival (EFS) (P= .02) [29]. More recently, a phase 3 randomized open-label study in a pediatric population showed also an advantage of defibrotide prophylaxis after allogeneic HSCT, with 12% SOS/VOD versus 20% in the control group (P= .0507), and no difference in adverse events (87% and 88%, respectively) [7].

We report our single center experience and analyze the outcome of 237 consecutive patients who received defibrotide as SOS/VOD prophylaxis during allogeneic HSCT for various hematological malignancies and severe aplastic anemia, including the first 52 patient who were published previously. These were compared to 52 historical control patients, who underwent transplantation just before the study, and 185 control patients after the study period when defibrotide was not any more available and who received prophylactic heparin alone, as well as ursodeoxicolic acid, also given for the prevention of other liver complications (e.g., graft-versus-host disease [GVHD]) [30].

MATERIAL AND METHODS

Study population

Between October 1999 and August 2009, 237 successive adult and pediatric patients with hematological malignancies or aplastic anemia underwent 248 allogeneic peripheral blood stem cell (PBSC) or bone marrow transplantation (BMT) and received defibrotide as SOS/VOD prophylaxis in the BMT units of the Geneva University Hospital. All patients gave their informed consent, and all the research studies were approved by the University and Institutional Review Boards. We previously published the data of the 52 first patients compared to 52 historical controls who had been successively transplanted in our center just before the study period (between February 1997 and September 1999) and received only heparin as SOS/VOD prophylaxis. We have expanded the study with 185 additional patients treated successively with defibrotide prophylaxis and added to the control group patients who underwent transplantation after 2010 (2011–2015), when defibrotide as prophylaxis was not available anymore in our center (change of provider of the drug and the price increase of the drug). In total, the control group comprised 241 patients with 248 transplantations.

Prophylaxis protocol and clinical monitoring

SOS/VOD prophylaxis with defibrotide (Prociclide; Crinos, Como, Italy) 200-400 mg (10-25 mg/kg/d in children weighing less than 30 kg) i.v. in normal saline solution over 2 hours 4 times daily was initiated the day before starting the conditioning regimen and continued until day 20 after transplantation. Patients at higher risk of developing SOS/VOD, such as those with pretransplantation liver disturbance, pretransplantation abdominal irradiation, previous stem cell transplantation [1,31,32] received the higher dosage (400 mg 4 times daily) as compared to standard doses (200 mg 4 times daily) in standard-risk adult patients. In addition, low-dose heparin (5000 IU i.v. continuous/24h if weight <70 kg or 10,000 IU if weight >70 kg) was given

routinely [33]. Patients were examined and their weight recorded daily. They were evaluated for the presence or absence of unexplained weight gain, liver pain, hepatomegaly, and ascites and for toxicities known to be related to defibrotide [25]. In case of suspicion of SOS/VOD development, ultrasonography with a Doppler test was performed to evaluate the liver, the presence of ascites and attenuated or inverted hepatic flow, as well as in some situations liver biopsy. Laboratory tests included daily complete blood count and electrolytes, and, 3 times per week, liver function tests (AST, ALT, alkaline phosphatase, direct and indirect bilirubin, gama-glutamyltransferase (GGT)), prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen.

Evaluation of SOS/VOD

As the study period was before the description of the new European Society for Blood and Marrow Transplantation criteria for SOS/VOD [9], the Baltimore criteria were used for the diagnosis of SOS/VOD [8], taking into account jaundice (bilirubin level 34.2 μmol/L or higher) and 2 or more of the following: hepatomegaly, right upper quadrant pain, ascites, unexplained weight gain (5% or more above baseline weight) [8].

Statistical analysis

Categorical variables between the study group and the historical control group were compared using the chi-square test or Fisher's exact test as appropriate, continuous variables were compared using the Mann-Whitney test. Variables are described by means of median and first and third quartiles (Q1; Q3). Overall survival (OS) and EFS (events were defined as first occurrence of either SOS/VOD, acute GVHD [aGVHD] ≥grade II, relapse or death) probabilities were calculated using the product limit method of Kaplan and Meier [34], with surviving patients being censored on July 18, 2016, and compared by the log-rank test. Multivariable OS and EFS analysis was conducted using Cox regression to examine the independent impact of clinical factors. Cumulative incidence of SOS/VOD was calculated using the Gray test for univariable analysis and the Fine-Gray method for proportional hazard regressions with death from other causes as competing event [35]. Cumulative incidence of relapse (with NRM as competing event), NRM (with relapse as competing event), and ≥grade II acute GvHD (with relapse as competing event) incidence were calculate using the same methods.

