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Research Article

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Treosulfan-Based Conditioning Regimen for Allogeneic Hepatopoietic Stem Cell Transplantation in Children: A Single-Center Experience

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Abstract

Objective: Treosulfan is an alkylating agent whose use is increasing in HSCT conditioning regimens. Studies have highlighted its efficacy alongside its low toxicity profile. In this single-center study, we retrospectively report our experience and results with treosulfan in pediatric stem cell conditioning regimens.

Methods: Fifty-seven patients who underwent stem cell transplantation with a treosulfan-based conditioning regimen between September 2017 and April 2023 at the Istanbul Medipol University Pediatric Bone Marrow Transplantation Unit were included in the study. Treosulfan doses were determined based on age (under 1 year: 10g/m²/day; 1-2 years: 12g/m²/day; over 2 years: 14g/m²/day for 3 days).

Results: Of the 57 patients, 27 (47%) experienced acute GVHD and 3 (5.2%) experienced chronic GVHD. Of the 27 patients who had acute GVHD, 20 had grade I-II GVHD, and 7 had grade III-IV GVHD. Among the 3 patients with chronic GVHD, 1 experienced grade III-IV GVHD and 2 had grade I-II acute GVHD. Among the 14 patients with acute skin GVHD, 3 had grade III-IV, and among the 4 patients with acute gastrointestinal (GI) GVHD, 1 had grade III-IV. Of the 8 patients with acute skin +GI GVHD, 2 had grade III-IV. One patient experienced grade IV skin and liver GVHD. Of the 3 patients with chronic GVHD, 2 developed bronchiolitis obliterans and 1 had chronic skin GVHD. VOD developed in 2 patients. One of these patients had leukocyte adhesion deficiency (LAD) type 3 and underwent a transplant from an MUD without defibrotide. The other patient, diagnosed with HLH, received a haploidentical transplant with defibrotide. Two patients experienced secondary engraftment failure. One had thalassemia major, and the other had Chediak-Higashi syndrome. All patients except these two were followed-up with full donor chimerism. Four of the 57 patients died (overall mortality: 7 %). One patient with ALL died from GVHD-sepsis, and another died due to relapsed disease. One patient with AML was lost due to bronchiolitis obliterans during the third year post-transplant, and another patient with AML succumbed to sepsis and toxicity within the first 100 days. There were no deaths among patients with non-malignant diagnoses. The 100-day mortality rate was 1.75 %, with one patient passing away during this period.

Conclusions: Treosulfan can be preferred in the conditioning regimens of pediatric patients due to its similar efficacy and lower toxicity profile. Our study, which includes a broad pediatric patient group, provides guidance in this regard.

Keywords Pediatric stem cell transplantation · treosulfan · treosulfan-based conditioning regimen

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INTRODUCTION

Treosulfan is an alkylating agent whose use is increasing in pediatric hematopoietic stem cell transplantation (HSCT) conditioning regimens. Studies have highlighted its efficacy alongside its low toxicity profile. Nevertheless, the most reported toxicities include skin, mucosal, gastrointestinal, and hepatic toxicities[1-5].

Treosulfan is a modified busulfan analog due to the change in its two hydroxyl groups, granting it a slightly different mechanism[6]. Busulfan, a long-used alkylating agent in HSCT regimens, has been associated with sinusoidal obstruction syndrome (SOS) / veno-occlusive disease (VOD), neurotoxicity, and pulmonary fibrosis[7]. In recent years, treosulfan has a lower toxicity profile than busulfan. Treosulfan is a prodrug that is converted into monoepoxide and diepoxide derivatives through a non-enzymatic, pH-dependent pathway. These metabolites are responsible for DNA alkylation, cross-linking, chromosomal aberrations, and consequently apoptosis induction, although they are concentrated relatively less in the lungs, liver, and brain compared with the bone marrow. Therefore, it offers similar myeloablative and immunosuppressive properties to busulfan while having a lower toxicity profile. Its activation via a pH-dependent mechanism rather than by hepatic enzymes is another reason for its lower hepatotoxicity[8].

