

## Original Research Article

### IS DEFIBROTIDE PROPHYLAXIS EFFECTIVE ON GRAFT VERSUS HOST DISEASE IN PATIENTS WITH ALLOGENEIC STEM CELL TRANSPLANTATION?

#### 2. Abstract

**Introduction:** Sinusoidal obstruction syndrome (SOS) is one of the complications of allogeneic stem cell transplantation (allo-SCT). Defibrotide (DF) is used effectively in SOS prophylaxis and treatment. Graft versus host disease (GVHD) is a significant cause of morbidity and mortality in allo-SCT. Here, we retrospectively investigated the effect of DF on the development of GVHD in these patients.

**Methods:** We evaluated 81 allo-transplanted patients due to various diagnoses (benign or malignant), retrospectively. Thirty-four patients used DF as prophylaxis while 47 patients did not receive it. Acute and chronic GVHD assessments were performed at +30/100<sup>th</sup> day and throughout the life of the patients, respectively.

**Results:** Acute GVHD was more common with DF use (82% vs 61%). There was no statistical significance in terms of the effect on chronic GVHD. We observed that one patient in the non- DF group developed SOS.

**Conclusions:** DF may be beneficial to prevent acute GVHD. However, we observed that GVHD and mortality were more common in patients using DF. This is probably due to the similarity of high-risk criteria between GVHD and SOS. We have not found a significant association between defibrotide use and the development of chronic GVHD.

**Keywords:** Endothelial; grade; mortality; prophylaxis, sinusoidal obstruction syndrome

### **3. Introduction**

Hepatic sinusoidal obstruction syndrome (SOS) is one of the complications of allogeneic stem cell transplantation (allo-SCT) due to endothelial dysfunction. Clinical features of this syndrome are hepatomegaly, jaundice, ascites, and fluid retention [1]. Defibrotide (DF) is used effectively in SOS treatment because of its endothelial protective and thrombolytic-fibrinolytic regulatory effects [2]. Also, the use of DF has increased in recent years to prevent development of allo-SCT related SOS [2]. On the other hand, graft versus host disease (GVHD) is the most important cause of morbidity and mortality in allo-SCT, regardless of whether it is acute, chronic, or overlap syndrome. The effect of DF on GVHD is less clear. Here, we retrospectively investigated the use of DF and its effect on the development of acute and chronic GVHD in our patients who underwent allo-SCT.

### **4. Methods**

Eighty-one patients with various diagnoses (including myeloid and lymphoid hematological malignancies and aplastic anemia), who underwent allo-SCT at the Hematology Department of Adnan Menderes University between the years of 2014-2020 were included in the study, which was designed to be single-center, retrospective, multidisciplinary, analytic, and cross-sectional. Regarding donor compatibility, we have included all allogeneic transplantation procedures, performed as related or unrelated 9-10 / 10, as well as haploidentical transplantations. Myeloablative, reduced intensity, and non-myeloablative conditioning regimens were used in accordance with the diagnoses. Of the patients; the rates of myeloid malignancy, lymphoid malignancy, and aplastic anemia were 65%, 30%, and 5%, respectively. Thirty-four of the patients received DF as prophylaxis, while 47 patients did not

(Table-1). All patients in the DF group received the medication prophylactically at a dose of 25 mg/kg/day intravenously, from the beginning day of the conditioning regimen until 21 days after transplantation. The National Institutes of Health Consensus Criteria and Glucksberg grading system were used for diagnosis and grading GVHD, respectively [3,4]. The evaluation was made for acute and chronic GVHD at + 30/100 days and lifetime, respectively. Patients were also observed for overlap syndrome. For statistical analysis; the data were evaluated using SPSS 21 software program (Chicago, IL, USA). Qualitative data were given as numbers and percentages while quantitative data were given as mean  $\pm$  standard deviation. The Chi-square test was used to demonstrate the difference between categorical variables in the study. A p-value below 0,05 was the cutoff for statistical significance.

