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Comparison of efficacy and toxicity of treosulfan-fludarabine and busulfan-cyclophosphamide conditioning regimens in patients undergoing allogeneic stem cell transplantation

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Abstract

In hematologic malignancy patients undergoing allogeneic HSCT, the optimal conditioning regimen is uncertain and comparative studies of conditioning regimens with each other are needed. In the current study, it was intended to compare the toxicity profile of two myeloablative conditioning regimens (treosulfan-fludarabine vs busulfan-cyclophosphamide) and their effects on clinical outcomes. The data of patients who underwent allogeneic HSCT between 2015 and 2020 in Inonu University Turgut Ozal Medical Center were retrospectively analyzed. Patients receiving treosulfan-fludarabine (treosulfan group) or busulfan-cyclophosphamide (busulfan group) as a conditioning regimen prior to allogeneic HSCT were matched 1:1 according to their disease and age. A total of 42 patients were included in this trial (busulfan:21, treosulfan:21). The mean age of the patients was 45.2±14 years, and regimen-related toxicities and clinical outcomes of both groups were similar (all p>0.05). The median follow-up time of the patients in the treosulfan regimen groups was 9 months, while it was 15 months in the busulfan regimen group (p=0.82). 54.8% of the patients (12 treosulfan, 11 busulfan) died after a median follow-up of 9.5 months. When the effects of the two conditioning regimens on were compared in 28 acute myeloid leukemia (AML) patients, the engraftment times, acute and chronic graft versus host disease incidences, and sinusoidal obstruction syndrome incidence were found to be similar in busulfan and treosulfan groups (all p>0.05). In addition, the estimated median progression-free survival (p=0.938) and overall survival (p=0.672) of the groups were similar. Treosulfan-fludarabine appears to be a conditioning regimen that can be used as an alternative to busulfan-cyclophosphamide. Prospective randomized studies are needed to confirm the data in our study.

Keywords: Busulfan; treosulfan; allogeneic transplantation; conditioning regimen

Introduction

Allogeneic hematopoetic stem cell transplantation (HSCT) is a potential curative treatment for a several hematological malignancies and nonmalignant diseases in adult patients.

The choice of conditioning regimen is of remarkable significance in hematological patients, as cytoreduction should not eliminate a reasonable toxicity profile of the chemotherapy protocol. Likewise, the choice of conditioning regimens is made by looking at a variety of factors such as the patient's age, disease risk, and remission status at the time of transplantation [1].

Myeloablative regimens were the usual treatment for many years in HSCT patients. At the same time, those usual conditioning regimens are associated with notable adverse events. Reduced intensity conditioning (RIC) regimens have been enhanced to make allogeneic HSCT available to older and/or fragile patients [2]. Since the most patients with myelodysplastic syndromes (MDS) are older adults (median age 60-70 years), a reduced dose conditioning regimen may be a rational therapeutic approach in these patients [3]. Also good results have been obtained in several trials using a busulfan based reduced conditioning regimen in MDS or secondary acute myeloid leukemia (sAML) [4, 5].

There is increasing evidence from trials that non-relapse mortality (NRM) is lower after reduced-intensity regimens than after myeloablative conditioning regimen [6]. However RIC regimen have been associated with higher relapse rate [7].

Treosulfan has been demonstrated to be a reliable agent within a toxicity-reduced myeloablative conditioning regimen in

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concomitant administration with fludarabine for allogeneic HSCT [8]. Also, in the literature, treosulfan-fludarabine-based conditioning regimen is considered to be a reliable and efficient option in chronic myeloid leukemia (CML), acute lymphoblastic lymphoma (ALL), and MDS patients [8-11].

In hematologic malignancy patients undergoing allogeneic HSCT, the optimal conditioning regimen is uncertain and comparative studies of conditioning regimens with each other are needed. In the current study, it was intended to compare the toxicity profile of two myeloablative conditioning regimens (treosulfan-fludarabine vs busulfan-cyclophosphamide) and their effects on clinical outcomes.

Materials and Methods

This retrospective study was approved by Inönü University Health Sciences Non-Interventional Ethics Committee on 26/01/2021 with the decision no 2021/1568. The data of patients who underwent allogeneic HSCT between 2015 and 2020 in Inonu University Turgut Ozal Medical Center were retrospectively analyzed. Patients receiving treosulfan-fludarabine (treosulfan group) or busulfan-cyclophosphamide (busulfan group) as a conditioning regimen prior to allogeneic HSCT were matched 1:1 according to their disease and age.

