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ORIGINAL ARTICLE

Total Body Irradiation in Pediatric Patients: Single Center Results

Pediatrik Hastalarda Tüm Beden Işınlaması: Tek Merkez Sonuçları

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Abstract

Introduction: Total body irradiation (TBI) with megavolt photon energy is a treatment that can be applied before bone marrow transplantation (BMT) in many hematologic diseases. Two-dimensional TBI (2D-TBI) is one of the oldest RT techniques. We performed a retrospective study to evaluate the radiotherapy (RT)-related acute adverse events in pediatric patients with TBI.

Methods: Patients who received TBI between January 1, 2021, and December 30, 2021, in the Radiation Oncology Clinic of Ankara City Hospital were evaluated retrospectively. The primary endpoint of the study was the assessment of RT-related acute adverse events (RT-AE). The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used for RT-AE.

Results: Twenty-one pediatric patients treated with 2D-TBI between February 20, 2021, and October 10, 2021, have been retrospectively analyzed. The median follow-up period is 7 (range 1–14) months. The median age of the patients is 11 (range 2–17) years. The median time to BMT following TBI is 4 (range 3–13) days. A total of 12 Gy was applied to 15 (71.4%) patients diagnosed with acute lymphoblastic leukemia and acute myeloid leukemia. A total of 3 Gy was applied to 5 (23.8%) patients due to aplastic anemia and thalassemia major. A total of 4 Gy was applied to 1 (4.8%) patient who had anaplastic large cell lymphoma. In the first week after TBI, all 21 (100%) patients were neutropenic in grade 3 or higher. One day after TBI, there was a 23.4% increase in grade 3 or higher leukopenia [p=0.042; OR (95% CI) 0.278 (0.132–0.585)].

Discussion and Conclusion: The 2D-TBI is applied with acceptable toxicity. TBI-related pneumonia was not observed in any of the patients in our treatment technique with a dose/rate of 0.053 Gy/min.

Keywords: Total body irradiation (TBI); Bone Marrow Transplant; Radiotherapy

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Total body irradiation (TBI) is a treatment technique that can be used in the treatment of different oncological and hematologic diseases (e.g., acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), thalassemia major (TM), and multiple myeloma), elimination of residue tumoral cells, suppression of bone marrow suction, and transplant rejection.[1] TBI, which has been used since the 1970s, has begun to be questioned about its use and necessity, especially due to its late side effects seen in the long-survival patient group. To avoid late TBI morbidities, the efficacy of TBI-free regimens is under investigation. Additionally, modified TBI schemes that attempt dose de-escalation at nontarget volumes are being trialed.[2–8] The two main approaches aimed at reducing TBI toxicity are as follows: first, the application of total marrow irradiation, total lymphoid irradiation, and total marrow and lymphoid irradiation, where nontarget body areas are preserved and allow dose escalation at targeted volumes; second, when radiation is applied to standard TBI areas, it is a shield added to structures such as lung gonads.[2–8] Computed tomography (CT) regimens without TBI are not suitable for all patients, and TBI is currently recommended as part of the bone marrow transplantation (BMT) regimen in high-risk patient groups.[1,2] The complete exclusion of TBI from treatment protocols does not seem possible today due to better survival with TBI occurring in selected patient groups such as very-high-risk ALL.[3–7] The For Omitting Radiation Under Majority (FORUM) study, which excluded TBI and whose results were announced in 2020, was terminated early because the significant contribution of TBI was observed. In the intention-to-treat population of this study, 2-year overall survival (OS), cumulative incidence of relapse, and treatment-related mortality were significantly better in the TBI arm.[7] TBI is the gold standard treatment prior to BMT in ALL patients over 4 years old.[9] In the study presented by Altouri et al.[10] in 2020, in addition to the standard indication, unlike the traditional approach, TBI was tried alone before BMT. In 14 adult patients with a diagnosis of refractory acute myeloid leukemia, only 18 Gy TBI without CT was applied, and TBI was found to be effective and safe despite the limitations of the study.