## **5. Results**

The results of the patients are presented in Table 1. Thirty-four patients received DF, while 47 patients did not. The mean age was  $39.5 \pm 10$  and  $45 \pm 11$  years for the DF group and the non-DF group, respectively. Thirteen patients (38%) in the DF group and 16 patients (34%) in the non-DF group received myeloablative conditioning regimens containing busulfan. The rest of the patients in both groups received non-myeloablative or reduced-intensity conditioning regimens. Acute GVHD was more common in patients who received DF, compared to patients who did not receive it (82% vs 61%). Although rates of chronic GVHD differ among DF users compared to non-users (31% vs 19%); it did not reach a statistically significant value (p: 0.274). While no patient died in the group that did not use DF, five patients died in the first 100 days in the group using DF. Overlap GVHD was observed in four patients. We

observed that one patient in the non-DF group developed SOS according to the European Bone Marrow Transplantation (EBMT) criteria [5].

## **6. Discussion**

SOS and GVHD share some common pathophysiological features, such as damage to the endothelial cells, and it is suggested that defibrotide has protective effects on activated endothelial cells [6-8]. The allo-SCT procedure itself, use of myeloablative conditioning regimen, recipient's cytomegalovirus seropositivity, and incompatible and unrelated donor selection are all considered common risk factors that render patients high risk for both SOS and GVHD [9,10]. There are few studies in the literature examining the relationship between DF use and GVHD. In an in vitro study on mice, DF use was shown to be effective in acute GVHD through T lymphocyte and neutrophil interaction [11]. In another experimental study by Martinez-Sanchez, DF use was shown to suppress acute GVHD by inhibiting "endothelial cell line" activation. [12]. Corbacioglu et al suggested lower incidence and severity of acute GVHD in the study involving 356 pediatric patients. In the study; compared with the control group; defibrotide is suggested to reduce acute GVHD from 48% to 37%, given the prescribing rate of corticosteroids as an initial approach to the treatment of acute GVHD. No difference was observed in chronic GVHD [8]. Acute GVHD was also less common in another clinical study by Tekgündüz et al (46,5% vs 82%), involving 195 patients [13]. In our study, we detected that DF use was higher in the patient group who developed acute GVHD. The reason for the difference between our study and other studies may be that the preference to use DF as a prophylaxis in our center is limited to high-risk patients because risk factors for GVHD and SOS are similar for a patient who is considered to undergo an allo-SCT. Although

chronic GVHD rates were different between DF users and non-users; it was found statistically insignificant, consistent with the literature. DF is an off-label drug in Turkey and formal permission can be obtained from the Turkish Drug and Pharmacy Agency; only if the following criteria are met: A history of abdominal radiotherapy involving liver; biopsy-proven liver fibrosis, cirrhosis or hemochromatosis; hepatitis B or C infection; previous SCT with myeloablative conditioning and the history of gemtuzumab ozagomycin treatment in the last 3 months [13]. Additionally, the presence of matched unrelated donors or the use of a busulphan-based conditioning regimen are also among the criteria, and we were able to use DF in one of these two indications for all our patients. To the best of our knowledge, our study is the first to evaluate the relationship between DF and acute and chronic GVHD in the adult population. The limitation of our study is that it is a retrospective study with a relatively low number of patients. It also has a relatively heterogeneous population in terms of diagnosis, transplant types, and conditioning regimens.

## **7. Conclusion**

SOS development; similar to GVHD, determines the success of the transplant and long-term morbidity and mortality. Although DF is suggested to be useful for alleviating acute GVHD; in our study, we detected that GVHD was more common in patients using DF, probably due to the similarity between GVHD and SOS risk factors. Considering the similar outcomes in other studies; DF appears to be ineffective on chronic GVHD. The effects of DF use on GVHD should be further clarified by prospective studies involving homogeneous and larger patient groups.

## **Compliance with Ethical Standards**

**Data availability:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**Ethical approval:** Since the study was designed as a retrospective study, ethics committee approval was not required.

