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

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 (AH SCT). Studies on the prophylactic effect of defibrotide to prevent hepatic VOD in adults are rare.

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

Methods: Study population comprised 86 consecutive AH SCT 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.

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

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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 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 (AH SCT) [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 AH SCT [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 evaluated whether prophylactic defibrotide use can reduce incidence and severity of VOD in adults undergoing AH SCT.
evaluated the clinical characteristics and outcome in patients diagnosed with VOD following AHSCRT 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 AHSCRT 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 AHSCRT 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 presence 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 AHSCRT received ursoeadoxycyclic 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 AHSCRT 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 demonstrated 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 AHSCRT 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/m²)
daily on day +1 and 10 mg/m² 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 AH SCT 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 previously 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 AH SCT 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 transplanted 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
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 AH SCT before December 2004 received defibrotide for VOD prophylaxis.

**Discussion**

VOD is a common complication after AH SCT 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 AH SCT in our center between January 2005 and December 2009. We investigated the incidence and clinical outcome of VOD in adults [18,19]. None of the historical controls who underwent AH SCT before December 2004 received defibrotide for VOD prophylaxis.

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].
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 AH SCT 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 transplanted patients, which gives useful information about the overall incidence of VOD among Turkish AH SCT recipients.

In adult patients undergoing AH SCT, 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 protocol for VOD prophylaxis after 2000. Limited number of studies have assessed the efficacy of defibrotide in VOD prophylaxis in adults [18,19]. Chalandon Yet 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 AH SCT 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 AH SCT [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 AH SCT [19]. In our study, patients who underwent AH SCT 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 fulfilling the criteria for VOD were included in the study by Chopra et al. [9]. In that study, defibrotide was given intravenously for a median of 14 days post-HSCT at doses ranging from 10 to 40 mg/kg in both children 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 AH SCT. 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 AH SCT. 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 AH SCT, use of busulfan-based conditioning regimen, prior abdominal radiation, pre-existing liver disease (hepatic fibrosis, cirrhosis and hemochromatosis), hepatitis B and/or hepatitis C infection with serological or virological evidence, prior history of myeloablative transplant, prior exposure to gemtuzumab ozogamicin 3 months before AH SCT.

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References