TBI is included in protocols to provide bone marrow suppression and reduce donor rejection before BMT. Both hematopoietic stem cells and leukemia cells are radiosensitive. The symbol D0 is used for objective evaluation of radiosensitivity. D_0 value is the dose of ionizing radiation that completely destroys a cell type, and this value varies between 0.5 and 1.4 Gy for hematopoietic stem cells. The D_0 value of human leukemia cell lines is 0.8–1.5 Gy.[11] *In vivo* D_0 values for peripheral blood cells tend to be slightly higher than *in vitro* values, and clinical trials on the subject also support these data. Shank et al.[12] examined the survival kinetics of peripheral blood cells in a previous study involving 14 children diagnosed with ALL and found that the D_0 value for peripheral blood lymphocytes was 3.7–5.4 Gy. In addition, the effect of radiation on hematopoietic cells has a chronic aspect. Myeloablative TBI has a long-lasting effect on the bone marrow with 30% reduced bone marrow cellularity even 1 year after BMT.[13] Another radiobiological parameter crucial for TBI regimens is the *a/b* value of the linear quadratic. Higher α/β values refer to less radio sensitivity per "fraction/dose rate." α/β value is less than 5 Gy in 2/3 of progenitor cells.[14] The most important reason for the effectiveness and usability of TBI is that hematopoietic cells are radiosensitive as mentioned and that they have the potential to be eliminated without severe side effects in other tissues.

The most effective dose and optimal radiotherapy (RT) technique for TBI has been modified over time. TBI has been administered a single dose of up to 10 Gy with cyclophosphamide for many years. Then, fractionated regimens were started to be used in which equal and better survival were achieved with fewer side effects.[2,15,16] Although there are different doses and schemes for TBI, the most commonly preferred doses for myeloablative purposes are 12–15 Gy given in 8–12 fractions over 4 days, with 2–3 treatments daily.[1] It was observed that doses above 12 Gy increased nonrelapse mortality and had no survival advantage despite less relapse.[17] Similarly, doses of 15 Gy and above were reported to have a negative effect on survival in previous studies.[18–20] For an effective and safe TBI, not only dose and technique but also dose/rate is essential. To reduce complications, the American Association of Physicists in Medicine (AAPM) TG-17 recommended that dose/rate should be <20 cGy/min.[21] In particular, it is recommended to keep the dose/rate lower than 0.04 to avoid radiation-related and fatal radiation pneumonia (RP).[22]

TBI was first described in 1969, and 2D techniques were used at that time.[23] Cobalt devices, which were used as the first RT devices, were replaced by modern LINAC devices. Traditionally, TBI was applied as an anteroposterior or bilateral body site (right and left) with skin surface distance/source axis distance (SAD)-based plans. Modern RT techniques such as intensity-modulated radiotherapy (IMRT), imagine-guided radiotherapy, volumetric modulated arc therapy (VMAT), and simultaneous integrated boost (SIB) can also be used for TBI. Treatment planning

can be modified with LINAC planning systems, planning is easier, and treatment times are shortened.[24] The protection of the gonads and lungs during planning can be given as an example of plan modification. Dosimetric results of the VMAT SIB technique, in which 12 Gy active is administered to the bone marrow while 8 Gy is given to the rest of the body, show the applicability of the treatment dosimetrically.[25,26] Current dosimetric research for alternative TBI is underway to reduce side effects and maintain effective treatment. Although the effectiveness and safety of many modern techniques have been proven, 2D techniques are still being used.

Reinforced the importance of TBI before BMT, especially after the significant survival advantage in the FORUM study,[7] reviewing TBI techniques and results and presenting the data obtained are necessary for TBI evolution. This study aimed to present the results of pediatric patients administered TBI using 2D techniques in our center.

