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Supportive Care

Defibrotide for Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease Prophylaxis in High-Risk Adult Patients: A Single-Center Experience 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 serious complication after hematopoietic stem cell transplantation (HSCT). SOS/VOD usually occurs within 3 weeks of HSCT, but the 2016 European Society for Blood and Marrow Transplantation diagnosis criteria have been revised to include late forms. Prophylactic use of defibrotide is recommended in the pediatric setting, but its value remains uncertain in the adult population. We report here a single-center series of 63 adult patients considered at high risk for SOS/VOD who received defibrotide prophylaxis in combination with ursodeoxycholic acid between May 2012 and August 2016. The median duration of defibrotide therapy was 23 days. Bleeding occurred in 14 patients (21.5%). Defibrotide prophylaxis was discontinued in 7 patients (10.8%): 4 cases (6.3%) due to bleeding and 3 cases (4.6%) because of the need for antithrombotic therapy. Overall, SOS/VOD occurred in 4 cases (6.3%) within 21 days after HSCT (days 13 and 14) in 2 cases and late-onset SOS/VOD (days 57 and 58) in the other 2 cases. SOS/VOD was moderate in 1 case, very severe in 3 cases, with 2 deaths related to SOS/VOD. Cumulative incidence of grades II to IV acute graft-versus-host disease and transplant-associated thrombotic microangiopathy were 22.2% and 3.2%, respectively. With a median follow-up of 31 months (range, 10.7 to 60.3), the rates of 2-year overall survival, progression-free survival, incidence of relapse, and nonrelapse mortality were 56.5%, 49%, 28.7%, and 22.3%, respectively. In our experience defibrotide prophylaxis is associated with a low incidence of SOS/VOD after allogeneic HSCT in a high-risk adult population with an acceptable safety profile.

INTRODUCTION

Sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), is a frequent and serious toxic complication of hematopoietic stem cell transplantation (HSCT). Although it has been described after both autologous and allogeneic HSCT, it seems much more frequent after the latter, with a reported incidence of 8% to 14% [1]. This can dramatically increase in high-risk populations.

The pathogenesis of SOS/VOD, often multifactorial, begins with activation and damage of sinusoidal endothelial cells. This is followed by the permeabilization of the endothelial barrier with penetration of blood cells and cellular debris into the space of Disse, leading to the narrowing of the sinusoidal lumen, and the development of a postsinusoidal portal hypertension [2].

The risk factors are related to the transplant, to patient or disease characteristics, or to liver status before HSCT [2-5]. The transplant-related risk factors include unrelated donor or HLA-mismatched donor, non–T cell–depleted transplant,

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myeloablative conditioning regimen, busulfan-based regimen, total body irradiation, and second (or more) HSCT. Predisposing patient or disease characteristics include older age (in the adult population), Karnofsky score below 90%, metabolic syndrome, norethisterone treatment, advanced disease (beyond second complete response or relapsing or refractory), thalassemia, and some genetic factors such as hemochromatosis C282Y allele. Hepatic status risk factors are previous history of hepatic disease such as cirrhosis or active viral hepatitis, elevation of transaminases or bilirubin, iron overload, hepatic irradiation, or treatment with hepatotoxic drugs such as inotuzumab ozogamicin or gemtuzumab ozogamicin, albeit the latter statement has been recently called into question [6].

SOS/VOD usually occurs within 3 weeks after HSCT but can develop later, and diagnosis criteria have been revised to include these late forms [4]. Symptoms include hyperbilirubinemia, weight gain, ascites, and painful hepatomegaly. Most severe forms evolve toward multiorgan failure with a mortality rate greater than 80% [3].

Ursodeoxycholic acid (UDCA) is commonly used for SOS/VOD prophylaxis. Heparin is used in some centers despite the fact that data on its efficacy are not supported by the literature [2,7]. Defibrotide is an oligonucleotide derived from porcine tissue that possesses anti-inflammatory and profibrinolytic properties and has proved its effectiveness in the treatment of SOS/VOD [8,9]. Used in prophylaxis, it could have a protective action on endothelial cells and could reverse the prothrombotic state observed in SOS/VOD [10]. Defibrotide has been used in the prevention of SOS/VOD in a pediatric randomized controlled trial [11]; however, data in the general adult population are scarce. We report our experience of defibrotide in combination with UDCA for SOS/VOD prophylaxis in a high-risk adult population undergoing allogeneic HSCT.