Peripheral blood of donor was used as a graft source in all patients. A total of 30 g/m^2 treosulfan from day -6 to -4 and a total of 150 mg/m^2 fludarabine from day -7 to -3 were administered to patients in the treosulfan regimen group. The patients in the busulfan group received a total of 12.8 mg/kg busulfan from day -7 to -4, and a total of 120 mg/kg cyclophosphamide on days -3 and -2.

For graft versus host disease (GVHD) prophylaxis, cyclosporine 3 mg/kg/day was given to the patients in both groups one day before allogeneic HSCT and then the cyclosporine dose was adjusted according to its trough blood concentrations, and cyclosporine continued until the day +180 in the absence of GVHD. In addition, patients were given methotrexate 15 mg/m^2 for day +1 and methotrexate 10 mg/m^2 on days +3, +6 and +11. Additionally, patients transplanted from unrelated donors were administered 30 mg/kg rabbit ATG in both regimens. Valacyclovir, fluconazole, and levofloxacin were given to the patients for infection prophylaxis. In addition, trimethoprim-sulfamethoxazole was started for Pneumocystis carinii prophylaxis after engraftment.

Toxicities due to conditioning regimens were defined according to Common Terminology Criteria for Adverse Events version 5.0. The diagnosis and distinction of acute and chronic GVHD was made within the framework of the criteria recommended by the National Institue of Health and, if possible, biopsy was taken from the affected organs such as the skin and gastroistestinal system [12]. Sinusoidal obstruction syndrome (SOS) was diagnosed according to the criteria recommended by the European Society for Blood and Marrow Transplantation [13].

If the patient had an absolute neutrophil count (ANC) of 500/mm^3 for 3 consecutive days after allogeneic transplantation, the patient was deemed to have neutrophil engraftment on the first day when the ANC was above 500/mm^3. Similarly, if the platelet count was 20000/mm^3 for 3 consecutive days, platelet engraftment time was accepted on the first day when the platelet count was over 20000/mm^3.

The risk stratification of AML patients showing the prognosis of them according to their cytogenetic results was made according to the classification recommended by European LeukemiaNet in 2017 [14].

Progression-free survival (PFS) was considered to be the time from the day of allogeneic HSCT to relapse of the primary disease, while overall survival (OS) was considered the time from transplantation day to death.

Statistical analysis

After analysis of the distribution of normality of quantitative variables such as follow-up times, hospitalization times, infused CD34+ counts, and hematopoietic engraftment times via Shapiro-Wilk test, these data were given as median and range, and the Mann-Whitney U test was utilized to compare these data between the busulfan and treosulfan groups. Comparison of categorical data such as donor type, GVHD and SOS incidences, gender between busulfan and treosulfan groups was done using the chi-square test. Survival analysis was done through the Kaplan-Meier test and the log-rank test was used to compare PFS and OS of the two groups.

Results

A total of 42 patients, two thirds (28/42) of whom were AML patients, were included in the study. Of the remaining 14 patients, 6 had primary myelofibrosis, 4 had MDS, 2 had ALL, and 2 had CML. Characteristic features, conditioning regimen-related toxicities and clinical outcomes of the patients are summarized in Table 1. The mean age of the patients was 45.2±14 years, and regimen-related toxicities and clinical outcomes of both groups were similar (all p>0.05). The median follow-up time of the patients in the treosulfan regimen group was 9 months, while it was 15 months in the busulfan regimen group (p=0.82). 54.8% of the patients (12 treosulfan, 11 busulfan) died after a median follow-up of 9.5 months.

When the effects of the two conditioning regimens were compared in 28 AML patients, the engraftment times, GVHD incidences, and SOS incidence were found to be similar in busulfan and treosulfan groups (Table 2). In addition, the estimated median PFS (p=0.938) and OS (p=0.672) of the groups were similar (Figure 1).

