Total Body Irradiation as a Component of Conditioning Regimen in Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric ALL

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ABSTRACT

The use of Total Body Irradiation (TBI) as part of allogeneic hematopoietic stem cell transplantation has shown promising results in reducing the risk of relapse in children with Acute Lymphoblastic Leukemia (ALL) without increasing the incidence of transplant-related mortality. This study aims to evaluate the outcomes and toxicity of TBI in combination with etoposide for allogeneic hematopoietic stem cell transplantation in pediatric ALL patients. The patient data from Ege University Hospital was used for this study. The following is a retrospective evaluation of 91 patients who underwent TBI in the allogenic transplant protocol with a diagnosis of ALL between January 2009 and December 2022. The patients received treatment according to two different protocols- the BFM 2003 protocol (19 cases) between 2009 and 2012 and the BFM 2012 protocol (62 cases) after 2012. Total body irradiation was administered in 6 fractions twice a day, totaling 12 Gy. The median age at diagnosis was 8 years (range: 1-17), and at the time of TBI application 10 years (range: 3-18). Sibling donors were used in 61 cases (67%), while 30 cases (33%) received transplants from unrelated donors. For 14 patients with central nervous system involvement at diagnosis or relapse, an additional 6 Gy cranial boost dose was administered according to the protocol. After a median follow-up of 56 months (range: 1-145), recurrence was observed in 9 cases (8.8%). Disease recurrence resulted in the loss of 9 cases, and 12 cases (13.2%) were lost due to treatment-related complications. Recurrence sites were identified as bone marrow in 6 cases and central nervous system in 3 cases. The 4-year overall survival rate was determined as 76.9. Four-year survival rate of 18.3% was observed in related donor transplantation, whereas it was 32.3% in unrelated donor transplantation ($p< 0.01$). Acute side effects related to total body irradiation of grade 2-3 were observed in 37 cases (41.7%). The most common acute side effects were nausea in 21 cases, parotitis in 11 cases, and headache in 3 cases. Late-onset side effects were observed in 47 cases. TBI related side effects was reported as sexual dysfunction in 3 cases, hypothyroidism in 6 cases, cataract in 3 cases, osteoporosis in 1 case, and veno-occlusive disease in 4 cases. Also, soft tissue sarcoma was diagnosed in 1 case 79 months after treatment. Transplant-associated Graft Versus Host Disease (GVHD) was observed in 13 cases (12.1%). Studies have shown that including total body irradiation (TBI) in the conditioning regimen for patients undergoing allogeneic transplantation is a reliable and effective protocol with favorable side effect profiles. For long-term outcomes, a more comprehensive multidisciplinary follow-up is recommended.

Keywords: Total body irradiation, Pediatric ALL,Side Effects, Stem cell transplantation

INTRODUCTION

Radiotherapy in hematopoetic stem cell transplantation (HSCT) was initially applied by Thomas and colleagues in the 1950s, and following the first application, total body irradiation (TBI) became widely used in HSCT procedures.[1,2] TBI is administered with the aim of preventing the rejection of donor bone marrow through its immunosuppressive effect, achieving myeloablation in the pre-transplant bone marrow, and particularly eliminating leukemic cells in areas where the penetration of chemotherapy is limited, such as the brain and testicules. TBI is a crucial component of condition regimens, especially in hematologic malignancies. studies have consistently demonstrated the superiority of protocols incorporating TBI, particularly in childhood high-risk Acute Lymphoblastic Leukemia (ALL), over regimens relying solely on chemotherapy.[3,4]

