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Effectiveness of defibrotide in the prevention of hepatic venooclusive disease among adult patients receiving allogeneic hematopoietic cell transplantation: A retrospective single center experience

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ABSTRACT

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is one of the most life-threatening early complications following hematopoietic cell transplantation (HCT). Due to the high mortality rate of severe VOD/SOS accompanied with multiorgan failure, there is a great interest in preventive strategies. The efficacy of defibrotide (DF) on the prevention of VOD/SOS has been clearly shown in high-risk pediatric patients, but evidence-based data on adults is scarce. In this report, we aimed to assess the impact of DF on the incidence of VOD/SOS in our center by posttransplant day 30 among patients who were treated with allogeneic HCT (allo−HCT). The study included a total of 56 patiens (28 males, 28 females). The median age of the study cohort was 43 (20−68). The daily dose of DF was 10 mg/kg and 25 mg/kg in 53 (94.6 %) and 3 (5.3 %) patients, respectively. Patients also recieved oral ursodeoxycolic acid (UDCA) 250 mg three-times daily started with conditioning until D + 90. Twenty-three (41.1 %) patients had at least one major EBMT-defined risk factor for development of VOD/SOS. One patient who belonged to a very high-risk group (with at least two major risk factors) developed very-severe VOD/SOS at posttransplant D + 20 and died as a result of multiorgan failure. The cumulative incidence of VOD/SOS at D + 30 was 1.9 %. Our findings indicate that 10 mg/kg daily intravenous DF combined with UDCA is quite effective in prevention of VOD/SOS in patients who underwent first allo-HSCT.

1. Introduction

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is one of the most life-threatening early complications following hematopoietic cell transplantation (HCT), which is characterized by jaundice, hepatomegaly, fluid retention and weight gain. Pathogenesis of VOD/SOS relates to damage to sinusoidal endothelial cells and hepatocytes as a result of conditioning regimen dependent injury. There is a great variation of VOD/SOS incidence among different reports mainly as a result of differences in patient characteristics, HCT type, conditioning regimens and definitions used to diagnose the entity. Defibrotide (DF) is indicated in the treatment of patients who developed severe/very severe forms of VOD/SOS. As the mortality of severe VOD/SOS accompanied with multiorgan failure is > 80 %, there is great interest in preventive strategies [1]. The advantage of defibrotide for the prevention of VOD/SOS has been clearly shown in a phase III randomized study among high-risk pediatric patients [2]. Experience of VOD/SOS prophylaxis with DF relates only to retrospective analysis and historically controlled prospective studies in adults. Although prospective, randomized data in the adult population is lacking, the drug is also recommended for prevention of VOD/SOS in high-risk adult patients based on the benefit observed in adult retrospective studies and the aforementioned phase 3 study in the pediatric population [3,4]. In this report, we aimed to assess the impact of defibrotide on the incidence of VOD/SOS in our center by posttransplant day 30 among patients who were treated with allogeneic HCT (allo−HCT).

2. Methods

2.1. Patients

All consecutive adult patients who underwent a first allogeneic

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peripheral blood stem cell transplantation from all donor types between March 2019 and October 2021 were included. In order to evaluate the VOD/SOS incidence, patients had at least 30 days of posttransplant follow-up or until death.

2.2. Prophylaxis of VOD/SOS and graft versus host disease (GvHD)

All patients received DF for VOD/SOS and rATLG (rabbit anti-T lymphocyte globulin ATG-Grafalon®; formerly ATG-Fresenius®), cyclophosphamide 50 mg/kg posttransplant D + 3/D+4 and cyclosporine (CsA) for GvHD prophylaxis, respectively. Patients who had at least two major risk factors (RFs) according to recently published European Society for Blood and Marrow Transplantation (EBMT-2020) criteria [3] were defined as having very high-risk for development of SOS/VOD and received DF at 25 mg/kg daily dose DF beginning with the conditioning regimen for 3 weeks or until discharge. All others received 10 mg/kg daily DF initiated with conditioning for 2 weeks. Patients who developed VOD/SOS were treated with 25 mg/kg daily DF until resolution of symphoms or death. In addition to DF, all patients recieved oral ursodeoxycolic acid 250 mg three-times daily started with conditioning until D + 90. The total dose of rATLG was 5−10 mg/kg and determined based on HLA match and remission status of the patients at allo−HCT.