RESULTS

Patients' characteristics

The characteristics of the patients are shown in Table 1.

The study and the control groups were similar with respect to age, sex, primary disease, type of chemotherapy used in the conditioning regimen, increased level of transaminases before transplantation, number of second transplantations, hemoglobin level, and history of liver dysfunction (data not shown) with some imbalance regarding the type of donor and the stem cell source (less unrelated donor and more PBSC in the study group). Patients in the study group had been transplanted more frequently with partially T cell depleted grafts (186 versus 93 patients in the control group) and less frequently with in vivo T-cell–depleted grafts (124 versus 158 patients in the control group). Methotrexate was given as GVHD prophylaxis regimen more frequently and mycophenolate mofetil less frequently in the study group. Finally, a higher proportion received myeloablative conditioning (MAC) versus reduced-intensity conditioning (RIC) conditioning regimen in the study group (MAC: n = 167; RIC: n = 81) compared to the control group (MAC: n = 123; RIC: n = 125).

Side effects

Defibrotide was well tolerated and did not have to be discontinued in any of the patients. Mild to moderate toxicity such as nausea, abdominal cramps and fever were documented, but it was difficult to determine whether they were directly attributable to defibrotide or to the conditioning or other drugs commonly used during transplantation. There were no grade 3 or 4 toxicities related to defibrotide nor any worsening of clinical bleeding.

Incidence of SOS/VOD

The median follow-up for the study group was 10 (range 2-16) years and for the control group 2.7 (range 1-18) years. None of the 237 patients (248 transplantations) in the defibrotide group developed SOS/VOD (Baltimore criteria) [8]. The 100-day cumulative incidence of SOS/VOD was 0% in the defibrotide group as compared to 4.8% (95% CI, 2.6-8%) in the control group which was statistically significantly different (P= .00046; Figure 1).

In the control group, 13 of 241 patients suffered from SOS/VOD (cause of death in 3 patients, 1 of which autopsy proven, for the 2 others autopsy was denied). It is noteworthy that none of the 5 females in the control group who developed SOS/VOD had been treated with norethisterone, known to increase the incidence of SOS/VOD [36]. Of note also, 10 out of 13 of SOS/VOD occurred in the earlier period of 1997-1999 (10/52 = 19%) as opposed to only 3 between 2010-2015.

Multivariable analysis, performed including other SOS risk factors, confirmed the favorable impact of defibrotide on 100-day SOS/VOD cumulative incidence (HR 1.38e-08 [95% CI, 3.28e-09-5.80e-08], P< .00001) (Table 2).

The other factors impacting negatively the incidence of SOS/VOD were lower age of the patients, lower Karnofsky performance status, higher pre-transplantation transaminase and bilirubin levels, year of transplantation < 2007, unrelated or mismatched donors, MAC regimen, or use of busulfan in the conditioning (Table 2).

We noted a tendency of a lower maximum level of total bilirubin up to 100 days post-transplantation in the study group treated with defibrotide (p=0.0617) but no difference in the rate of patients with a total bilirubin > 50 μM between the 2 groups (P= .2408) (Table 3).

This was different from the previous study on 52 patients and 52 control patients which showed that this was statistically significantly lower in the defibrotide treated group of patients (P< .0001 and P= .004, respectively) [29]. However, the parameters linked to clot formation on damaged endothelial cells were less manifest in the group treated with defibrotide. The aPTT, as well as the PT were significantly reduced in the study group (P< .0001 and P = .0005, respectively; Table 2). As a result, the number of patients with an aPTT > 50 seconds was significantly lower (P< .0001) but not the number of those with a PT > 1.5 international normalized ratio (P= .7475). On the other hand, maximum fibrinogen levels were higher (P< .0001) in the patients treated with defibrotide. All the effects seen above remained significant, after the patients with SOS/VOD in the control group had been omitted from the analysis, but there were no more a tendency to have a maximum level of total bilirubin lower in the defibrotide group compared to the control group (Table 3).