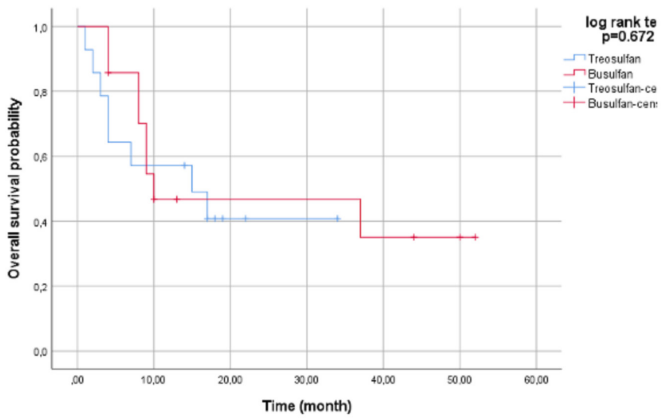

Figure 1. Overall survival of AML patients receiving busulfan or treosulfan

Table 1. Characteristic features and clinical outcomes of groups

	Treosulfan (n=21)	Busulfan (n=21)	p value
Gender			
Male	14 (66.7%)	12 (57.1%)	0.751
Female	7 (33.3%)	9 (42.9%)	
Age, median	49 (17-66)	44 (20-64)	0.378
Median HCT-CI score	1 (0-6)	2 (0-10)	0.054
Donor type			
MSD	17 (81%)	19 (90.5%)	0.663
MUD	4 (19%)	2 (9.5%)	
Infused median number of CD34+ cells x10^6/kg	7.3 (5.1-10)	7.72 (5-13.2)	0.234
Neutrophil engraftment time, median	15 (9-25)	13 (10-26)	0.074
Platelet engraftment time, median	14 (9-35)	13 (10-24)	0.212
Length of hospitalization after transplantation, median	21 (14-60)	18 (13-75)	0.137
Mortality within the first 100 days after transplantation, n	5 (23.8%)	2 (9.5%)	0.41
Febrile neutropenia, n	14 (66.7%)	16 (76.2%)	0.733
Acute renal failure, n	2 (9.5%)	3 (14.3%)	1
SOS, n	7 (33.3%)	6 (28.6%)	1
Cardiac toxicity, n	3 (14.3%)	1 (4.8%)	0.606
Multiorgan failure, n	0 (0%)	2 (9.5%)	0.488
Hemorrhage, n	0 (0%)	1 (4.8%)	1
Acute GVHD, n	5 (23.8%)	2 (9.5%)	0.41
Chronic GVHD, n	4 (19%)	7 (33.3%)	0.483
Estimated median OS, month	17	10	0.635

Abbreviations:
HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index, MSD: Matched sibling donor, MUD: Matched unrelated donor, SOS: Sinusoidal obstruction syndrome, GVHD: Graft versus host disease, OS: Overall survival

Table 2. Characteristics and clinical outcomes of AML patients receiving busulfan or treosulfan

	Treosulfan (n=14)	Busulfan (n=14)	p value
Gender			
Male	8 (57.1%)	8 (57.1%)	1
Female	6 (42.9%)	6 (42.9%)	
Age, median	48 (17-66)	44.5 (20-64)	0.629
Donor type			
MSD	11 (78.6%)	13 (92.9%)	0.596
MUD	3 (21.4%)	1 (7.1%)	
Median HCT-CI score	1 (0-5)	2.5 (1-6)	0.006
AML risk stratification			
Intermediate	13 (92.9%)	13 (92.9%)	1
Adverse	1 (7.1%)	1 (7.1%)	
Infused median number of CD34+ cells x10^6/kg	7 (5.1-10)	7.72 (5-9.9)	0.202
Neutrophil engraftment time, median	15 (11-25)	13.5 (11-15)	0.146
Platelet engraftment time, median	14.5 (9-35)	13 (11-17)	0.319
Length of hospitalization after transplantation, median	21 (14-60)	18 (15-75)	0.533
Mortality within the first 100 days, n	3 (21.4%)	0 (0%)	0.222
Febrile neutropenia, n	10 (71.4%)	11 (78.6%)	1
Acute renal failure, n	1 (7.1%)	1 (7.1%)	1
SOS, n	5 (35.7%)	4 (28.6%)	1
Cardiac toxicity, n	2 (14.3%)	0 (0%)	0.481
Multiorgan failure, n	0 (0%)	1 (7.1%)	1
Hemorrhage, n	0 (0%)	1 (7.1%)	1
Acute GVHD, n	4 (28.6%)	2 (14.3%)	0.648
Chronic GVHD, n	2 (14.3%)	4 (28.6%)	0.648

Abbreviations:
HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index, MSD: Matched sibling donor, MUD: Matched unrelated donor, SOS: Sinusoidal obstruction syndrome, GVHD: Graft versus host disease

Discussion

We compared a treosulfan-based conditioning regimen with a commonly used myeloablative conditioning busulfan-based regimen, allogeneic HSCT in patients with AML, ALL, CML, myelofibrosis and MDS. We demonstrated that survival (OS and PFS), engraftment time and mortality within the first 100 days after the two regimens the busulfan-based myeloablative regimen busulfan-cyclophosphamide and treosulfan-based regimen treosulfan-fludarabin, is similar.