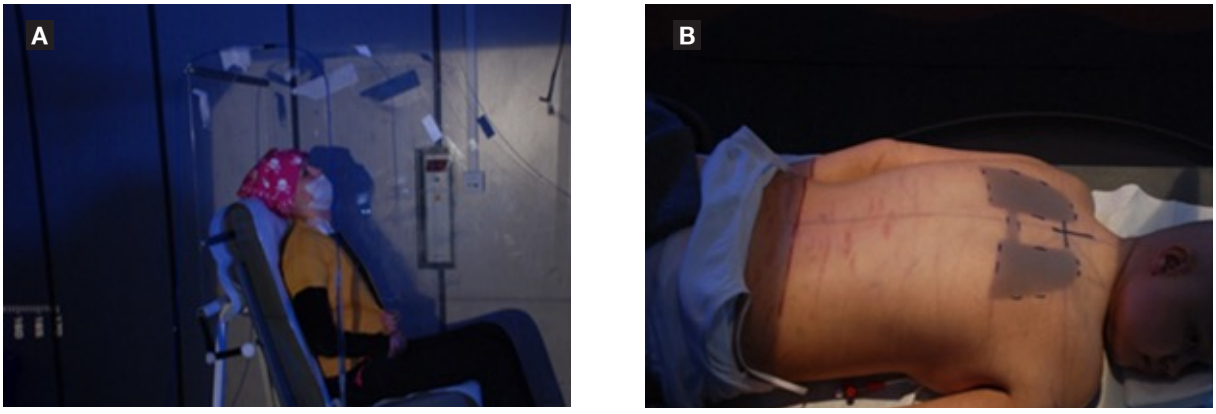
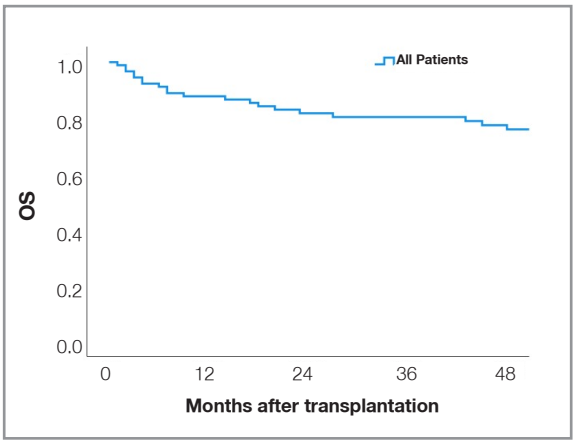


Figure 1. The figure **(A)** shows lateral field and patient specific chair. The figure (B) shows anterior-posteriror field and patient specific blocks for lungs and head and neck region

The FORUM study has reinforced the position of TBI in current approaches by demonstrating the superiority of TBI in combination with etoposide over chemotherapy alone in high-risk childhood leukemias.[5] ALL is the indication for bone marrow transplantation where its efficacy has been most clearly demonstrated. Studies reporting successful outcomes with TBI-containing transplant regimens also exist for Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML), Multiple Myeloma, and Hodgkin Lymphoma, although it is not as commonly preferred in standard practice as in ALL.[6] Despite its proven efficacy in clinical studies, concerns may arise in the selection of TBI in condition regimens, especially in pediatric cases, due to the potential side effects of extensive field irradiation. Even with much lower radiation doses compared to solid tumor applications, the use of broad field radiation may lead to various early and late side effects. Early treatment-related effects may include nausea, vomiting, diarrhea, stomatitis, temporary taste loss, parotitis, and radiodermatitis. Late effects may manifest as interstitial pneumonitis, hepatic veno-occlusive disease, cataracts, fertility loss, endocrine side effects, osteoporosis, growth retardation, and secondary malignancies.[7-17] This study aims to retrospectively evaluate the treatment outcomes, recurrence patterns, and treatment-related side effects of 91 patients treated over 14 years at a single center.