EFS, OS, relapse incidence, NRM and incidence of GVHD

Figure 2 shows the EFS (Figure 2A) and OS (Figure 2B), the CI of NRM (Figure 2C) and of relapse (Figure 2D) of the patients in the defibrotide treated group compared to the control group.

The day 100 EFS was not significantly different with 60% (95% CI, 54%-66%) in the defibrotide group versus 53% (95% CI, 47%-59%) in the control one (P= .165), but the 1-year EFS was statistically different with 38% (95% CI, 32%-44%) versus 28% (95% CI, 22%-34%) (P= .0097) (Figure 2A; Table 4).

The day 100 OS, as well as the 1-year OS, was not different between both groups, although there was a tendency for a higher 1-year OS of 73% (95% CI, 67%-78%) in the defibrotide

Table 1
Characteristic of the Patients

Characteristic	Study Group (With Defibrotide)	Control Group (Without Defibrotide)	*P* Value
No. of transplantations	248	248	
No. of patients	237	241	
Age			
Years (median, range)	45.00 (2-69)	47.00 (0-70)	.0983
Pediatric (<18 years)	21	15	
Adults	216	226	
Sex			.8525
Male	157	155	
Female	91	93	
Diagnosis			.0738
CML	31	16	
AML	67	96	
ALL	33	36	
MDS/MDPS	36	35	
MPN	11	14	
Lymphoma	29	21	
AA	14	9	
MM	16	15	
Other*	11	6	
Donor type			.0067
MRD	136	107	
MUD	69	97	
MMRD/MMUD	37	43	
Identical twin	6	1	
SC source			.0247
PBSC	221	202	
BM	27	40	
PBSC/BM	0	2	
CB	0	4	
Second transplantation	14	14	1
Ex vivo TCD	186	93	<.0001
In vivo TCD (ATG or alemtuzumab)	124	158	.0021
GVHD prophylaxis			.0001
CsA + MTX	108	94	
CsA + MMF	74	106	
CsA	57	28	
Other	9	20	
Conditioning regimen (intensity)			<.0001
MAC	167	123	
RIC	81	125	
Conditioning regimen (drugs)			.0758
With cyclophosphamide	155	127	
With busulfan	79	70	
With VP-16	17	29	
TBI doses			<.0001
1200 cGy	62	49	
1000 cGy	57	13	
600 cGy	11	9	
400 cGy	0	20	
200 cGy	2	17	
0 cGY	116	130	
Increased transaminases before conditioning	78	72	.5575

CML indicates chronic myeloid leukemia; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; MDPS, myelodysplastic/myeloproliferative syndrome; MPN, myeloproliferative neoplasia; AA, aplastic anemia; MM, multiple myeloma; MRD, matched related donor; MUD, matched unrelated donor; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; SC, stem cell; BM, bone marrow; CB, cord blood; TCD, T-cell depletion; ATG, anti-thymoglobulin; CsA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation.

* Other indications included hemoglobinopathies, histiocytic disorders, solid tumors and unknown.

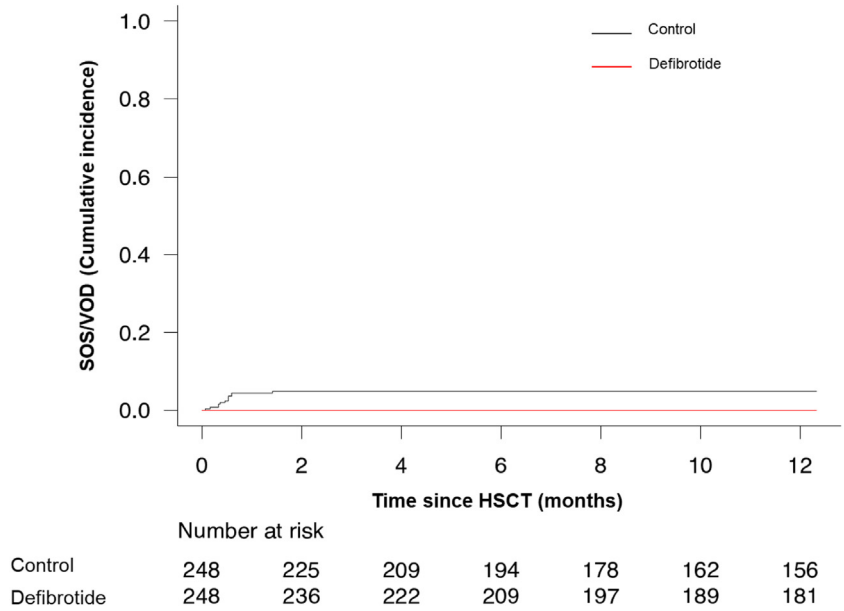

Figure 1. Cumulative incidence of SOS/VOD after allogeneic stem cell transplantation in patients treated with defibrotide prophylaxis (*red*) or without (*black*).

study group as compared to the control group with 65% (95% CI, 59%-71%) (*P*= .070) (Figure 2B, Table 4).