In traditional conditioning regimens involving Busulfan-Cyclophosphamide, liver toxicity, pulmonary hypertension, interstitial pneumonitis, skin and mucosal toxicities, and convulsions are significant complications that require careful management, with VOD being particularly prominent. However, these complications occur less frequently in treosulfan-based regimens, along with lower rates of graft-versus-host disease (GVHD)[8].

In this single-center study, we retrospectively report our experience and results with treosulfan in pediatric stem cell conditioning regimens.

MATERIAL AND METHODS

Fifty-seven patients who underwent stem cell transplantation with a treosulfan-based conditioning regimen between September 2017 and April 2023 at the Istanbul Medipol University Pediatric Bone Marrow Transplantation Unit were included in the study. The patients' data were retrospectively analyzed. All patients receiving treosulfan between September 2017 and April 2023 were recruited in this study. Informed consent was obtained from all parents. The study was approved by the responsible independent ethics committees and competent authorities and was performed in accordance with the Declaration of Helsinki.

Treosulfan doses were determined based on age (under 1 year: 10 g/m²/day; 1-2 years: 12 g/m²/day; over 2 years: 14 g/m²/day for 3 days). Defibrotide was not used for transplants performed until the end of 2018. From 2019 onwards, VOD prophylaxis with defibrotide was initiated in selected patients, and defibrotide use became routine after 2020.

RESULTS

The median transplant age of the 57 patients was 6 years. The youngest patient was 3 months and 14 days old, and there were 6 patients under 1 year of age and 15 patients under 2 years of age. The oldest patient was 18 years and 7 months old.

Among the patients, 17 had immunodeficiency/bone marrow failure, 13 had acute lymphoblastic leukemia (ALL), 10 had myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), 2 had non-Hodgkin lymphoma (NHL), 11 had thalassemia major, 1 had sickle cell anemia, 2 had hemophagocytic lymphohistiocytosis (HLH), and 1 had Hunter syndrome.

Thirty-three transplants were performed using full-matched unrelated donors (MUD), 16 with matched sibling donors (MSD), and 8 were haploidentical transplants from a parent.

In 52 patients, the conditioning regimen consisted of fludarabine-treosulfan-thiotepa; in 3 patients, it was fludarabine-treosulfan; and in 2 patients, it was fludarabine-treosulfan- thiotepa-cyclophosphamide. The treosulfan dose was 10g/m²/day for patients under 1 year, 12g/m²/day for those between 1 and 2 years, and 14g/m²/day for patients over 2 years, for 3 days.

Of the 57 patients, 27 (47%) experienced acute GVHD and 3 (5.2%) experienced chronic GVHD. Of the 27 patients who had acute GVHD, 20 had grade I-II GVHD, and 7 had grade III-IV GVHD. Among the 3 patients with chronic GVHD, 1 experienced grade III-IV GVHD and 2 had grade I-II acute GVHD. Four patients who underwent skin biopsies because of suspected acute skin GVHD were determined not to have GVHD, and their conditions were evaluated as drug eruptions.

The statistical data on the diagnoses and donor types of the patients who developed acute GVHD are shown in Tables 1 and 2.

Among the 14 patients with acute skin GVHD, 3 had grade III-IV, and among the 4 patients with acute gastrointestinal (GI) GVHD, 1 had grade III-IV. Of the 8 patients with acute skin +GI GVHD, 2 had grade III-IV. One patient experienced grade IV skin and liver GVHD.

