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Defibrotide for Prevention and Treatment of Veno-Occlusive Disease in Adults: Single-Center Experience

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Abstract

Background: Hepatic veno-occlusive disease (VOD) has been reported at a rate up to 50% following intensive conditioning regimens used in allogeneic hematopoietic stem cell transplantation (AHSCT). Studies on the prophylactic effect of defibrotide to prevent hepatic VOD in adults are rare.

Purpose: The research presented here aimed to evaluate whether propylactic defibrotide use can reduce incidence and severity of VOD in adults undergoing AHSCT. Also, we aimed to assess the benefit of defibrotide for treatment of VOD.

Methods: Study population comprised 86 consecutive AHSCT patients transplanted between January 2005 and December 2009. 17 of the patients at high risk of developing VOD could have access to defibrotide and received defibrotide prophylaxis.

Results: Modified Seattle criteria were used for VOD diagnosis. 14 of 86 patients (10 severe, 3 moderate, 1 mild) were diagnosed with VOD (16.2%). VOD incidence was similar between patients transplanted before December 2004 and after January 2005 (9.3% and 16.2%, respectively; p =0.14, HR =1.88, 95% CI 0.82- 4.29). 13 of 14 patients diagnosed with VOD in the study population were treated with defibrotide whereas only 2 of 12 in the control group received defibrotide for treatment (92.8% and 16.6%, respectively; p =0.0002, HR =65 , 95% CI 5.13-823.1). Mortality rate of VOD in the controls was significantly higher than the study population (66.6% and 21.4%, respectively; p =0.044, HR =0.13, 95% CI 0.02-0.78).

Conclusions: Mortality rate related to VOD was lower in the defibrotide group. Therefore, we conclude defibrotide might be beneficial for treatment of VOD in adults.

Keywords: Allogeneic hematopoietic stem cell transplantation; Hepatic veno-occlusive disease; Prophylactic effect

Abbreviations: VOD: Hepatic veno-occlusive disease; AHSCT: Allogeneic hematopoietic stem cell transplantation; HSCT: Hematopoietic stem cell transplantation; TPA: Tissue plasminogen activator; CR: Complete response; MOF: Multiple organ failure; HR: Hazard ratio; CI: Cornfield 95% confidence limits; AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; CML: Chronic myeloid leukemia; MM: Multiple myeloma; GVHD: Graft-versus-host disease

Introduction

Hepatic veno-occlusive disease (VOD) -also known as sinusoidal obstruction syndrome- is considered one of the leading causes of morbidity and mortality after hematopoietic stem cell transplantation (HSCT) [1]. Pathophysiology is thought to be multifactorial: endothelial injury in both sinusoids and small hepatic venules leading to subendothelial deposition of platelet and coagulative material, which results in centrilobular necrosis and post-sinusoidal obstruction [2]. Defibrotide is a mixture of porcine oligodeoxyribonucleotides that has antithrombotic, anti-ischemic and anti-inflammatory properties. This agent seems to have a protective effect against endothelial cell injury by increasing fibrinolysis and reducing procoagulant activity yet without an increase in bleeding events [3-5]. In support of these observations, several studies focused attention on the use of defibrotide as a potentially effective and reliable agent for preventing and treating VOD [6,7].

Defibrotide use was first reported in patients diagnosed with severe VOD following stem cell transplantation performed between 1995 and 1997 [8]. Since then, several studies in both adults and children have demonstrated encouraging responses with defibrotide in severe VOD [9-13]. Following the demonstration of the efficacy of defibrotide in the treatment of VOD, several studies investigated the role of this agent in prophylaxis [14-19]. In the review by Zhang L et al. it was mentioned that most studies regarding prophylaxis involved pediatric patients and only one of them was a randomized controlled trial [20]. To the best of our knowledge, only few studies have investigated the role of defibrotide for prophylaxis in adult patients following allogeneic hematopoietic stem cell transplantation (AHSCT) [18,19]. The controlled trial of Chalandon et al. suggested that defibrotide given in addition to heparin may be effective in VOD prophylaxis [18]. The study of Dignan F et al. which included adult case series implies that prophylaxis with defibrotide may reduce the incidence of VOD following AHSCT [19]. In conclusion, there is limited information on the impact of defibrotide in the VOD prophylaxis in adults.