METHODS

We included in our study 63 consecutive patients who underwent an allogeneic HSCT with defibrotide prophylaxis between May 2012 and August 2016 in our tertiary care hospital. Patients gave written informed consent in accordance with the modified Helsinki declaration and local Ethical Committee. Patients' medical records were retrospectively reviewed, and data on risk factors were collected. All patients were at high risk of SOS/VOD according to the European Society for Blood and Marrow Transplantation (EBMT) criteria [4].

The incidence of SOS/VOD and other HSCT-related complications were determined, and tolerance was evaluated by the incidence of hemorrhagic events. Pre-existing liver disease was defined by any hepatic disease history excluding specific liver involvement by the hematologic disease itself, hepatic irradiation, or active viral hepatitis, which are mentioned separately. Iron overload was defined regardless of hepatic consequences, by serum ferritin elevation above 1000 ng/mL, because it is the most commonly used threshold [12].

SOS/VOD Prophylaxis

All patients received i.v. defibrotide at 25 mg/kg per day divided in 4 daily doses of 6.25 mg/kg in 5% dextrose over 2 hours, from the start of the conditioning regimen to engraftment. Defibrotide therapy was stopped in case of severe bleeding or need for antithrombotic therapy. All patients received UDCA for SOS/VOD prophylaxis until day +90 after transplant.

Other Transplant Modalities

Conditioning regimen consisted in fludarabine-busulfan (n = 19), thiotepa-busulfan-fludarabine (n = 19), sequential conditioning (thiotepa-based, n = 15; clofarabine-based, n = 3; amasacrine-based, n = 1), or total body irradiation-based reduced intensity conditioning (n = 6). Graft-versus-host disease (GVHD) prophylaxis and other transplant modalities are described in Table 1. Central venous catheter and prophylactic anti-infective therapy were used routinely. Empiric i.v. antibiotics and blood product transfusions were given as required. In this group of patients receiving defibrotide prophylaxis, prophylactic platelet transfusions were administrated whenever platelet level fell below 30×10^9/L.

Table 1
Patient Characteristics and Risk Factors for SOS/VOD (N = 63)

Characteristic	Value
Median age at HSCT, yr (range)	48.5 (16-71)
Gender, male	39 (61.9)
Primary disease	
Acute myelogenous leukemia	30 (47.6)
Acute lymphoblastic leukemia	3 (4.8)
Lymphoid neoplasms (chronic lymphocytic leukemia, lymphoma)	17 (27.0)
Myelodysplastic syndrome and myeloproliferative neoplasm	10 (15.9)
Plasma cell dyscrasia	2 (3.2)
Aplastic anemia	1 (1.6)
Type of graft	
Peripheral blood stem cells	50 (79.4)
Bone marrow	8 (12.7)
Umbilical cord blood	5 (7.9)
Type of donor (cord blood grafts excluded)	
Matched related donor	10 (15.9)
Haploidentical donor	26 (41.3)
Matched unrelated donor	20 (31.7)
Mismatched unrelated donor	2 (3.2)
Non–ex vivo T cell–depleted transplant	63 (100)
Myeloablative conditioning	12 (19.0)
Reduced-intensity conditioning	32 (50.8)
Sequential conditioning	19 (30.2)
Conditioning regimen	
Fludarabine-busulfan	19 (30.2)
Thiotepa-busulfan-fludarabine	19 (30.2)
Thiotepa-based sequential conditioning	15 (23.8)
Clofarabine-based sequential conditioning	3 (4.8)
Amsacrine-based sequential conditioning	1 (1.6)
TBI-based reduced-intensity conditioning	6 (9.5)
Other SOS/VOD high-risk criteria	
Previous allogeneic HSCT	20 (31.7)
Previous autologous HSCT	27 (43.0)
Advanced disease (beyond second complete remission or refractory/relapse)	28 (44.4)
Transaminase > 2.5 ULN	11 (17.5)
Serum bilirubin > 1.5 ULN	1 (1.6)
Pre-existing liver disease	17 (27.0)
Active viral hepatitis	2 (3.2)
Previous abdominal or hepatic irradiation	9 (14.3)
Previous use of gemtuzumab ozogamicin	23 (37.0)
Iron overload (ferritin > 1000 ng/mL)	32 (50.8)
Immunosuppression	
Antithymocyte globulin	55 (87.3)
Cyclosporine A	63 (100)
Mycophenolate mofetil	53 (84.1)
Cyclophosphamide	26 (41.3)
Methotrexate	2 (3.2)
Other treatments for SOS/VOD prophylaxis	
Heparin	6 (9.5)
UDCA	63 (100)

Values are n (%) unless otherwise defined. TBI indicates total body irradiation; ULN, upper limit of normal.