Table 1. Patients with Grade I-II Acute GVHD

Donor Type	Immunodeficiency /Bone Marrow Failure	Thalassemia	Sickle Cell Anemia	ALL	MDS/ AML	HLH
Matched Sibling Donor (MSD)	-	-	-	2	2	-
Matched Unrelated Donor (MUD)	5	2	1	3	2	-
Haploidentical Donor	-	-	-	-	2	1

Table 2. Patients with Grade III-IV Acute GVHD

Donor Type	Immunodeficiency /Bone Marrow Failure	Thalassemia	ALL	MDS/AML
Matched Sibling Donor (MSD	-	1	1	-
Matched Unrelated Donor (MUD	1	-	1	1
Haploidentical Donor	-	-	1	1

Of the 3 patients with chronic GVHD, 2 developed bronchiolitis obliterans and 1 had chronic skin GVHD. One patient with bronchiolitis obliterans had AML, while the other had thalassemia major. The patient with chronic skin GVHD underwent transplantation because of immunodeficiency.

Among the 11 patients with thalassemia major, 3 developed GVHD (27%). One patient experienced grade IV acute skin GVHD with an MSD, another had grade II acute skin GVHD and bronchiolitis obliterans with an MUD, and the third had grade II skin + GI GVHD with an MUD.

A comparison of GVHD incidence among different donor types using the Fisher's exact test revealed no significant differences: MSD vs. MUD (p=0.468), MSD vs. Haploidentical (p=0.193), and MUD vs. Haploidentical (p= 0.249). These findings suggest that the donor type did not significantly impact the incidence of GVHD in our cohort. The incidence of grade III-IV GVHD was also analyzed among different donor types. Pairwise comparisons using Fisher's exact test confirmed the absence of significant differences between MSD vs. MUD (p = 1.000), MSD vs. Haploidentical (p= 0.578), and MUD vs. Haploidentical (p= 0.246). These results suggest that severe GVHD (grade III-IV) was not significantly influenced by the donor type in our cohort.

VOD developed in 2 patients. One of these patients had leukocyte adhesion deficiency (LAD) type 3 and underwent a transplant from an MUD without defibrotide. The other patient, diagnosed with HLH, received a haploidentical transplant with defibrotide.

Two patients experienced secondary engraftment failure. One had thalassemia major, and the other had Chediak-Higashi syndrome. All patients except these two were followed-up with full donor chimerism.

Of the 13 patients with ALL, 6 underwent transplantation during their first remission, and none experienced a relapse. Three patients were transplanted during their second remission, one of whom relapsed 3 years after the transplant. The current status of this patient, who resides abroad, has been unknown since 2022. Four patients relapsed after their first transplants with busulfan and underwent additional transplants—three received second transplants, and one received a third transplant. One patient was lost due to relapse after the second transplant, while the other two patients are in remission, as is the patient who underwent a third transplant.

Of the 10 patients with MDS/AML, 8 received transplants during their first remission. One of these patients was lost due to bronchiolitis obliterans during the third year after the transplant. Another patient, who had VOD following pre-transplant treatment with gemtuzumab ozogamicin, passed away within the first 100 days post-transplant. Two patients relapsed after the transplant and received second transplants, and both are currently in remission.

Nine of the 57 patients died (overall mortality: 15.7 %). Two patients with ALL died from GVHD-sepsis, and 2 another died due to relapsed disease. One patient with AML was lost due to bronchiolitis obliterans during the third year post-transplant, and 3 patient with AML succumbed to sepsis. One of 3 was in the first 100 days of transplantation. One patient of AML died due to cardiotoxicity in the third year of transplantation. There were no deaths among patients with non-malignant diagnoses. The 100-day mortality rate was 1.75 %, with one patient passing away during this period. The median follow-up duration for the 48 surviving patients was 32 months (12-72 months). One patient with ALL experienced a relapse after transplantation and is being followed up with the disease.