MATERIALS AND METHODS

Ninety-one patients under the age of 18 diagnosed with Acute Lymphoblastic Leukemia (ALL) and treated with TBI and etoposide condition regimen at the Ege University Departments of Radiation Oncology and Pediatric Hematology Oncology between January 2009 and November 2022 were retrospectively evaluated. The condition regimen was administered according to the BFM 2003 protocol (19 cases) and the BFM 2012 protocol in the period after 2012 (72 cases). Total body irradiation technique was applied over 3 days/6 fractions with a total dose of 12 Gy, while the lung dose was limited to 10 Gy. Five of the six fractions were delivered laterally with a specially designed car seat at a Source-to-Axis Distance (SAD) of 400 cm and Gantry angles of 82^0 (Figure 1), and one fraction was administered on a stretcher with Gantry angles of 0^0, 22^0, and 39^0 according to the patient's height with the necessary 2 or 3 overlapped AP-PA fields. No organ shielding was applied in lateral fields, while in AP-PA fields, the head-neck region and lungs were protected with patient-specific blocks to ensure the homogeneity of the total dose along the entire body axis (Figure 1). The extra scatter created by perspex plates on both sides of the car seat ensures that the skin dose reaches 90-95% of the prescribed dose. The dose rate is 300 MU/min, and the energy is 6 MV. No specialized treatment planning system is used, and dose calculations are manually performed based on body contour measurements taken for each position. Entrance-exit



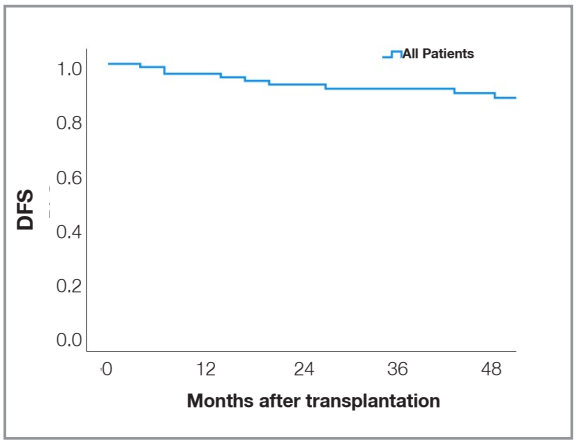


Figure 2. The graphs show Kaplan–Meier estimates of **(A)** Overall Survival (OS); **(B)** disease free survival (DFS)

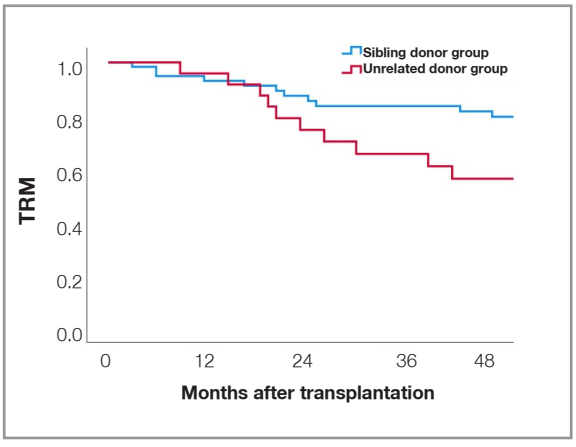


Figure 2 C. The graphs show Kaplan–Meier estimates of **(C)** transplant related mortality (TRM)

doses are measured with an ion chamber in the first fraction of each treatment, and the calculated doses are compared to check whether they are within ±10% limits. Treatment was administered under sedation when necessary for patients under 5 years old. The median age at diagnosis was 8 years (range: 1-17), and the median age during TBI administration was 10 years (range: 3-18). Sixty-one cases (67%) received transplantation from a sibling, while 30 cases (33%) received transplantation from a matched unrelated donor. Fourteen patients with central nervous system involvement at diagnosis or relapse received an additional 6 Gy cranial boost dose before TBI, as per protocol. Subsequent to TBI and etoposide, patients underwent transplantation from an HLA-matched sibling or unrelated donor. Complete remission was defined as bone marrow involvement below 5% and the absence of extramedullary disease. Relapse was defined as the detection of over 5% blast cells in the bone marrow or extramedullary region (cerebrospinal fluid, testes, ovaries).

Ethical approval for the study was obtained from the Ege University Hospital Ethics Committee (October 17, 2024; No: 24-10.1T/41).

Statistical Analysis

Patient data and follow-up information were processed using IBM SPSS version 22.0 based on files in the Ege University Department of Radiation Oncology archives. Kaplan-Meier method was utilized for disease-free and overall survival calculations.