We aimed to assess the efficacy of defibrotide in treatment and prevention of VOD. Defibrotide prophylaxis was given to patients with high risk to develop VOD, who were transplanted at the Adult Hematopoietic Stem Cell Transplantation Unit of Istanbul Medical Faculty between January 2005 and December 2009. We retrospectively

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evaluated the clinical characteristics and outcome in patients diagnosed with VOD following AHSCT between January 2005 and December 2009. We also aimed to investigate time-related changes in the incidence and clinical outcome of VOD by comparing patients who underwent AHSCT from January 2005 to December 2009 and historical patients transplanted between January 1995 and December 2004.

Materials and Methods

Patient population

Our study population included 86 patients who received an AHSCT from January 2005 to December 2009 at the Adult Hematopoietic Stem Cell Transplantation Unit of Istanbul Medical Faculty. Of patients at high risk to develop VOD, 17 could have access to defibrotide. We enrolled 128 historical controls transplanted without defibrotide prophylaxis between January 1995 and December 2004. Patient medical records were retrospectively reviewed.

Risk factors for development of VOD

High risk population for the development of VOD were identified according to the following risk factors: 1) patient-related factors: pre-existing hepatic disease, previous treatment including prior abdominal irradiation or use of gemtuzumab ozogamicin, viral hepatitis in both donor and recipient, iron overload in patients with β thalassaemia major, older transplant recipient age, poor performance status, advanced malignancy at the time of transplantation; 2) transplantation-related factors: second myeloablative transplant, donor-recipient HLA disparity, use of busulfan conditioning regimen particularly in combination with cyclophosphamide [6,21,22].

VOD definition and severity

Modified Seattle criteria were used for VOD diagnosis [23]. A diagnosis of VOD was made according to two of the following clinical features within 20 days of transplantation: serum bilirubin >2 mg/dl (34 μM/L), hepatomegaly or right upper quadrant pain, and weight gain of >2% from pretransplant baseline [23]. Severity of VOD was classified as mild, moderate or severe [24]. Patients with mild VOD experienced no apparent adverse effects and received no therapy for liver dysfunction. Patients with moderate VOD had fluid retention that required diuretics and/or liver pain that required analgesics. Severe VOD, was defined by the persistence of symptoms after day 100 or death before day 100 in the presence of ongoing VOD or development of MOF characterized by pulmonary, renal dysfunction and encephalopathy [11].

Prophylactic treatment for VOD

After 2000, all patients who underwent AHSCT received ursodeoxycholic acid 250 mg three times daily (from the first day of cytotoxic therapy until day +35) for VOD prophylaxis and to prevent other hepatic complications. In addition, among patients transplanted between January 2005 and December 2009, 17 patients at high risk to develop VOD could gain access to defibrotide and received defibrotide from the start of conditioning regimen until day +21.

The doses of the prophylactic defibrotide in the above-mentioned patients were as follows: 2.5 mg/kg i.v. over two hours four times daily (n=10) and 6.25 mg/kg of defibrotide i.v. four times daily (n=7). None of the historical controls who underwent AHSCT before December 2004 received defibrotide for VOD prophylaxis.

Management of VOD and response criteria

Initial therapy approach was supportive including restriction of fluids, diuretic therapy and renal replacement therapy in severe cases. Before December 2004, two of 12 patients diagnosed with VOD could have had access to defibrotide. Tissue plasminogen activator (TPA) (60 mg given in divided doses over 2-4 days) and heparin (150 U/kg per day over 10 days) were the treatment in the remaining patients with MOF. After January 2005, 13 of 14 patients diagnosed with VOD could have access to defibrotide. Complete response (CR) to therapy was demostrated by resolution of VOD as defined by decrease in bilirubin levels to <2 mg/dl and improvement in other VOD and MOF related symptoms and signs such as pulmonary and renal dysfunction, as well as encephalopathy.

Statistical Analysis

All statistical calculations were performed using the SPSS version 16 (Prentice Hall, Upper Saddle River, New Jersey). Results were expressed as median values (range). The chisquare statistics were used to compare categorical variables among the study population and historical controls. The hazard ratio (HR) were accompanied by Cornfield 95% confidence limits (CI). A p value of less than 0.05 was considered significant.