2.3. Definitions

We used revised criteria proposed by teh EBMT for diagnosis and evaluation of severity of VOD/SOS [5]. The risk scores of patients regarding VOD/SOS are also calculated according to criteria proposed by CIBMTR and patients with a risk score > 10 % were classified as high-risk [6]. But the CIBMTR score was not used for defining the daily dose of DF. Matched related/unrelated donors had 10/10 HLA match considering HLA-A, -B, -C, DRB1 and DQB1 allelic typing. Patients having a 9/10 HLA matched related and unrelated donor were defined as well-matched related (WMRD) and well-matched unrelated (WMUD), respectively. Donor-recipient pairs with ≥ 2 HLA mismatches were treated as haplotransplants. The definition of the conditioning intensity (myeloablative-MA or reduced-intensity conditioning-RIC) was made according to widely accepted criteria [7]. In all patients the HCT comorbidity index (HCT-CI) [8], comorbidity-age index (aHCT-CI) [9], EBMT score [10], disease-risk index (DRI) [11] and transplant-conditioning intensity [12] were calculated. Neutrophil and thrombocyte engraftment were defined according to standard criteria.

2.4. Endpoints

The primary endpoinst of the study were cumulative incidence (CI) of VOD/SOS at day-30 after allo-HSCT and VOD/SOS-associated mortality.

2.5. Statistics

All statistical analysis were performed with the IBM SPSS Statistics (version 25.0; IBM Corp., USA) software. Frequency (percentage) and median (min-max) values were calculated as descriptive statistics for categorical and quantitative variables, respectively. The Kaplan-Meier method and competing risk analysis were used to estimate CI of VOD/SOS. Competing risk was death for VOD/SOS. The median follow-up was calculated as the time from allo-HSCT to death or last follow-up for censored patients. All patients gave written informed consent for all aspects of allo−HCT before transplant. The study was approved by the local institutional review board and conducted in accordance with declaration of Helsinki.

3. Results

The study included a total of 56 patiens (28 males, 28 females). The median age of the study cohort was 43 (20−68). The demographic and clinical features of participants are summarized in Table 1. The dose of DF was 10 mg/kg and 25 mg/kg in 53 (94.6 %) and 3 (5.3 %) patients, respectively. Risk factors for VOD/SOS and HSCT-associated outcomes are presented in Table 2. 23 (41.1 %) patients had at least one major EBMT-defined RF for development of VOD/SOS. The median CIMBTR risk score of the study cohort was 3.27 % (1.34 %–12.82 %). Three (5.3 %) patients belonged to the very high-risk group according to EBMT criteria. One patient who belonged to very high-risk group developed very-severe VOD/SOS at posttransplant D + 20 and died as a result of multiorgan failure. CI of VOD at D + 30 was 1.9 %.

4. Discussion

The main finding of our study is that 10 mg/kg daily intravenous DF

Table 1
Demographic and clinical features of the study cohort.

Variable	Results
Age (years) (median; range)	43 (20−68)
Gender (female; male) (n; %)	28 (50 %) / 28 (50 %)
Primary diagnosis (n; %)	
AML	28 (50 %)
ALL	16 (28.6 %)
NHL	5 (8.9 %)
MDS	3 (5.4)
MM	3 (5.4 %)
PNH	1 (1.8 %)
Donor type (n; %)	
MRD	29 (51.8 %)
WMUD	13 (23.2 %)
MUD	7 (12.5 %)
Haplo	7 (12.5 %)
Stem cell source (n; %)	
PB	53 (94.6 %)
BM	3 (5.4 %)
Infusion of HSCT product (n; %)	
Fresh	47 (83.9 %)
Cryopreserved	9 (16.1 %)
Infused $CD34^+$ cells (10^6/kg) (median; range)	8.35 (3.9−15.25)
Conditioning regimen (n; %)	
Busulfan-Fludarabine	30 (53.6 %)
Total body irradiation-Etoposide	21 (37.5 %)
Treosulfan-Fludarabine-Total body irradiation	3 (5.3 %)
Cyclophasphamide-ATG	1 (1.8 %)
Fludarabine-Melfalan	1 (1.8 %)
Conditioning intensity (n; %)	
MAC	52 (92.9 %)
RIC	4 (7.1 %)
TCI score (n; %)	
1−2	1 (1.8 %)
2.5−3.5	29 (51.8 %)
4−6	26 (46.4 %)
EBMT score (n; %)	
0	1 (1.8 %)
1	5 (8.9 %)
2	18 (32.1 %)
3	16 (28.6 %)
4	9 (16.1 %)
5	7 (12.5 %)
HCT-CI (n; %)	
0	16 (28.6 %)
1−2	25 (44.6 %)
≥ 3	15 (26.8 %)
aHCT-CI (n; %)	
0	6 (10.7 %)
1−2	22 (39.3 %)
3−4	26 (46.4 %)
≥ 5	2 (3.6 %)
DRI	
Low	6 (10.8 %)
Intermediate	26 (46.4 %)
High	17 (30.4 %)
Very high	7 (12.5 %)

Table 2
VOD/SOS risk factors and HSCT-associated outcomes.