Diagnosis Criteria for SOS/VOD

SOS/VOD was retrospectively diagnosed according to the new criteria defined by the EBMT in 2016 [4]. So as not to underestimate the incidence of SOS/VOD in our population, we chose to classify as SOS/VOD if the criteria were met even if the diagnosis had not been evoked at the time of patient's care. The severity was assessed according to EBMT criteria.

The classical form, occurring during the first 21 days after HSCT, was diagnosed by the association of bilirubin ≥ 2 mg/dL (or 34 μmol/L) and 2 or more of the following criteria: painful hepatomegaly, weight gain > 5%, and/or ascites. This classical form was distinguished from the late form, which was defined by either classical SOS/VOD beyond day 21, histologically proven SOS/VOD after day 21, or the association of 2 or more of the following criteria: bilirubin ≥ 2 mg/dL (or 34 μmol/L), painful hepatomegaly, weight gain > 5%, ascites, and hemodynamic and/or ultrasound evidence of SOS/VOD.

Patients were monitored for SOS/VOD occurrence by daily clinical examination, laboratory testing, and, if necessary, abdominal ultrasound. Once SOS/VOD was diagnosed, patients received supportive care including intensive care unit admission if required, fluid restriction, diuretic treatment, and pursuit or reintroduction of defibrotide at the same dose used for prophylaxis.

Statistical Analysis

Results are expressed as median and interquartile range for duration of prophylaxis and as absolute value (proportion) for demographic characteristics, risk factors, and incidence. Acute and chronic GVHD were diagnosed and graded according to standard criteria [13,14]. Overall survival and progression-free survival were calculated by the Kaplan-Meier method. SOS/VOD, transplant-associated thrombotic microangiopathy (TA-TMA), relapse, nonrelapse mortality, and GVHD were calculated using the cumulative incidence method in a time-dependent fashion. For SOS/VOD, TA-TMA, relapse, and GVHD, death of the patient was considered as a competing risk of the event. For nonrelapse mortality the competing event was relapse. All analyses were performed with IBM SPSS 20 (IBM, Armonk, NY) and R 3.0 (R Development Core Team, Vienna, Austria).

RESULTS

A total of 63 patients received defibrotide prophylaxis between May 2012 and August 2016 and were included in the study. Demographic characteristics and risk factors of SOS/VOD are presented in Table 1.

Defibrotide Prophylaxis Toxicity

The median duration of defibrotide treatment was 23 days (interquartile range, 21 to 28). Fifteen bleeding events occurred in 14 patients (22.2%) and were all reversible. No grade IV adverse events were observed in our patients. Characteristics of bleeding events are detailed in Table 2. Nine of 11 cases of hemorrhagic cystitis (81.8%) were associated with BK virus. A gastrointestinal bleeding occurred in 2 patients and was related to an ulcerative esophagitis in the first case and with colonic angiodysplasia in the second case. None of these 2 patients presented GVHD at time of bleeding. Prophylaxis was discontinued in 7 patients (11.1%): in 4 (6.3%) due to bleeding and in 3 (4.8%) because of the need for antithrombotic therapy. Of note, 6 patients received concomitant administration of defibrotide and intravenous unfractionated heparin at 100 UI/kg per day. None of them had a hemorrhagic event, and defibrotide was not discontinued.

Incidence of SOS/VOD

The cumulative incidence of SOS/VOD, as defined by the new EBMT criteria, was 6.3% (95% confidence interval, 2% to 14.2%). SOS/VOD occurred in 4 cases, 2 in the first 21 days after HSCT (days 13 and 14) and 2 as late-onset SOS/VOD (days 57 and 58). SOS/VOD was moderate in 1 case and very severe in 3. Two of the 4 patients died of SOS/VOD. Of note, in 1 case of SOS/VOD, defibrotide prophylaxis had been prematurely interrupted after 21 days of treatment because of the necessity of antithrombotic therapy (unfractionated heparin) in a context of deep vein thrombosis. Case descriptions and specific management are described in Table 3, and serum bilirubin kinetics is presented in Figure 1.

Table 2
Defibrotide-Related Bleeding

	No. of Patients (%)
Bleeding site*	
Gastrointestinal	2 (3.2)
Intracerebral	1 (1.6)
Urinary tract (hemorrhagic cystitis)	11 (17.4)
Severity*	
Grade 2	5 (7.9)
Grade 3	9 (14.3)
Grade 4	0 (0)

* One patient experienced 2 bleeding episodes.