Results

Baseline characteristics

Our study group consisted of a whole cohort of 86 patients (51 males, 35 females). Patient characteristics in the study population who underwent AHSCT between January 2005 and December 2009 are shown in Table 1. The median age was 33 (18-54) years. The three most common primary diseases were acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML) (35%, 29% and 16%, respectively). Bone marrow was the source of stem cells in 55% of our patients. Myeloablative conditioning regimens were used in 86% of patients. Conditioning regimens were busulphan-based in 70 patients (82%). Combination of cyclosporine (12.5 mg/kg daily divided in two doses) and a short-course of methotrexate (15 mg/m^2

Number of patients, n	86
Median age, years (range)	33 (18-54)
Females (%)	35 (41%)
Stem cell source	86 (100%)
Bone marrow	47 (55%)
Peripheral blood	39 (45%)
Primary disease	86 (100%)
Acute myeloid leukemia	30 (35%)
Acute lymphoblastic leukemia	25 (29%)
Chronic myeloid leukemia	13 (16%)
Multiple myeloma	5 (6%)
Non-Hodgkin lymphoma	4 (5%)
Aplastic anemia	3 (3%)
Hodgkin lymphoma	3 (3%)
Myelodysplastic syndrome	1 (1%)
Granulocytic sarcoma	1 (1%)
Thalassemia major	1 (1%)
Full intensity regimens	74 (86%)
Busulfan/cyclophosphamide	69 (81%)
Busulfan/cyclophosphamide/alemtuzumab	1 (1%)
BEAM	1 (1%)
Cyclophosphamide/ATG	3 (3%)
Reduced-intensity regimens	12 (14%)
FLAG-IDA	2 (2%)
Fludarabin/melphelan	6 (7%)
Fludarabin/busulfan	4 (5%)
	17 (19.7%)

Table 1: Clinical characteristics of patients who underwent AHSCT between January 2005 and December 2009.

daily on day +1 and 10 mg/m^2 daily on days +3, +6 and +11) was given for graft-versus-host disease (GVHD) prophylaxis.

Incidence and severity of VOD

A retrospective review of the Istanbul Medical Faculty database revealed that 14 of 86 patients (16.2%) developed hepatic VOD. Of 14 patients, 10 had severe VOD (71.4%), 3 moderate (21.4%) and 1 mild VOD (7.2%). Characteristics of the patients diagnosed with VOD are summarized in Table 2. 11 of 14 patients underwent AHSCT from HLA-matched siblings (78.6%). Two patients received stem cells from HLA-matched unrelated donors and one patient from one-antigen-mismatched related donor. Defibrotide was given in 13 of 14 patients (92.8%). The doses of defibrotide treatment and route of administration are outlined in Table 2. CR was obtained in 11 patients (78.6%). Three of 14 patients (21.4%) succumbed to MOF. All these three patients had experienced acute GVHD following AHSCT. Of the 14 patients, 7 had already been under defibrotide prophylaxis when VOD was diagnosed. After the diagnosis of VOD, the dose of defibrotide was increased from 2.5 mg/kg four times i.v. daily to 6.25 mg/kg four times i.v. daily in 5 patients and from 6.25 mg/kg four times i.v daily to 10 mg/kg four times i.v. daily in 2 patients.

Evaluation of time-related changes in the incidence and clinical outcome of hepatic VOD

The incidence of VOD was 9.3% (12 in 128) in our historical control group who were transplanted between January 1995 and December 2004. At that time, only two patients could have had access to defibrotide for the treatment of VOD (16.6%). CR was achieved in these two patients. 8 of 12 patients succumbed to their disease (66.6%) -5 of them due to MOF, 3 due to hemorrhagic complications.

Comparison of patients who underwent AHSCT from January 2005 to December 2009 and between January 1995 and December 2004 is outlined in Table 3. 17 of the patients at high risk population for developing VOD could have access to defibrotide prophylaxis whereas no patients in the historical controls received defibrotide prophylaxis. The incidence of VOD was similar between patients transplanted before December 2004 and after January 2005 (9.3% and 16.2%, respectively; p=0.14, HR=1.88, 95% CI 0.82-4.29). 13 of 14 patients diagnosed with VOD in the study population were treated with defibrotide whereas only 2 of 12 patients received defibrotide for treatment in the control group (92.8% and 16.6%, respectively; p=0.0002, HR=65 , 95% CI 5.13-823.1). Rates of VOD-associated mortality was significantly lower in patients diagnosed with VOD after January 2005 compared to those diagnosed before December 2004 (21.4% and 66.6%, respectively; p=0.044, HR=0.13, 95% CI 0.02-0.78).