There were also no statistically significant differences between both groups concerning the one year NRM with 14% (95% CI, 10%-18%) for the defibrotide study group versus 19% (95% CI, 14%-24%) for the control group (*P*= .148) (Figure 2C, Table 4), as well as for the 1 year RI with 32% (95% CI, 27%-38%) for the defibrotide study group versus 28% (95% CI, 22%-34%) for the control group (*P*= .331) (Figure 2D and Table 4).

Finally, the incidence of aGVHD was significantly lower in the study group with 31% (95% CI, 25%-37%) for the defibrotide study group as opposed to 42% (95% CI, 42%-46%) for the control group (*P*= .026) (Table 4). However, this difference was not confirmed in multivariable analysis (Table 5).

DISCUSSION

SOS/VOD is a complication occurring after allogeneic or autologous blood or marrow stem cell transplantation with an incidence which is variable between 0 and 60% depending on different factors, the more important being the type of transplantation with a higher incidence with allogeneic HSCT as opposed to autologous HSCT, the age of patients (younger worse), the intensity of conditioning regimen (MAC with higher incidence than RIC, the use of busulfan and higher doses of it increasing the risks [37]. It also seems to have decreased in the recent period, possibly in relationship with the decreased use of MAC regimen, better supportive care, improved BMT technologies [37,38]. Most of the time, patients with mild or moderate disease do well with a predicted survival between 77% to 91% at day 100. In contrast, patients with severe disease have a dismal outcome with an expected survival of 2% at day 100 [39], although this has improved recently with earlier diagnosis and intervention, better supportive care and introduction of new therapies such as defibrotide [3,26-28,40]. The diagnosis remains complicated because of lack of consensus with regard to the classification of the different stages of the disease (mild, moderate, severe) [11]. For the same reason, the interpretation of studies on prophylactic or therapeutic drugs has been problematic. Recently there have been efforts to

Table 2
Multivariable Analysis of the Cumulative Incidence of SOS/VOD

	Hazard Ratio	Lower 95% CI	Upper 95% CI	*P* Value
Age (>50 versus <50 years)	0.147	0.032	0.685	.01500
Karnofsky (<90% versus >90%)	1.679	0.360	7.821	.51000
AST/ALT (high versus normal)	34.410	5.813	203.700	.00010
Bilirubin (high versus normal)	31.660	1.886	531.500	.01600
HSCT year (<2007 versus >2007)	113	5.57	2310	.00210
Donor (unrelated versus related)	2.098	0.539	8.169	.29000
Donor (mismatched versus matched)	0.307	0.037	2.563	.28000
Conditioning (RIC versus MAC)	0.077	0.008	0.703	.02300
Busulfan use (yes versus no)	22.810	6.079	85.580	<.00001
TBI (yes versus no)	2.758	0.564	13.490	.21000
TCD	0.670	0.107	4.178	.67000
HSCT number (second versus first)	2.501	0.468	13.370	.28000
Defibrotide use (yes versus no)	0.0000000138	0.00000000327	0.0000000578	<.00001

AST indicate aspartate transferase; ALT, alanine transferase.

Table 3
Comparison Between the Study Group and the Control Group With or Without Patients With SOS/VOD