RESULTS

Median follow-up of 56 months revealed a 4-year overall survival rate of 76.9% and a disease-free survival rate of 91.2% (Figure 2). Relapse was detected in 9 cases (8.8%), with a mean relapse duration of 20 months (4-48). All 9 cases with relapse were lost due to uncontrolled disease. The relapse site was observed in 6 cases (6.5%) in the bone marrow and 3 cases (3.1%) in the central nervous system (CNS). Among the 14 patients who received whole-brain cranial boost (WBRT) due to CNS involvement, isolated CNS relapse was identified in 2 cases. Patient characteristic and relapse

Table 1. Patient characteristics and relapse patterns (n= 91)

	Relapse (n= 8)	No Relapse (n= 83)
Median age at diagnosis (years)	6	8
Median age at TBI (years)	8	10
Cranial boost, n (%)	2 (25%)	12 (14.5%)
Protocol, n (%)		
BFM 2003	2 (25%)	17 (20.5%)
BFM 2012	6 (75%)	66 (79.5%)
Donor type, n (%)		
Sibling	5 (62.5%)	55 (66.3%)
Unrelated	3 (37.5%)	28 (33.7%)
Relapse site, n (%)		
CNS	2 (25%)	1 (1.2%)
Bone marrow	0 (0%)	5 (6.0%)
Cranial only	6 (75%)	0 (0%)

patterns are shown in Table 1. Twelve cases (13%) were lost due to treatment-related complications. When disease-free survival and donor type were compared, transplant related mortality 4-year survival rate of 18.3% was observed in related donor transplantation, whereas it was 32.3% in unrelated donor transplantation ($p< 0.01$) (Figure 2). Acute side effects related to total body irradiation were observed in 37 out of 89 cases (41.7) Epilepsy was observed in 2 cases (2.2%) in patients who underwent WBRT. Infertility was observed in 3 cases (3.3%). Soft tissue sarcoma developed in 1 case (1.1%) after 79 months but is currently under remission. Hypothyroidism was observed in 5 cases (5.5%) and cataracts were seen in 3 cases (3.3%) without any associated vision loss. Radiation pneumonitis was observed in eight cases (8.8%). Veno-occlusive disease was observed in four cases (4.4%). One case presented with bone/cartilage damage and continues bedridden due to osteopenia-related fractures. Graft versus host disease related to transplantation.was observed in 11 cases (12.1%). Late side effects are shown in Table 2.

DISCUSSION

Allogeneic Bone Marrow Transplantation (alloBMT) preparative regimens, particularly those involving TBI, are preferred treatment methods in pediatric patients with high-risk hematologic malignancies due to their superior treatment outcomes. While fractionated applications are generally considered standard in pediatric cases, various approaches have been reported. Survey results evaluating the treatment preferences of pediatric centers indicate that although conventional techniques are frequently favored, the choice of application depends on the infrastructure and preferences of the centers. In the current study, all patients were treated with the conventional hybrid two lateral and anterior-posterior extended SSD technique. The quality control of treatment applications for the cases was followed and reported by the ESTRO guidelines.[18] In a Phase 3 randomized controlled study comparing TBI-etoposide with busulfan-fludarabine-thiotepa preparative regimens, including 543 pediatric patients diagnosed with ALL and published in 2021, a 2-year overall survival of 91% in the TBI arm and 75% in the chemotherapy arm was determined. This study contributes to the existing literature by emphasizing the importance of TBI in alloBMT preparations, specifically in pediatric cases, and supports the findings of recent randomized controlled trials.[5] The results highlight the potential advantages of TBI-based regimens in improving overall survival in pediatric patients with ALL. It is essential for future research to further explore the long-term effects and potential complications associated with TBI, considering the evolving landscape of treat-