Variable	Results
Daily dose of DF (mg/kg) (n; %)	
10	53 (94.6 %)
25	3 (5.3 %)
Very high risk according to EMBT criteria (n; %)	
No	53 (94.6 %)
Yes	3 (5.3 %)
At least one risk factor according to EMBT criteria (n; %)	
No	33 (58.9 %)
Yes	23 (41.1 %)
VOD/SOS risk > 10 % according to CIBMTR criteria (n; %)	
No	54 (96.4 %)
Yes	2 (3.6 %)
Neutrophil engraftment at D + 28 (n; %)	
Yes	49 (87.5 %)
No	7 (12.5 %)
Platelet engraftment at D + 28 (n; %)	
Yes	47 (83.9 %)
No	9 (16.1 %)
Neutrophil engraftment (days) (median; range)	16 (11−26)
Platelet engraftment (days) (median; range)	19 (6−55)
Cumulative incidence of VOD/SOS at 30-day (%)	1.9 %

for two weeks combined with UDCA is quite effective in prevention of VOD/SOS in patients who underwent a first allo-HSCT. Only one patient with at least two major RFs (very-high risk group) developed VOD/SOS and died as a result of this complication. DF and UDCA are two agents with evidence-based data indicating their efficacy in the prevention of VOD/SOS. Based on the pooled results of 3 randomized studies, a systematic review dealing with the role of UDCA in the prevention of VOD/SOS suggested that UDCA prophylaxis, compared with no prophylaxis, significantly reduced the risk of VOD/SOS (relative risk, 0.34, 95 % confidence interval 0.17−0.66) [13]. Endothelial activation/dysfunction play a pivotal role in development of early HSCT-drived complications [14]. Although the mechanism of action of DF is not fully elucidated, it seems to act through endothelial protection and restoration of the thrombotic/fibrinolytic balance. A large meta-analysis including 1230 patients showed that DF significantly decreased the incidence of SOS/VOD (4.7 % vs 13.7; $p < 0.005$) [15]. Therefore the combination DF and UDCA seems reasonable for prevention of VOD/SOS.

Although the role of DF in treatment of severe/very severe VOD/SOS is established, its optimal use for prevention in adults is stil a controversial issue. Most studies dealing with VOD/SOS prophylaxis with DF are prospective/retrospective cohort studies with historical controls or case studies. Studies differ significantly in study population, timing, dose and duration of defibrotide, diagnostic criteria of VOD/SOS and concomitant use of other agents like heparin or UDCA [16–19]. To our knowledge, the only prospective, phase III, randomized study in this era has been performed in pediatric HCT recipients and showed that DF significantly decreased the incidence of VOD/SOS in high-risk pediatric patients who reveived autologous or allogeneic HSCT [2]. Although the recommended dose of DF for prevention of SOS/VOD is 25 mg/kg initiated with the start of the conditioning and administered at least D + 21 or until patient discharge [3], retrospective experience suggest that DF may be also effective at lower doses and treatment durations [17,19]. All but 3 patients (94.7 %) of our study cohort received 10 mg/kg DF for 2 weeks initiated with the first day of conditioning regimen.

Our study has several limitations including relatively small size of the study cohort, retrospective single-center analysis and inclusion of mainly standard risk patients. Although 23 (41.1 %) patients of our study cohort had at least one major RF according to EMBT criteria, only 3 patients had very-high risk of VOD/SOS. It can be argued that the great majority of our patients would not develop VOD/SOS even without DF prophylaxis. But we should keep the following points in mind for decision making: 1-VOD/SOS occurs in 15 % of patients who underwent HSCT [20]. 2-The overall survival of patients with DF treatment who develop VOD/SOS associated multiorgan failure is poor (39 % at D + 100) [21]. 3- Evidence-based tools for discriminating high-risk adult patients are still lacking. With the aforementioned limitations in mind, it is still impressive that no patient receiving DF at a dose of10 mg/kg suffered from VOD/SOS.

Although results of a recently completed prospective, randomized, phase III study (NCT02851407) in adult/pediatric patients comparing DF and best-supportive care alone in the prevention of VOD/SOS has not been published, available evidence justifies the use of DF in patients undergoing HSCT and having high risk of developing VOD/SOS. If we consider the very high cost of the drug, certain questions are still relevant regarding prevention: are current EBMT-2020 criteria optimal for defining a high-risk population who will get more benefit from DF prophylaxis? Are criteria for defining high-risk pediatric patients also relevant for adults? What is the optimal dose and duration of DF? Bearing these important unresolved issues in mind, our present study may be accepted as an effort to define the optimal use of DF in the prevention of VOD/SOS. We hope that future studies will broaden our knowledge and define how to use this agent in an efficient and cost-effective manner.

Declaration of Competing Interest

The authors report no declarations of interest.

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