Parameters	Study Group (S)	Control Group (C)	*P* Value S Versus C*	Control Group Without VOD (C1)	*P* Value S Versus C1
Maximum total bilirubin (μmol/L)†	22 (17; 31)	26 (17; 39)	.0617	24 (16; 37)	.2759
No. of patients with total bilirubin >50 μmol/L (%)	29/248 (11.7%)	48/248 (19.4%)	.2408	37/235 (15.7%)	.5416
Maximum aPTT (s)	35.2 (30.3; 41.7)	44.5 (36.5; 55.3)	<.0001	44.5 (36.4; 55.3)	<.0001
No. of patients with maximum aPTT >50 seconds	21/248 (8.5%)	82/248 (33%)	<.0001	79/235 (33.6%)	<.0001
Maximum PT (INR)	1.10 (1.00-1.20)	1.12 (1.04-1.24)	.0005	1.12 (1.03-1.23)	.0045
No. of patients with maximum PT > 1.5 INR	9/228 (3.95%)	15/245 (6.1%)	.7475	11/232 (4.7%)	1
Maximum fibrinogen (g/L)	7.2 (5.7-8.5)	5.8 (4.9-7.0)	<.0001	5.8 (4.9-7.0)	<.0001
No. of patients with maximum fibrinogen >6 g/L	178/248 (71.8%)	116/248 (46.8%)	.0005	108/235 (46%)	.0003

aPTT indicates activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio.
Bilirubin levels were observed during the first 100 days.
* *P* value calculated by Mann-Whitney test or Fisher's exact test.
† Values are given as median and first and third quartiles (Q1;Q3).

characterize better the disease and define new criteria for the diagnosis of SOS/VOD, as well as regarding the different stages of severity for the adult and pediatric population but there is still not true consensus on using systematically those criteria [9,41,42]. Because the present study was done in the years when those criteria were not yet developed, we used only the Baltimore criteria for the diagnosis of SOS/VOD, and therefore we may have underdiagnosed mild VOD in both groups. Moreover the incidence of SOS/VOD of 4.8% we found in the control group is very close to the incidence of 4.9% found in the CIBMTR study that was used to determine the CIBMTR risk score for SOS/VOD on patients transplanted between 2008 and 2013 close to the period of our study [42].

Recently, some progress has been made in treating severe SOS/VOD mainly using defibrotide [24-27,40,43]. Defibrotide use was not only efficient but the side effect of systemic bleeding was shown not to be an issue [24–26]. Because it may be difficult to improve the CR rate of 25% to 55% obtained in these studies, we have tested the benefit of defibrotide as a prophylactic agent for SOS/VOD. We previously published the first result of our non-randomized series of 52 patients who received defibrotide SOS/VOD prophylaxis and no SOS/VOD occurred in those successive allogeneic transplant patients [29]. This compared favorably to the historical control series of 52 successive patients who underwent transplantation before the study, 10 of whom developed SOS/VOD that was fatal in 3 cases. The high incidence of SOS/VOD in the control group is comparable to other published reports at the time of this initial study (15%-29%) [44–46]. We now have completed the study with a much higher number of patients who were successively transplanted with defibrotide prophylaxis. Indeed, to our knowledge those 237 patients represent the highest series of patients with defibrotide prophylaxis reported to date. The results confirmed those found in the preliminary one on 52 patients, with no SOS/VOD found in the prophylaxis group as compared to 4.8% in the control group which was statistically significantly different (Figure 1). This was also confirmed in the multivariable analysis (Table 2), with defibrotide showing one of the strongest beneficial effect in this analysis. The other factors impacting on SOS/VOD incidence were as already