**Informed consent:** Informed consent was obtained from all individual participants included in the study.

## 9. References

1. Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. *Br J Haematol*, 168 (2015), pp. 481-491. doi: 10.1111/bjh.13215.
2. Defibrotide. Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–2017 Dec 27. Available at: <https://pubmed.ncbi.nlm.nih.gov/31643815/>
3. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005 Dec;11(12):945-56. doi: 10.1016/j.bbmt.2005.09.004.
4. Chao NJ. Clinical manifestations, diagnosis, and grading of acute graft-versus-host disease. <https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-grading-of-acute-graft-versus-host-disease>
5. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf 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 Jun; 50(6): 781–789. doi: 10.1038/bmt.2015.52
6. Ertault-Daneshpouy M, Leboeuf C, Lemann M, Bouhidel F, Ades L, Gluckman E. Pericapillary hemorrhage as criterion of severe human digestive graft-versus-host disease. *Blood*, 22 Jan 2004, 103(12):4681-4684. DOI: 10.1182/blood-2003-05-1548

7. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis* 2002 Feb;22(1):27-42. doi: 10.1055/s-2002-23204.
8. Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A 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 Apr 7;379(9823):1301-9. doi: 10.1016/S0140-6736(11)61938-7.
9. Soyer N, Gündüz M, Tekgündüz E, Deveci B, Özdoğu H, Şahin HH. Incidence and risk factors for hepatic sinusoidal obstruction syndrome after allogeneic hematopoietic stem cell transplantation: A retrospective multicenter study of Turkish hematology research and education group (ThREG). *Transfus Apher Sci.*2020 Aug;59(4):102827. <https://doi.org/10.1016/j.transci.2020.102827>
10. Flowers MED, Inamoto Y, Carpenter PA, Lee SJ Kiem HP, Petersdorf EW et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood.* 2011 Mar 17; 117(11): 3214–3219. doi: 10.1182/blood-2010-08-302109
11. García-Bernal D, Palomo M, Martínez CM, Millán-Rivero JE, García-Guillén AI, Blanquer M et al. Defibrotide inhibits donor leucocyte-endothelial interactions and protects against acute graft-versus-host disease. *J Cell Mol Med.* 2020 ;24:8031-8044.
12. Martinez-Sanchez J, Hamelmann H, Palomo M, Mir E, Moreno-Castaño AB, Torramade S et al. Acute Graft-vs.-Host Disease-Associated Endothelial Activation in vitro Is Prevented by Defibrotide. *Front Immunol.* 2019 ;10:2339.
13. Tekgündüz E, Kaya AH, Bozdağ SC, Koçubaba Ş, Kayıkçı Ö, Namdaroğlu S et al. Does defibrotide prophylaxis decrease the risk of acute graft versus host disease following allogeneic hematopoietic cell transplantation? *Transfus Apher Sci.* 2016;54:30-4. <https://doi.org/10.1016/j.transci.2016.01.009>

## 10. Table Caption List

**Table 1:** The comparison of patients according to defibrotide use

	<b>DF</b> N: 34 (41.9)	<b>Non-DF</b> N: 47 (58.1)	<b>p</b>
<b>Mean age</b>	39.5±10	45±11	>0.05
<b>Sex</b>			
Female	15(44.1)	17(36.1)	
Male	19(55.8)	30(63.8)	>0.05
<b>Disease type</b>			
-Myeloid	25(73.5)	28(59.5)	
-Lymphoid	7(20.5)	18(38.2)	0.028
-Aplastic anemia	2(5.8)	1(2.1)	
<b>Conditioning regimen</b>			
-MAC	13(38.2)	16(34)	
-non MAC	5(14.7)	17(36.1)	0.043
-RIC	16(47)	14(29.7)	
<b>Transplantation type</b>			
10/10 related	11(32.3)	39(82.9)	
10/10 unrelated	11(32.3)	3(6.3)	0.001
9/10 related	2(5.8)	2(4.2)	
9/10 unrelated	7(20)	1(2.1)	
Haploidentical	3(8.8)	2(4.2)	
<b>Mean CD34 dose( x10<sup>6</sup> / kg)</b>	8.1	7.6	>0.05
<b>Mean donor age</b>	35±13	43±14	0.013
<b>Acute GVHD</b>			
-without	6(17.6)	18(38.2)	
-with	28(82.3)	29(61.7)	0.047
<b>Chronic GVHD</b>			
-without	25(73.5)	38(80.8)	
-with	9(26.4)	9(19.1)	0.274
<b>Overlap GVHD</b>	2(5.8)	2(4.2)	
<b>SOS development</b>	-	1(2.1)	

N:number  
conditioning

MAC: Myeloablative conditioning

RIC: Reduced intensity