Materials and Methods

For our research, pediatric patients who received TBI between January 1, 2021, and December 30, 2021, were evaluated at Ankara City Hospital, Radiation Oncology Clinic, retrospectively. Patient interviews, patient files, and electronic system data were used to obtain data. Demographic status of the patients, primary diagnosis, RT dose details, CT protocols, hematologic assessments of the patients before and after RT, acute side effects associated with RT, and recent conditions of the patients were noted. The study was conducted in accordance with the Helsinki Declaration. The ethical suitability of the study was approved by Ankara City Hospital Ethics Committee No. 1 on March 9, 2022, with the number E1-21-2-2451.

Patient Selection

Pediatric patients treated with diagnoses of TM, AML, ALL, and aplastic anemia and who underwent protocols containing TBI in the BMT preparatory regimen were analyzed. Patients under the age of 18 years who underwent TBI in our clinic and whose file data were complete were included in the study. Patients over the age of 18 years were excluded from the study. TBI schemes of the patients were determined in the pediatric hematology council in accordance with the applied protocols. External RT was applied to three different schemes.

Simulation and Treatment Plan

Patients were treated using Eclipse (Varian Oncology System, Inc., CA, USA). In our pediatric patient group, the lateral area (right vs left opposite) was preferred, where the patients were comfortable and the RT dose could be applied homogeneously. Although treatments can be applied in shorter times with 2D techniques than with modern techniques, a treatment fraction can last 30–40 min. During this time, the comfort of the patient is also important in terms of ensuring immobilization.

In our center, TBI is applied with 2D RT technique in two lateral areas (two lateral positions, right side/left side). Patients are positioned by reaching out first to the right and then to the left lateral, then pulling the knees to the abdomen. In this positioning, it is combined at chest level to close the lungs of the patient. Umbilicus, head, lung, and pelvis were taken as reference points in patients. The umbilicus is taken as an isocenter. Rice masses are placed around the patients for dose homogenization, and these rice masses are determined separately for each patient according to the previously determined tissue-maximum ratio value in our linear accelerator device. The patient is positioned at a distance of 466 cm between the reference points and the device.

After the patient is positioned with Gantry at 90°, the collimator at 45°, and the midline distance 466 cm, the MU value is calculated according to the half thickness value of the patient. The patients were treated with an "output dose rate" of 300 Gy/min at 6 MV energy.

In Vivo Dosimeter

In vivo dosimeters are devices that prevent major errors in external beam radiotherapy and allow us to evaluate the patient in real time and passive mode.[27] In TBI, the use of *in vivo* dosimeter is important to monitor dose changes caused by the risk of movement of the patient due to the length of the treatment time and the technical difficulties brought on by large area irradiations. Because a different value is obtained from the one calculated in the same fraction, it allows the dose to be corrected before the end of the treatment. A metal-oxide silicon field effect transistor (MOSFET) is used for *in vivo* dosimetry in our clinic. For each patient, skin dose was measured with MOSFETs placed at five different reference points (head, neck, lung, umbilicus, and pelvis). In TBI, the skin is not protected and can even be considered among targeted areas due to the cells in circulation. In megavoltage-level energies, the skin dose is lower than the dose at the D_{max} point (build-up). Therefore, the use of tissue equivalent material bolus is another option. Dose homogeneity on the craniocaudal axis was controlled over skin doses with the MOSFETs we used.[27,28]

Dose Rate Calculation

In addition to the total dose and fraction dose, the dose rate is also important in TBI. The dose rate is calculated based on the inverse-square law according to treatment distances.[27–30] For calculations, 30 × 30 × 30 cm solid phantom is used, our D_{max} distance is 1.3 cm, the output dose is 0.05116, the SAD is 466 cm, and the distance from the source to the point of interest (SPD) is 457.3 cm. The dose rate calculated according to these values is 0.053 Gy/min.