Clinical outcome of patients who received defibrotide prophylaxis

Among the patients transplantated between January 2005 and December 2009 and carrying high risk to develop VOD, 17 patients could have access to defibrotide from the start of conditioning regimen

UPN	Age / G	Diagnosis	Risk factors for VOD	Acute GVHD	VOD Therapy	Outcome
1	31/M	ALL	One-antigen-mismatched related donor	+	Symptomatic	Exitus from MOF
2*	41/M	AML	Previous fungal liver infection	–	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
3	33/F	ALL	-	_	10 mg/kg/day i.v. DF	CR
4*	21/F	Blastic-phase CML	Advanced disease	–	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
5*	30/F	AML	Advanced disease	–	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
6*	27/M	MDS	Iron overload	+	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	Exitus from MOF
7*	29/M	ALL	Advanced disease	–	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
8	45/M	AML	_	_	25 mg/kg/day i.v. DF	CR
9	39/M	ALL	_	_	25 mg/kg/day i.v. DF	CR
10	25/M	ALL	_	_	4x400 mg oral DF	CR
11	41/M	AML	Unrelated donor	_	4x400 mg oral DF	CR
12	18/M	Thalassemia major	Hemosiderosis, hepatic fibrosis	–	4x400 mg oral DF	CR
13*	35/M	AML	Unrelated donor	+	The dose of DF was increased from 25mg/kg/day i.v. to 40 mg/kg/day	Exitus from MOF
14*	30/F	ALL	Advanced disease	–	The dose of DF was increased from 25mg/kg/day i.v. to 40 mg/kg/day	CR

UPN indicates unique patient number; G, gender; M, male; F, female; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; VOD, veno-occlusive disease; GVHD, graft versus host disease; DF, defibrotide; MOF, multiple organ failure

* indicates patients who had received DF prophylaxis

Table 2: Characteristics of patients diagnosed with VOD between between January 2005 and December 2009.

	Study population (January 2005-December 2009)	**Historical control group** (January 1995-December 2004)	**P value**
VOD incidence	14/86 (16.2%)	12/128 (9.3%)	0.14
	13/14 (92.8%)	2/12 (16.6%)	0.0002
VOD-associated mortality	3/14 (21.4%)	8/12 (66.6%)	0.044

Table 3: Comparison of patients transplantated from January 2005 to December 2009 and between January 1995 and December 2004.

UPN	Age / G	Diagnosis	Risk factors for VOD	Acute GVHD	DF prophylaxis dose	Diagnosis for VOD	VOD Therapy	Outcome after DF treatment
1	41/M	AML	Previous fungal liver infection	_	10 mg/kg/day i.v.	+	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
2	21/F	Blastic-phase CML	Advanced disease	_	10 mg/kg/day i.v.	+	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
3	30/F	AML	Advanced disease	_	10 mg/kg/day i.v.	+	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
4	27/M	MDS	Iron overload	+	10 mg/kg/day i.v.	+	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	Exitus from MOF
5	29/M	ALL	Advanced disease	_	10 mg/kg/day i.v.	+	The dose of DF was increased from 10 mg/kg/day i.v. to 25 mg/kg/day	CR
6	35/M	AML	Unrelated donor	+	25mg/kg/day i.v.	+	The dose of DF was increased from 25mg/kg/day i.v. to 40 mg/kg/day	Exitus from MOF
7	30/F	ALL	Advanced disease	_	25mg/kg/day i.v.	+	The dose of DF was increased from 25mg/kg/day i.v. to 40 mg/kg/day	CR
8	19/M	ALL	Use of busulfan conditioning regimen	-	10 mg/kg/day i.v.	_	-	-
9	20/M	AML	Use of busulfan conditioning regimen	+	10 mg/kg/day i.v.	_	-	-
10	28/M	MDS	Iron overload	-	10 mg/kg/day i.v.	-	-	-
11	19/M	AML	Use of busulfan conditioning regimen	+	10 mg/kg/day i.v.	_	-	-
12	21/M	ALL	Pre-existing hepatic disease	-	10 mg/kg/day i.v.	_	-	-
13	49/F	AML	Use of busulfan conditioning regimen	-	25mg/kg/day i.v.	_	-	-
14	28/F	MM	Prior abdominal irradiation	-	25mg/kg/day i.v.	_	-	-
15	33/M	AML	Unrelated donor	-	25mg/kg/day i.v.	_	-	-
16	19/M	ALL	Pre-existing hepatic disease	-	25mg/kg/day i.v.	_	-	-
17	39/M	ALL	Advanced disese	-	25mg/kg/day i.v.	-	-	-