DISCUSSION

High-dose busulfan is widely used in hematology and oncology, particularly as part of conditioning regimens before allogeneic or autologous HSCT [9]. Over the past 40 years, its pharmacology has been extensively studied in both malignant and nonmalignant diseases. Its metabolism

and pharmacokinetics are well-documented, and its non-hematological toxicities can be effectively managed, especially with appropriate premedication. For certain patients, therapeutic drug monitoring can help optimize and personalize the conditioning regimen [10]. More recently, the alkylsulfonate drug treosulfan, initially developed as a myeloablative agent in combination with cyclophosphamide [11], has gained widespread use alongside fludarabine for conditioning before allogeneic HSCT . As survival rates have rapidly increased over the past 30 years, protection from transplantation toxicities has gained greater importance, and studies on this topic have proliferated. Among these studies, treosulfan has found a place for itself due to its effectiveness as an immunosuppressive and cytotoxic agent, along with its low toxicity profile [12-16].

Unlike busulfan, treosulfan is considered a prodrug that undergoes non-enzymatic conversion under physiological conditions into biologically active epoxybutane derivatives. Wasterhoff *et al.*suggest that treosulfan's high hydrophilicty may limit its efficient distribution in the bone marrow [17].

Treosulfan has primarily been used in combination with fludarabine for the treatment of relapsed hematological malignancies; however, concerns remain regarding its toxicity profile [18]. The same total dose of treosulfan (ranging from 30g/m² to 42g/m²) has been recommended for both adults and pediatric patients, including adolescents and very young children, and it has been considered a drug that can be administered without therapeutic monitoring [19]. However, as noted by Glowka *et al.*, its pharmacokinetics, particularly in pediatric populations, is not well understood [20]. This is likely due to its natüre as a prodrug, which results in the formation of multiple reactive metabolites [21].

In a Phase 2 clinical trial published by Lazzari and colleagues in 2021, long-term results showed that treosulfan at a dose of 42g/m² (14g/m²/day over 3 days) had myeloablative potential and was safe[22]. However, the optimal dose for infants remains an unresolved issue, and pharmacokinetic studies suggest that in addition to treosulfan, its active epoxide compounds should also be investigated for systemic exposure[23-24]. At our center, we could monitor busulfan levels in busulfan-based regimens, but because we could not track treosulfan levels, we determined our doses based on age. A study conducted in 2020 with 65 pediatric patients diagnosed with hematological malignancies followed a similar dosing strategy based on age, and their results were comparable to ours[25]. Another study involving 15 patients with primary immunodeficiency emphasized that patients achieved full chimerism with treosulfan, regardless of the genetic diagnosis or donor type[26]. Additionally, a study conducted with 29 pediatric patients diagnosed with benign conditions also reported successful engraftment [27].

Furthermore, studies comparing busulfan-based conditioning regimens to those with treosulfan highlighted that treosulfan offered similar myeloablation and immunosuppression and comparable engraftment success, but with a lower toxicity profile and reduced rates of GVHD[7,28,29].

CONCLUSIONS

Treosulfan can be preferred in the conditioning regimens of pediatric patients due to its similar efficacy and lower toxicity profile. However, our study has some limitations. Despite the relatively broad patient group, this was a single-center, retrospective study with limited long-term follow-up data. In addition, it is not a comparative study, and treosulfan dosing was not specifically analyzed; instead, doses were determined based on previously conducted studies and adjusted according to the age of the patient. Further comparative studies are necessary to evaluate its effectiveness and safety. Nevertheless, our study, which includes a broad pediatric patient group, provides guidance in this regard.

Ethics Committee Approval	This study was approved by the ethics committee of Istanbul Medipol University (09.06.2023).
Informed Consent	Written consent was obtained from the participants.
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study- ;N.B., Y.Y., K.Ö., I.O.A., S.N. Data Acquisition- N.B.; Data Analysis/Interpretation- M.E., S.A.; Drafting Manuscript- N.B., I.O.A., S.N.; Critical Revision of Manuscript- Y.Y., M.E., S.A., K.Ö.; Final Approval and Accountability- N.B., Y.Y., M.E., S.A., K.Ö., I.O.A., S.N.
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