Outcomes and Transplant-Related Events

The median follow-up was 31 months (range, 10.7 to 60.3). The 2-year overall survival, progression-free survival, incidence of relapse, and nonrelapse mortality were 56.5%, 49%, 28.7%, and 22.3%, respectively. The cumulative incidence of grades II to IV and grades III to IV acute GVHD were 22.2% and 7.9%, respectively. The cumulative incidence of moderate to severe chronic GVHD was 9.9%. Finally, the cumulative incidence of TA-TMA was 3.2% (95% confidence interval, .6% to 9.9%).

DISCUSSION

SOS/VOD is one of the major complications after HSCT (8% to 14% in allogeneic HSCT) and a leading cause of morbidity and mortality. Defibrotide prophylaxis has shown promising results in a few retrospective monocentric studies [15-21] and in a pediatric randomized trial [11]. Four studies evaluated the role of defibrotide as a prophylaxis in high-risk pediatrics patients and showed no to minimal incidence of SOS/VOD with this intervention [15,17,20,21]. This incidence was significantly reduced compared with historical control subjects in the 2 studies in which this methodology was used [15,21]. Three additional studies reported very low incidence of SOS/VOD with defibrotide prophylaxis (ranging from 0% to 2.0%) in heterogeneous cohorts of patients undergoing either autologous or allogeneic HSCT [16,18,19]. In a pediatric randomized trial recruiting patients undergoing either autologous or allogeneic HSCT, Corbacioglu et al. [11] showed that defibrotide prophylaxis might reduce the incidence of SOS/VOS by 30 days after HSCT (Z test for competing risk analysis $P = .0488$; log-rank test $P = .0507$). Additionally, in this study the incidence and severity of acute GVHD was significantly reduced in the defibrotide group. In our cohort of 63 high-risk patients undergoing allogeneic HSCT with defibrotide prophylaxis, we observed a low incidence of SOS/VOD (6.3%).

Our study has several caveats. First, it shares the limitations of retrospective and monocentric studies. Second, one of the main drawbacks is the absence of histologically proven diagnosis of SOS/VOD in our patients. Nevertheless, histologic proof may be difficult to obtain, and in practice diagnosis is often based on clinical criteria such as those developed by the EBMT. Despite the lack of a control group, our results are consistent with previous reports and argue for the effectiveness of defibrotide in the prevention of SOS/VOD. Compared with those studies, ours has the advantage of taking into account late forms of SOS/VOD as defined by the EBMT criteria. Another advantage of our cohort is the cumulative number of risk factors in our patients. Indeed, it is a very high-risk population, especially given the high proportion of patients undergoing their second (or additional) HSCT and/or suffering from advanced disease and/or iron overload.

When dealing with a new prophylactic strategy, safety should be of main concern, and given the profibrinolytic properties of defibrotide, the bleeding risk is at the forefront of side effects. However, the incidence and severity of such events in our study seems acceptable, especially considering the fact that a number of these events may not be directly attributable to defibrotide in thrombocytopenic patients and in the case of BK virus infection. On these grounds our experience

Table 3
Descriptions of the 4 Cases of SOS/VOD

	Gender, Age at HSCT (yr)	Disease	Disease Status and Other Risk Factors of SOS/VOD	SOS/VOD Symptoms	Day of Diagnosis Time Since First Symptoms (day)	SOS/VOD Grade	Management	Outcome
1	Female, 34*	ALL	Advanced (CR5) Third allogeneic HSCT Iron overload (SF = 3714 ng/mL) Previous TBI	Bilirubin elevation (up to 170 mmol/L), Transaminases < 2 ULN, weight gain > 10% with ascites and pleural effusion, acute kidney injury (>2× baseline), MOF	58 (late SOS/VOD) 5	4	Symptomatic treatment	Deceased at day 75
2	Male, 36	AML	Advanced (refractory) Second allogeneic HSCT Iron overload (SF = 1787 ng/mL) Hepatosplenic candidosis Previous use of GO	Bilirubin elevation (up to 122 mmol/L), Transaminases < 2 ULN, weight gain > 5% hepatalgia acute kidney injury (>2× baseline)	14 8	4	Pursuit of defibrotide, symptomatic	Alive
3	Female, 62	AML	CR2 Second allogeneic HSCT Iron overload (SF = 6000 ng/mL)	Bilirubin elevation (up to 124 mmol/L), doubling within 48 hours Transaminases > 8 ULN, weight gain > 5% with ascites acute kidney injury (>2× baseline), MOF	61 (late SOS/VOD) 4	4	Symptomatic	Deceased at day 66
4	Male, 63	AML	Advanced (refractory) Iron overload (SF = 2179 ng/mL) Previous use of GO	Bilirubin elevation, (up to 73 mmol/L), weight gain > 5% with ascites, renal function >1.2× baseline	13 5	2	Pursuit of defibrotide, symptomatic	Deceased at day 42 due to super-refractory status epilepticus in a context of HHV-6 meningoencephalitis