UPN indicates unique patient number; G, gender; M, male; F, female; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; VOD, veno-occlusive disease; GVHD, graft versus host disease; DF, defibrotide; MOF, multiple organ failure

Table 4: Characteristics of patients who received defibrotide prophylaxis between January 2005 and December 2009 (n=17).

until day +21 at the following doses: 10 mg/kg i.v. daily (n =10) and 25 mg/kg i.v. daily (n =7). Characteristics of the patients who received defibrotide prophylaxis were outlined in Table 4. Risk factors for VOD were as follows: advanced disease at the time of transplantation (n =5), use of busulfan conditioning regimen (n =4), unrelated donor (n =2), pre-existing hepatic disease (n =2), prior abdominal irradiation (n =2), previous fungal liver infection (n=1) and iron overload (n =1). The primary diagnoses were as follows: AML (n =7), ALL (n =6), MDS (n =2), CML (n =1) and multiple myeloma (MM) (n =1). 7 of the 17 patients was diagnosed with VOD despite defibrotide prophylaxis (41.1%). After the diagnosis of VOD, the dose of defibrotide was increased from 10 mg/kg i.v. daily to 25 mg/kg i.v. daily in 5 patients and from 25 mg/kg i.v daily to 40 mg/kg i.v. daily in 2 patients. CR was obtained in 5 patients (71.4%). Two of 7 patients (28.6%) succumbed to MOF. None of the historical controls who underwent AHSCT before December 2004 received defibrotide for VOD prophylaxis.

Discussion

VOD is a common complication after AHSCT and occurs as a result of the conditioning regimen administered [21]. The occurrence of VOD has been reported in up to 60% of patients following stem cell transplantation, with variable incidences in different studies depending on the type of transplantation, conditioning regimen and criteria used for diagnosis [25]. VOD is associated with substantial morbidity and mortality. Severe VOD has a dismal outcome with mortality over 90% while patients with mild or moderate disease have a predicted survival of 77% to 91% at day 100 [25]. Successful management of VOD includes approaches both for disease treatment and prevention. Especially, prevention strategies are critical to reduce morbidity and mortality from VOD. Several studies have reported the benefit of defibrotide in the treatment of VOD in adults [9,11,13]. Since then, a limited number of studies have investigated the role of defibrotide in the prophylaxis of VOD in adults [18,19]. This is a cohort of 86 consecutive patients who underwent AHSCT in our center between January 2005 and December 2009. We investigated the incidence and clinical outcome of VOD in these patients in comparison to 128 historical controls transplanted between January 1995 and December 2004. This study also raised the question about the utility of defibrotide in the prevention and treatment of VOD.

In the review of a total of 135 reports of VOD in a population including >50 HSCT patients, the mean incidence of VOD was reported as 13.7%, with absolute values ranging from 0 to 62.3% [25]. The

incidence of VOD in our study group transplanted before December 2004 and historical controls transplanted after January 2005 was 9.3% and 16.2%, respectively (p=0.14, HR =1.88, 95% CI 0.82-4.29). In summary, in our study, the overall VOD incidence in 214 patients who underwent AHSCT from January 1995 to December 2009 was 12.1%. The incidence of VOD, transplant-related morbidity and mortality decreased following the improved insight to the biology of HSCT, the use of reduced-intensity regimens, i.v. or dose-adjusted busulfan, fractionated TBI regimens and T-cell depletion [26-30]. Despite these advances, our current analysis demonstrated no decrease in the incidence of VOD over time. Possible contributing factors to this finding include the increased access of older age patients to transplantation, the increased eligibility of relapsed or refractory disease for transplantation due to advances in novel remission induction therapies and increase in the number of multi-transfused patients. The limitation of our study is that our study population was matched with historical controls and therefore all variables were not controlled. In contrast, the strength of this study is the presence of large number of transplantated patients, which gives useful information about the overall incidence of VOD among Turkish AHSCT recipients.

In adult patients undergoing AHSCT, there is no uniform consensus for an optimal strategy to prevent VOD. A number of studies investigated the role of ursodeoxycholic acid in the prophylaxis of VOD and other hepatic complications including GVHD [31-33]. In the prospective, randomized, open-label multicenter study by Ohashi K.et al., the incidence of VOD was significantly lower in the ursodeoxycholic acid arm compared to placebo [32].