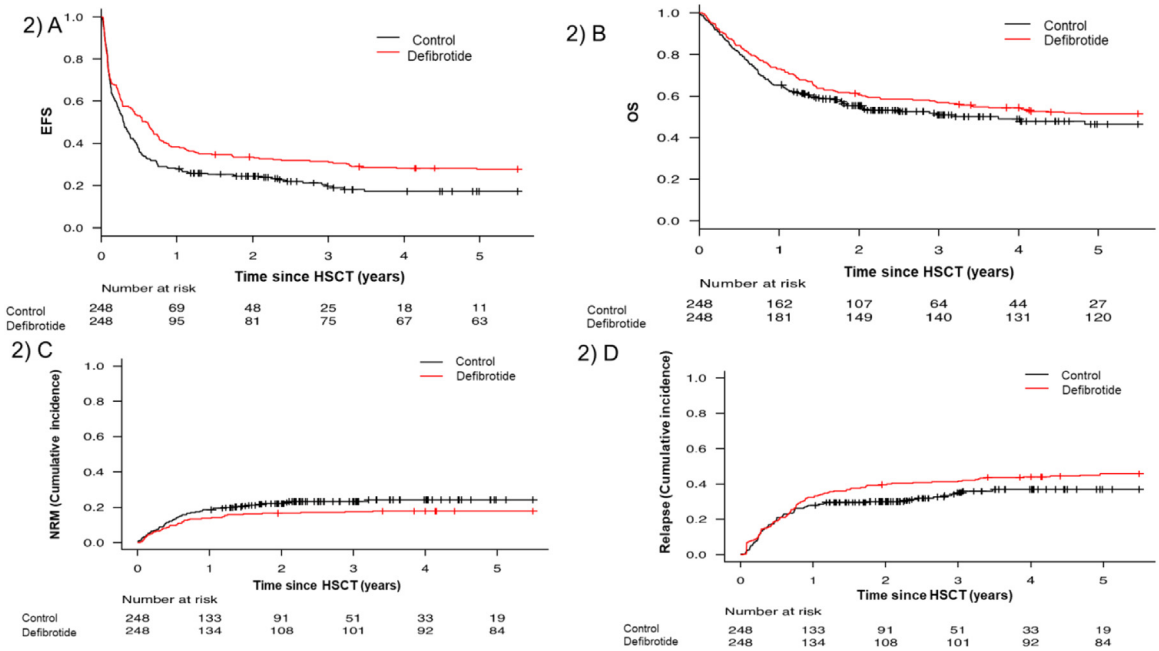

Figure 2. (A) EFS, (B) OS, (C) cumulative incidence of NRM, and (D) cumulative RI after allogeneic stem cell transplantation in patients treated with defibrotide (*red*) or without (*black*).

Table 4
Comparison of Outcomes Between Patients With and Without Defibrotide Prophylaxis

Parameters	Study Group	Control Group	*P* Value
Day 100 EFS	60% (95% CI, 54-66)	53% (95% CI, 47-59)	.165
Day 100 OS	91% (95% CI, 86-94)	90% (95% CI, 85-93)	.635
EFS (1 year)	38% (95% CI, 32-44)	28% (95% CI, 22-34)	.0097
OS (1 year)	73% (95% CI, 67-78)	65% (95% CI, 59-71)	.070
NRM (1 year)	14% (95% CI, 10-18)	19% (95% CI, 14-24)	.148
RI (1 year)	32% (95% CI, 27-38)	28% (95% CI, 22-34)	.331
aGVHD grade ≥II	31% (95% CI, 25-37)	42% (95% CI, 36-48)	.026

EFS indicates event free survival; aGVHD, acute graft versus host disease.

known the conditioning (MAC worse than RIC), the age of patients (younger age than 50 years worse), the level of transaminase and bilirubin prior to transplant (higher being worse), the year of transplantation (before 2007 worse), Table 2. Another strong predictive factor, apart from defibrotide use, was the use of busulfan in the conditioning which had a negative impact. However, in our series, we did not find as previously described any impact of the Karnofsky score [42] nor a one from total body irradiation (TBI). The latter may be explained by the fact that we use a lower dose of 10 Gy TBI in the MAC for adults older than 40 years because it was shown to be less toxic without increasing the risk of relapse by our group [47]. Although this study was not prospective and randomized, we consider these results as notable because of the consequent number of patients analyzed and because the control group and the study group successively underwent transplantation in the same transplantation center and shared slightly different clinical characteristics (except for the more frequent PBSC transplantation, matched related donors use, ex vivo T-cell depletion, TBI- based conditioning regimen and higher TBI dose, MAC conditioning regimen and less in vivo T-cell depletion, less mycophenolate mofetil in the study group). These differences do not seem to have impacted the differences seen between both groups on the incidence of SOS/VOD because globally there were more patients with increased risk factors for SOS/VOD in the study group, which rather should have favored the control group in having less SOS/VOD and not the opposite.

This study shows that not only the incidence of SOS/VOD ($P< .0001$), but also the 1-year EFS ($P= .0097$), is significantly different (Figure 2 A). In contrast, only a trend to a better 1-year OS ($P= .070$) was found, possibly owing to the low incidence of mortality caused by the SOS/VOD. A further trend was found for a better 1-year NRM (14% (95% CI, 10-18) versus 19% (95% CI, 14-24) ($P= .148$), which may have led to a tendency of better OS in the defibrotide group. However the multivariable analysis was not able to confirm those trends except for the EFS with a hazard ratio of 0.76 (95% CI, 0.580-1.003) ($P= .0524$) (Table 5).