ALL indicates acute lymphoblastic leukemia; CR, complete remission; SF, serum ferritin; MOF, multiorgan failure; AML, acute myelogenous leukemia; GO, gemtuzumab ozogamicin; HHV-6, human herpesvirus-6.

* Defibrotide prophylaxis was prematurely interrupted after 21 days of treatment due to the necessity of antithrombotic therapy (unfractionated heparin) in a context of deep vein thrombosis.

is consistent with previous studies assessing the incidence of hemorrhagic events after allogeneic HSCT [22].

The reported incidence of clinically significant acute GVHD usually ranges between 35% and 50%. Interestingly, and similarly to Corbacioglu et al. [11], we found that defibrotide may be associated with a reduced incidence of clinically significant acute GVHD. However, a definite conclusion is impossible given the lack of a control group and the great heterogeneity of our population in terms of source of graft or compatibility of donors.

Several complications of allogeneic HSCT have been attributed to activation and lesion of endothelial cells and grouped under the name "endothelial cell activation syndromes," namely capillary leak syndrome, engraftment

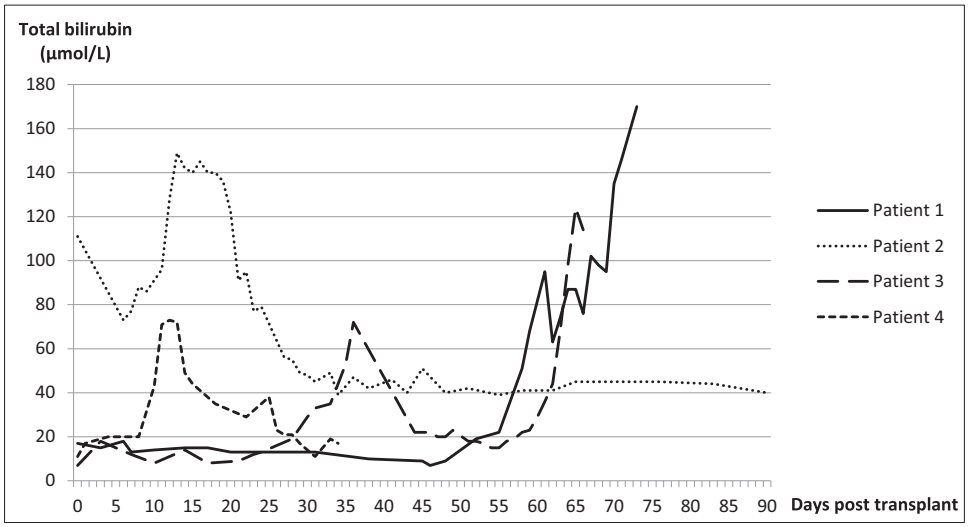

Figure 1. Total bilirubin kinetics in the 4 cases of SOS/VOD. Total bilirubin kinetics are given as surrogates of SOS/VOD evolution. Patients 1 and 3 died of SOS/VOD, respectively, at days 75 and 66 post-transplantation, whereas patients 2 and 4 recovered. Patient 4 subsequently died at day 42 of human herpesvirus-6 meningoencephalitis.

syndrome, SOS/VOD, and TA-TMA. The reported incidence of TA-TMA ranges from 2.5% to 12.7% depending on the diagnosis criteria [23], with greater incidence associated with less restrictive criteria, regardless of renal or neurologic dysfunction. Using the criteria for "overall TMA" defined by Cho et al. [23], namely the association of hemolysis and significant schizocytosis (2 per high power field) with or without renal or neurologic dysfunction, we found that the cumulative incidence of TA-TMA in our study was low (3.2%). This result needs to be taken with caution, given the retrospective nature of the study. Whether defibrotide prophylaxis, through its protective action on the endothelium, can reduce the incidence of endothelium cell activation syndromes such as TA-TMA needs to be investigated further by targeting this specific endpoint with precise criteria.