Based on this finding, we added ursodeoxycholic acid to the protocole for VOD prophylaxis after 2000. Limited number of studies have assessed the efficacy of defibrotide in VOD prophylaxis in adults [18,19]. Chalandon Y.et al. reported a retrospective series of 52 consecutive patients who received i.v. defibrotide at a dose of 10-25 mg/kg daily from day -7 until day +20 following AHSCT concurrent with i.v. heparin administration [18]. Baltimore criteria were used for VOD diagnosis. 86.5% of the patients had received myeloablative conditioning. None of the 52 patients developed VOD compared to 19.2% (10 in 52) of historical controls who received heparin alone (p =0.02). Consequently, that particular study suggested that defibrotide concurrent with heparin may be efficient prophylaxis for VOD [18]. Dignan et al. reported a retrospective series of 58 adult patients who received defibrotide without concurrent use of heparin at a total dose of 10 mg/kg i.v. daily from day +1 to +21 following AHSCT [19]. Diagnosis of VOD was based on the Baltimore criteria. 63.8% of patients received reduced-intensity conditioning regimens and none of the patients fulfilled the criteria for VOD [19]. Consequently, that study suggested that prophylaxis with defibrotide alone may reduce the incidence of VOD following AHSCT [19]. In our study, patients who underwent AHSCT from January 2005 to December 2009 and had a high risk for development of VOD received defibrotide prophylaxis without concurrent i.v. heparin from the start of conditioning regimen until day +21 (17 in 86 patients, 19.7%). The doses of prophylactic defibrotide were as follows: 10 mg/kg/day i.v. defibrotide (n=10) and 25 mg/kg/day i.v. defibrotide (n=7). VOD was diagnosed based on the Modified Seattle criteria. 86% of patients (74 in 86) received myeloablative conditioning regimens. 7 of the 17 patients developed VOD under defibrotide prophylaxis. After an increase in the dose of defibrotide, CR was obtained in 5 patients (71.4%) while 2 (28.6%) succumbed to MOF. In summary, the incidence of VOD was high in our patients who received defibrotide prophylaxis. Thus, we did not suggest that prophylaxis with defibrotide may reduce the incidence of VOD. We observed that the incidence of VOD was higher in patients on 10 mg/kg/day i.v. defibrotide prophylaxis compared to 25 mg/kg/day i.v. (50% and 28.6%, respectively). Thus, we aim to assess the role of defibrotide prophylaxis at a dose of 25 mg/kg/day i.v. in a larger series of adult patients in our further studies.

In summary, there are no randomised trials investigating the use of prophylactic defibrotide in adult patients with VOD. Recently, Dignan et al. mentioned that the optimal dose and duration of defibrotide prophylaxis and the best route of defibrotide administration are yet to be elucidated. Further work including randomised trials to definitively test the role of defibrotide in prevention of VOD in adults and dose-finding studies are required [34].