This study has several limitations. It is retrospective and spans a period of more than 15 years (1997-2015) with potential improvement on transplant supportive care and transplantation strategies, such as, for instance, decreased use of MAC during this same period [37,38]. For those reasons, there are also some differences in the characteristics of the 2 group of

Table 5
Multivariable Analysis of EFS and aGVHD Between Patients With and Without Defibrotide Prophylaxis

	Hazard Ratio	Lower 95% CI	Upper 95% CI	*P* Value
EFS				
Age (>50 versus <50 years)	1.118	0.859	1.457	.4070
Karnofsky (<90% versus >90%)	1.488	1.169	1.893	.0012
AST/ALT (high versus normal)	0.953	0.736	1.234	.7146
Bilirubin (high versus normal)	1.601	1.231	2.088	.0005
HSCT Year (<2007 versus >2007)	1.1722	0.871	1.158	.2963
Donor (unrelated versus related)	1.621	1.278	2.056	.00007
Donor (mismatched versus matched)	0.987	0.726	1.341	.9321
Conditioning (RIC versus MAC)	1.317	0.994	1.758	.0554
Busulfan use (yes versus no)	1.187	0.861	1.635	.2953
TBI (yes versus no)	1.195	0.871	1.642	.2695
TCD	0.585	0.433	0.792	.0005
HSCT number (second versus first)	0.571	0.338	0.969	.0376
Defibrotide use (yes versus no)	0.762	0.579	1.003	.0521
aGVHD				
Age (>50 versus <50 years)	1.342	0.952	1.891	.0930
Karnofsky (<90% versus >90%)	1.099	0.782	1.543	.5900
AST/ALT (high versus normal)	1.076	0.755	1.533	.6800
Bilirubin (high versus normal)	1.347	0.921	1.969	.1200
HSCT Year (<2007 versus >2007)	0.917	0.621	1.354	.6600
Donor (unrelated versus related)	1.489	1.067	2.079	.0190
Donor (mismatched versus matched)	0.904	0.570	1.433	.6700
Conditioning (RIC versus MAC)	1.014	0.711	1.444	.9400
Busulfan use (yes versus no)	1.106	0.750	1.631	.6100
TBI (yes versus no)	0.971	0.652	1.447	.8900
TCD	0.503	0.341	0.743	.0006
HSCT number (second versus first)	0.745	0.353	1.570	.4400
Defibrotide use (yes versus no)	0.829	0.578	1.187	.3000

patients as shown in Table 1. However, we believe that those results are still valuable because, on one hand, the majority of the control group patients have undergone transplantation in the more recent period where it has been shown that the incidence of SOS/VOD has decreased as compared to earlier period [37,38]. Of note, in the present study, the incidence of SOS/VOD was much lower in the control group of the period of 2010 to 2015, with 1.6% as opposed to 19% in the control group of the 1990s. This has to be integrated in the decision whether to use defibrotide as a prophylactic agent for all transplant patients. This is particularly true because, although the safety is not a concern, the huge price of the drug, which impacts severely on the cost/benefit for patients, is an important one. Therefore the benefit of prophylaxis may be more for patients with higher risk for development of SOS/VOD, and in the presence of such patients the introduction of defibrotide prophylaxis may be discussed to decide whether to implement it before starting the conditioning. This was also well discussed in a recent review mentioning the risk factors and the potential use of defibrotide as a prophylaxis for such high-risk patients [48].

On the other hand, most of the differences seen between both groups in the characteristics of the patients are not favorable to the defibrotide group (more PBSC, more MAC, more TBI and higher doses of TBI in the defibrotide group, more pediatric patients, all known to increase the risk of SOS/VOD), whereas the only factor favoring the study group is the lower number of unrelated donor transplantations. Concerning T-cell depletion, there was more ex vivo T-cell depletion in the study group but on the other hand more in vivo T-cell depletion in the control group.

In conclusion, these data suggest, on a substantial number of patients, that defibrotide may prevent SOS/VOD after allogeneic stem cell transplantation as shown in the randomized study in the pediatric population [7]; however, because of the decreased incidence of SOS/VOD in the last decade and the huge price of defibrotide, the use of it for prophylaxis should be carefully discussed, and the cost/benefits for transplant patients should be carefully considered. A randomized phase 3 clinical trial in adult and pediatric patients was recently completed in March 2022 (ClinicalTrials.gov Identifier: NCT02851407), and the results are still pending.

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