Table 2. Late side effects observed in all patients

Late Side Effects	Patients - n (%)
Total : 91	
No side effect	44 (48.4%)
Hypothyroidism	5 (5.5%)
Epilepsy	2 (2.2%)
Osteoporosis	2 (2.2%)
Secondary malignancy	1 (1.1%)
Graft-versus-host disease	11 (12.1%)
Asthma	9 (9.9%)
Cataract	3 (3.3%)
Veno-occlusive disease	4 (4.4%)
Radiation pneumonitis	8 (8.8%)
Infertility	3 (3.3%)
Growth retardation	2 (2.2%)
Diabetes	1 (1.1%)
Skin dryness	1 (1.1%)
Total	91

ment options and emerging technologies. The superiority of TBI applications over chemotherapy preparation regimens is known based on the data from a randomized controlled trial (RCT) in this aspect. The four-year survival results in our study indicate that similar success rates can be achieved in a single-center experience when compared to the survival results of a randomized trial. In a prospective study conducted by Chaillet et al. evaluating acute toxicity after a single fraction of 10 Gy Total Vertebral Irradiation (TBI), headache was observed in 42%, xerostomia in 61%, and parotid gland toxicity in 74% of cases within the first 24 hours. In comparison with our study, fractionated regimens appear to be more reliable in terms of acute side effects than a single fraction.[7] In a study by Buchali et al., retrospectively evaluating 162 cases, parotid toxicity was observed in 7% of cases following TBI. In our study, parotid toxicity was observed in 11% of cases during the acute period. Both studies applied TBI at the same doses, and the frequency of parotid toxicity was found to be similar.[8] In many randomized controlled trials, nausea associated with TBI has shown successful results in the symptomatic treatment of antiemetics such as 5-HT3 antagonists. In our study, patients included in the study also used 5-HT3 antagonists as antiemetics, and nausea during the acute toxicity period was controlled.[9,10] Interstitial pneumonitis is a major dose-limiting factor for TBI. Increasing fractionation and reducing dose rate reduce early pneumonitis and late fibrosis. The dose rate range of 5-20 cGy was found to be suitable. In a study by Weiner et al., at a dose rate of 7.5 cGy, pneumonitis was detected at 13%, while at a dose rate of 15 cGy, it was found to be 43%. In our study, the frequency of pneumonitis was found to be 11% and was consistent with the literature. However, it should be noted that the total dose plays a key role in pneumonitis risk.[15] The lens is one of the most radiosensitive tissues in the body. Cataract development is affected by fractionation and dose rate. Lens protection is not recommended due to the risk of retro-ocular relapse. In a study by Ozsahin et al., cataracts were found to be 39% after a single fraction of TBI and 13% in fractionated regimens. This has been confirmed in the Seattle long-term analysis showing the risk of cataracts to be 85%, 50%, 34%, and 19% after 10-Gy single-fraction TBI, >12-Gy fractionated TBI, 12-Gy fractionated TBI, and no TBI, respectively. The frequency of cataracts in our study was 3.29%, and no lens protection was applied to the cases receiving TBI.[16] In a study evaluating thyroid functions after transplantation by Sklar et al., hypothyroidism was detected in 43% of cases. However, in our study, hypothyroidism was observed in only 6.5% of cases, possibly due to differences in the preparative regimen; Sklar et al. study utilized a single fraction TBI.[17] Veno-occlusive disease occurs as a result of endothelial damage, hepatocyte damage, and thrombosis. In the NORDIC transplantation group study, the frequency of veno-occlusive disease in the arm randomized with TBI was determined to be 1%. In our study, however, the frequency of veno-occlusive disease was found to be 4.39%, presumably due to differences in fractionalization, total dose, or the administration of heparin.

Conclusion

The use of TBI (Total-Body Irradiation) has shown to be superior to preparative regimens in terms of overall survival, relapse-free survival, and treatment-related mortality. However, it is crucial to evaluate the long-term side effects of this treatment method, particularly in pediatric patients. In our study, we found that late-term side effects were

not observed in 60.5% of cases within a median follow-up period of 56 months. Therefore, considering the effectiveness, cost, and side effects, TBI can confidently be chosen as the primary treatment option.

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