Several studies investigated the efficacy of defibrotide in the treatment of VOD [8-13]. In adult and pediatric patients diagnosed with VOD, defibrotide was associated with CR rates of 36-76% and post-HSCT survival rates of 32-79% on day +100 without substantial toxicity [8-12]. 40 patients from 19 European centers fullfilling the criteria for VOD were included in the study by Chopra et al. [9]. In that study, defibrotide was given intravenously for amedian of 14 days post-HSCT at doses ranging form 10 to 40 mg/kg in both childs and adults. CR rates and survival rates beyond day +100 were 55% and 43%, respectively. Consequently, Chopra R. et al. suggested that defibrotide is an effective treatment for VOD following HSCT [9]. Subsequently, in the study by Richardson PG et al., multi-institutional use of defibrotide in 88 patients after HSCT resulted in CR rates of 36% and survival rates of 35% at day +100. In that study, the median age of patients treated with defibrotide was 35 years (range, 8 months to 62 years) [11]. A randomized phase II dose-finding study was conducted by Richardson PG et al. in 2010 [13]. Adults and pediatric patients were randomized to receive lower dose i.v. defibrotide (25 mg/kg/day, n=75) or higher dose defibrotide (40 mg/kg/day, n=74) in divided doses every 6 hours for ≥ 14 days or until CR, VOD progression or severe toxicity was observed [13]. The CR rate and post-HSCT survival rates were 46% and 42%, respectively and there was no significant difference between the two arms. In addition, the incidence of treatment-related adverse events did not differ between the treatment arms [13]. According to this data, intravenous defibrotide at a dose of 25 mg/kg/day is recommended in the treatment of adults with VOD [13]. In our study, 14 of 86 patients transplanted between January 2005 and December 2009 developed VOD (16.2%) -10 severe, 3 moderate and 1 mild. 13 of the 14 patients were treated with defibrotide (92.8%). Patients were given either oral or intravenous defibrotide, whichever available. Defibrotide doses were increased in 7 of the 14 patients (50%) already under defibrotide prophylaxis. In patients who had not received prophylaxis, defibrotide was administered as follows: 25 mg/kg i.v. daily in 2 patients, 10 mg/kg i.v. daily in one patient and oral defibrotide 400 mg four times daily in 3 patients. One patient who could not have access to defibrotide succumbed to VOD-related MOF whereas CR was obtained in 11 of 13 patients who received defibrotide treatment (84.6%). Overall, VOD-related mortality in 14 patients diagnosed with VOD was 21.4 % (3 in 14). All three patients had experienced acute GVHD following AHSCT. CR was obtained in all of our 3 VOD patients treated with oral defibrotide. To our knowledge, no previous study has compared the efficacy of oral and intravenous defibrotide in VOD treatment. This issue was not addressed in the particular study due to our small number of cases treated with oral defibrotide. The use of defibrotide for the treatment of VOD in patients transplanted from January 2005 to December 2009 was significantly higher than the historical controls transplanted between January 1995 and December 2004 (p =0.0002). In addition, mortality rate of VOD in controls was significantly higher than

the study population (p =0.044). In summary, our results demonstrate that defibrotide is an effective treatment for VOD following AHSCT. But our study is a historically-controlled case study which was not adequately controlled for selection bias. Further randomised trials are needed to definitively assess the role of defibrotide in prevention and treatment of VOD in adult patients.

In our current clinical practice, we use defibrotide prophylaxis in patients harboring high pretransplant risk factors to develop VOD including unrelated AHSCT, use of busulfanbased conditioning regimen, prior abdominal radiation, pre-existing liver disease (hepatic fibrosis, cirrhosis and hemochromatosis), hepatitis B and/or hepatitis C enfection with serological or virological evidence, prior history of myeloablative transplant, prior exposure to gemtuzumab ozogamicin 3 months before AHSCT.