In our cohort of high-risk patients undergoing allogeneic HSCT, defibrotide used in combination with UDCA was associated with a low incidence of SOS/VOD, according to the EBMT diagnosis criteria, with an acceptable safety profile. These results are encouraging and support the need for an adult randomized trial to define the exact place of defibrotide in the SOS/VOD prevention strategy. Such a trial is currently ongoing (www.clinicaltrials.gov identifier: NCT02851407) and recruiting both adult and pediatric patients at high risk of SOS/VOD. Finally, the effect of defibrotide prophylaxis on the occurrence of other HSCT complications, such as acute GVHD or endothelium cell activation syndromes, should be explored in future studies.

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REFERENCES

1. Dalle J-H, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. *Biol Blood Marrow Transplant*. 2016;22:400-409.
2. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2015;50:781-789.
3. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant*. 2010;16:157-168.
4. Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2016;51:906-912.
5. Yakushijin K, Atsuta Y, Doki N, et al. Sinusoidal obstruction syndrome after allogeneic hematopoietic stem cell transplantation: incidence, risk factors and outcomes. *Bone Marrow Transplant*. 2016;51:403-409.
6. Battipaglia G, Labopin M, Candoni A, et al. Risk of sinusoidal obstruction syndrome in allogeneic stem cell transplantation after prior gemtuzumab ozogamicin treatment: a retrospective study from the Acute Leukemia Working Party of the EBMT. *Bone Marrow Transplant*. 2017;52:592-599.
7. Cheuk DKL, Chiang AKS, Ha SY, Chan GCF. Interventions for prophylaxis of hepatic veno-occlusive disease in people undergoing haematopoietic stem cell transplantation. *Cochrane Database Syst Rev*. 2015;5:CD009311.
8. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant*. 2010;16:1005-1017.
9. Corbacioglu S, Carreras E, Mohty M, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: final results from the international compassionate-use program. *Biol Blood Marrow Transplant*. 2016;22:1874-1882.
10. Falanga A, Vignoli A, Marchetti M, Barbui T. Defibrotide reduces procoagulant activity and increases fibrinolytic properties of endothelial cells. *Leukemia*. 2003;17:1636-1642.
11. Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet*. 2012;379:1301-1309.
12. Maradei SC, Maiolino A, de Azevedo AM, Colares M, Bouzas LF, Nucci M. Serum ferritin as risk factor for sinusoidal obstruction syndrome of the liver in patients undergoing hematopoietic stem cell transplantation. *Blood*. 2009;114:1270-1275.
13. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15:825-828.
14. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21:389-401.
15. Corbacioglu S, Hönig M, Lahr G, et al. Stem cell transplantation in children with infantile osteopetrosis is associated with a high incidence of VOD, which could be prevented with defibrotide. *Bone Marrow Transplant*. 2006;38:547-553.
16. Park M, Park HJ, Eom H-S, et al. Safety and effects of prophylactic defibrotide for sinusoidal obstruction syndrome in hematopoietic stem cell transplantation. *Ann Transplant*. 2013;18:36-42.
17. Versluys B, Bhattacharaya R, Steward C, Cornish J, Oakhill A, Goulden N. Prophylaxis with defibrotide prevents veno-occlusive disease in stem cell transplantation after gemtuzumab ozogamicin exposure. *Blood*. 2004;103:1968.
18. Dignan F, Gujral D, Ethell M, et al. Prophylactic defibrotide in allogeneic stem cell transplantation: minimal morbidity and zero mortality from veno-occlusive disease. *Bone Marrow Transplant*. 2007;40:79-82.
19. Chalandon Y, Roosnek E, Mermillod B, et al. Prevention of veno-occlusive disease with defibrotide after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2004;10:347-354.
20. Cappelli B, Chiesa R, Evangelio C, et al. Absence of VOD in paediatric thalassaemic HSCT recipients using defibrotide prophylaxis and intravenous busulphan. *Br J Haematol*. 2009;147:554-560.
21. Qureshi A, Marshall L, Lancaster D. Defibrotide in the prevention and treatment of veno-occlusive disease in autologous and allogeneic stem cell transplantation in children. *Pediatr Blood Cancer*. 2008;50:831-832.
22. Bacigalupo A. Haemopoietic stem cell transplants: the impact of haemorrhagic complications. *Blood Rev*. 2003;17:S6-S10.
23. Cho B-S, Yahng S-A, Lee S-E, et al. Validation of recently proposed consensus criteria for thrombotic microangiopathy after allogeneic hematopoietic stem-cell transplantation. *Transplantation*. 2010;90:918-926.