Most trials have demonstrated that myeloablative conditioning and reduced intensity regimen are associated with similar survival [15-17]. However, reduced intensity regimen has been associated with higher relapse rates compared to myeloablative regimen. The use of myeloablative regimen as a conditioning regimen is supported in eligible AML or MDS patients. Fludarabin-busulfan and cyclophosphamide-busulfan were the used most commonly regimens [7]. There is presently no constant definition of treosulfan conditioning regimen as reduced intensity regimen or myeloablative regimen. However, the treosulfan-fludarabine regimen is referred to as a myeloablative conditioning regimen with reduced toxicity. [16, 18].

In the deficiency of randomized trials, the ideal treosulfan dose could not be determined. In a study, a total of 30, 36, 42 g/m^2 treosulfan doses were used, and no difference was observed between OS and PFS in these different dose groups. The frequency and severity of adverse events were also similar in all three dose groups. However, the highest relapse rate was observed in the 30 g/m^2 treosulfan dose group (2). In the present study, we used total 30 g/m^2 treosulfan dose.

Previous clinical trials demonstrated lower GVHD rate with treosulfan based regimen [16, 19]. Beelen et al noticed that a remarkably recovered transplantation associated mortality rate was observed in the treosulfan-based regimen group for chronic GvHD patients compared with the busulfan-based RIC regimen group. In this study by Beelen et al., lower doses of busulfan (6.4 mg/kg busulfan total dose) were utilized compared to other studies, and the busulfan regimen was mentioned as reduced intensity regimen. This effect may be due to extensive immunity dysfunction in patients observed GvHD in the busulfan-based regimen [18]. In addition, treosulfan-fludarabine regimen is a good conditioning regimen option for HSCT in primary immunodeficiency disease. Also, treosulfan has been increasingly used to substitute busulfan as it is associated with lower risks of veno-occlusive disease [20]. However, in a study, treosulfan-based regimen compared to busulfan-based regimen or FLAMSA as conditioning regimen for patients with AML, the GVHD incidence was found to be similar in the three regimen groups. [21]. Likewise, in the current study, acute and chronic GVHD rates were similar in both groups. Also, the frequency of other adverse events (eg. febrile neutropenia, acute renal failure, SOS) is similar in both groups.

In the literature, trials comparing the busulfan-cyclophosphamide regimen with the treosulfan-fludarabine regimen are limited. Shimoni et al. compared fludarabine/treosulfan conditioning regimen with busulfan-based myeloablative (busulfan/cyclophosphamide, busulfan/fludarabine) and reduced-intensity (busulfan/fludarabine) preparative regimen in AML and MDS patients. Shimoni et al. found that NRM and OS rates were similar all four conditioning regimens. However, when the risk of relaps prevails, a more intensive regimen such as busulfan cyclophosphamide has an advantage over other regimens [22]. Likewise, we demonstrated that survival (OS and PFS), after the two regimens the busulfan cyclophosphamide and treosulfan-fludarabin, is similar.

The limitations of our study are the limited number of patients and the retrospective nature of the study. Lack of access to some data (response to treatment before HSCT, chimerism status) is also among the limitations of our study.

In the present study, unlike the literature, we found that the toxicities of a busulfan-based myeloablative regimen and the treosulfan-based reduced toxicity myeloablative regimen were similar, which may be related to the small number of our patients. However, in accordance with the literature, we have supported with real life data that the survival of the two groups is similar.

In conclusion, treosulfan-fludarabine appears to be a conditioning regimen that can be used as an alternative to busulfan-cyclophosphamide. Prospective randomized studies are needed to confirm the data in our study.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This retrospective study was approved by Inönü University Health Sciences Non-Interventional Ethics Committee on 26/01/2021 with the decision no 2021/1568.

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