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References

1. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED (1984) Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology 4: 116-122.
2. Shulman HM, Fisher LB, Schoch HG, Henne KW, McDonald GB (1994) Veno-occlusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. Hepatology 19: 1171-1181.
3. Berti F, Rossoni G, Biasi G, Buschi A, Mandelli V, et al. (1990) Defibrotide, by enhancing prostacyclin generation, prevents endothelin-1 induced contraction in human saphenous veins. Prostaglandins 40: 337-350.
4. Ulutin ON (1993) Antithrombotic effect and clinical potential of defibrotide. Semin Thromb Hemost 19 Suppl 1: 186-191.
5. Falanga A, Vignoli A, Marchetti M, Barbui T (2003) Defibrotide reduces procoagulant activity and increases fibrinolytic properties of endothelial cells. Leukemia 17: 1636-1642.
6. Ho VT, Revta C, Richardson PG (2008) Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. Bone Marrow Transplant 41: 229-237.
7. Morabito F, Gentile M, Gay F, Bringhen S, Mazzone C, et al. (2009) Insights into defibrotide: an updated review. Expert Opin Biol Ther 9: 763-772.
8. Richardson PG, Elias AD, Krishnan A, Wheeler C, Nath R, et al. (1998) Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. Blood 92: 737-744.
9. Chopra R, Eaton JD, Grassi A, Potter M, Shaw B, et al. (2000) Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. Br J Haematol 111: 1122-1129.
10. Corbacioglu S, Greil J, Peters C, Wulffraat N, Laws HJ, (2004) Defibrotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multicentre study demonstrates therapeutic efficacy upon early intervention. Bone Marrow Transplant 33: 189.
11. Richardson PG, Murakami C, Jin Z, Warren D, Momtaz P, et al. (2002) Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. Blood 100: 4337.
12. Bulley SR, Strahm B, Doyle J, Dupuis LL (2007) Defibrotide for the treatment of hepatic veno-occlusive disease in children. Pediatr Blood Cancer 48: 700-704.
13. Richardson PG, Soiffer RJ, Antin JH, Uno H, Jin Z, et al. (2010) 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 16: 1005-1017.
14. Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, et al. (2012) Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. Lancet 379: 1301-1309.
15. Qureshi A, Marshall L, Lancaster D (2008) Defibrotide in the prevention and treatment of veno-occlusive disease in autologous and allogeneic stem cell transplantation in children. Pediatr Blood Cancer 50: 831-832. Blood Cancer 50: 831.
16. Corbacioglu S, Hönig M, Lahr G, Stöhr S, Berry G, et al. (2006) 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 38: 547-553.
17. Cappelli B, Chiesa R, Evangelio C, Biffi A, Roccia T, et al. (2009) Absence of VOD in paediatric thalassaemic HSCT recipients using defibrotide prophylaxis and intravenous Busulphan. Br J Haematol 147: 554-560.
18. Chalandon Y, Roosnek E, Mermillod B, Newton A, Ozsahin H, et al. (2004) Prevention of veno-occlusive disease with defibrotide after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 10: 347-354.
19. Dignan F, Gujral D, Ethell M, Evans S, Treleaven J, et al. (2007) Prophylactic defibrotide in allogeneic stem cell transplantation: minimal morbidity and zero mortality from veno-occlusive disease. Bone Marrow Transplant 40: 79-82.
20. Zhang L, Wang Y, Huang H (2012) Defibrotide for the prevention of hepatic veno-occlusive disease after hematopoietic stem cell transplantation: a systematic review. Clin Transplant 26: 511-519.
21. McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, et al. (1993) Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med 118: 255-267.
22. Wadleigh M , Richardson PG, Zahrieh D, Lee SJ, Cutler C, et al. (2003) Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. Blood 102: 1578.
23. Shulman HM, Hinterberger W (1992) Hepatic veno-occlusive disease--liver toxicity syndrome after bone marrow transplantation. Bone Marrow Transplant 10: 197-214.
24. Bearman SI, Anderson GL, Mori M, Hinds MS, Shulman HM, et al. (1993) Venoocclusive disease of the liver: development of a model for predicting fatal outcome after marrow transplantation. J Clin Oncol 11: 1729-1736.
25. Coppell JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, et al. (2010) Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 16: 157-168.
26. Kashyap A, Wingard J, Cagnoni P, Roy J, Tarantolo S, et al. (2002) Intravenous versus oral busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic venoocclusive disease (HVOD), HVOD-related mortality, and overall 100-day mortality. Biol Blood Marrow Transplant 8: 493.
27. Ramasamy K, Lim ZY, Pagliuca A, Grundy R, Devereux S, et al. (2006) Incidence and management of hepatic venoocclusive disease in 237 patients undergoing reduced-intensity conditioning (RIC) haematopoietic stem cell transplantation (HSCT). Bone Marrow Transplant 38: 823-824.
28. Clopés A, Sureda A, Sierra J, Queraltó JM, Broto A, et al. (2006) Absence of veno-occlussive disease in a cohort of multiple myeloma patients undergoing autologous stem cell transplantation with targeted busulfan dosage. Eur J Haematol 77: 1-6.
29. Soiffer RJ, Dear K, Rabinowe SN, Anderson KC, Freedman AS, et al. (1991) Hepatic dysfunction following T-cell-depleted allogeneic bone marrow transplantation. Transplantation 52: 1014-1019.
30. Girinsky T, Benhamou E, Bourhis JH, Dhermain F, Guillot-Valls D, et al. (2000) Prospective randomized comparison of single-dose versus hyperfractionated total-body irradiation in patients with hematologic malignancies. J Clin Oncol 18: 981-986.
31. Essell JH, Schroeder MT, Harman GS, Halvorson R, Lew V, et al. (1998) Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 128: 975-981.
32. Ohashi K, Tanabe J, Watanabe R, Tanaka T, Sakamaki H, et al. (2000) The Japanese multicenter open randomized trial of ursodeoxycholic acid prophylaxis for hepatic veno-occlusive disease after stem cell transplantation. Am J Hematol 64: 32-38.

33. Ruutu T, Eriksson B, Remes K, Juvonen E, Volin L, et al. (2002) Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. Blood 100: 1977-1983.

34. Dignan FL, Wynn RF, Hadzic N, Karani J, Quaglia A, et al. (2013) Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. BCSH/BSBMT guideline: diagnosis and management of veno occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol 163: 444.