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

Running Title: Effect of Defibrotide on Graft Versus Host Disease

Keywords:endothelial;grade**;** mortality; prophylaxis, sinusoidal obstruction

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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 inthese 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 +30/100th day and throughout the life of the patients,respectively.

Results: Acute GVHDwas more common with DF use (82%vs 61%). There was no statistical significance in terms of the effect on chronic GVHD. We observed that onepatient 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 significantassociationbetween defibrotide use and the development of chronic GVHD.

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

1. 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 thrombocytic-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.

2. Methods

Eighty-one patients with various diagnoses (including myeloid and lymphoid hematological malignancies and aplastic anemia), who underwentallo-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 ± 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.

3. 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 ± 10 and 45 ± 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" [5]."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 fourpatients. We observed that onepatient in the non-DF group developed SOS according to theEuropean Bone Marrow Transplantation (EBMT)criteria" [5].

4. 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 renderpatientshigh 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].Also, DFwas suggested to act as globalendothelial protectant and decrease the risk of GVHD when incorporated into the triplet therapy as post-transplant cyclophosphamide, low dose rabbit anti-t-lymphocyte globulin andcyclosporine after allo-SCT[14].On the other hand, in another study by Tilmont et al, among the 482 included patients, 64 of them received DF after allo SCT while418 did not, and DF was not found to prevent the occurrence of acute GVHD (P =0.9) or the occurrence of severe acute GVHD (P = 0.058) significantly[15].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 andformal permission can be obtainedfrom 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 thehistory of gemtuzumabozagomycin 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. 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.

5. 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.

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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.

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Conflict of interest: İrfan Yavaşoğlu declares that he had no conflict of interest. Atakan Turgutkaya declares that he had no conflict of interest. HilalEroğluKüçükdilerdeclares that she had no conflict of interest. GürhanKadıköylü declares that he had no conflict of interest. GökhanSargın declares that he had no conflict of interest. Ali ZahitBolaman declares that he had no conflict of interest.

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.

Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Ali ZahitBolaman, GürhanKadıköylü, İrfan Yavaşoğlu, GökhanSargın, AtakanTurgutkaya and HilalEroğluKüçükdiler. The first draft of

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8.Table Caption List

Table-1: Comparison of patients according to defibrotide use

Table 1: The comparison of patients according to defibrotide use

	DF N: 34 (41.9)	**Non-DF** N: 47 (58.1)	**p**
Mean age	39.5±10	45±11	>0.05
Sex Female Male	15(44.1) 19(55.8)	17(36.1) 30(63.8)	>0.05
Disease type -Myeloid -Lymphoid -Aplastic anemia	 25(73.5) 7(20.5) 2(5.8)	 28(59.5) 18(38.2) 1(2.1)	0.028
Conditioning regimen -MAC -Non-MAC	 13(38.2) 21(61.7)	 16(34) 31(65.8)	0.043
Transplantation type 10/10 related 10/10 unrelated 9/10 related 9/10 unrelated Haploidentical	 11(32.3) 11(32.3) 2(5.8) 7(20) 3(8.8)	 39(82.9) 3(6.3) 2(4.2) 1(2.1) 2(4.2)	0.001
Mean CD34 dose($x10^6$ / kg)	8.1	7.6	>0.05
Mean donor age	35±13	43±14	0.013
Acute GVHD -without -with	 6(17.6) 28(82.3)	 18(38.2) 29(61.7)	0.047
Chronic GVHD -without -with	 25(73.5) 9(26.4)	 38(80.8) 9(19.1)	0.274
Overlap GVHD	2(5.8)	2(4.2)	
SOS development	-	1(2.1)	

N:number MAC: Myeloablative conditioning RIC: Reduced intensity conditioning