Primary and Secondary Endpoints

The primary endpoint of the study is RT-related side effect assessment for the first 100 days after RT. The side effects of the hematologic, pulmonary, and gastrointestinal systems (GIS) of the patients were assessed. The Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0 was used for side effect assessment.[31] For each patient, hemogram results were noted at 24 h after the first fraction, at 48 h after the first fraction, and 7 days after the end of RT. For lymphopenia, an absolute lymphocyte count (ALC) of 500 cells/mL is defined as grade 3 lymphopenia and an ALC <200 cells/mL was defined as grade 4 lymphopenia. For neutropenia, an absolute neutrophil count between 500 and 1000 μL^{-1} is defined as grade 3 neutropenia and <500 μL^{-1} is defined as grade 4 neutropenia. If the platelet value is between 25 000 and 50 000 μL^{-1}, it is defined as grade 3 thrombocytopenia; if it is <25 000 μL^{-1}, it is defined as grade 4 thrombocytopenia. A hemoglobin (Hb) value <8.0 g/dL is defined as grade 3. The patients were evaluated by a specialist radiologist in terms of RP. Grade 2 RP is defined as RP symptomatic (medical intervention indicated and limiting instrumental ADL). Grade 3 RP is defined as severe symptoms (limiting self-care ADL, oxygen indicated, and urgent intervention indicated) (e.g., tracheostomy or intubation). Grade 4 RP is defined as a life-threatening condition. For Grade 2 enterocolitis, abdominal pain, mucus, or blood in stool has been described. Grade 3 EC is defined as severe or persistent abdominal pain, fever, ileus, and peritoneal signs. Grade 4 EC is defined as life-threatening consequences (urgent intervention indicated). The secondary endpoint of the study is the assessment of neutrophil engraftment time (NET) and platelet engraftment time (PET) after BMT.

Statistical Analysis

Descriptive statistics for continuous (quantitative) variables were expressed as mean, standard deviation, minimum–maximum, and median values; categorical variables were expressed as number (n) and percentage (%). The categorical demographic characteristics of the patients were calculated using the Chi-squared test and Fisher's exact test. The Kaplan–Meier was used in univariate survey analysis and compared with the log-rank test. The Cox regression test was used in multivariate analysis. Analyses were performed with IBM SPSS Package Program version 23.0 (IBM Corporation, Armonk, NY, USA). The hazard ratio (HR) and 95% confidence interval (CI) values were noted for significant results. The statistical significance level was accepted as $p<0.05$.

Results

A total of 24 patients who were treated with TBI were evaluated in our clinic between January 1, 2021, and December 30, 2021. Three patients aged 18 years and over were excluded from the study, and the rest of the 21 pediatric patients were included in the analysis. The median follow-up period of the study was 7 (range 3–14) months. The median age of the patients was 11 (range 2–17). CT was applied to all patients prior to TBI. The median period up to BMT after TBI was 4 (range 0–13) days. A total of 12 Gy RT, 2 Gy × 2 (BID), was applied to 15 (71.4%) patients diagnosed with ALL and AML in 3 days. A total of 3 Gy was administered in 3 Gy × 1 fraction to 5 (23.8%) patients receiving TBI due to aplastic anemia and TM. A total of 4 Gy was administered in 1 day in 2 Gy × 2 fractions to 1 (4.8%) patient diagnosed with anaplastic large cell lymphoma. In BID-applied TBI protocols, there were 8-h intervals between irradiations administered on the same day. The median NET was 14 (range 10–20) days. The median PET was 22 (0–35) days.

Grade 3 and higher neutropenia were observed in 12 patients (57.1%) before TBI (basale). When analyzed according to basale, 10 patients (47.6%) (p=0.080) at 24 h after the first fraction; 11 patients (52.4%) (p=0.198) at 48 h after the first fraction, and 21 patients (100%) on week 1 after end of the TBI.

Grade 3 and higher leukopenia were observed in 3 (14.3%) patients prior to TBI (basale). When analyzed according to basale, grade 3 and higher leukopenia were observed in 8 (38.1%) patients at 24 h after the first fraction. There was a 23.4% increase in grade 3 and higher leukopenia after 24 h than the first fraction [p=0.042, OR (95% CI) 0.278 (0.132–0.585)]. At 48 h after the first fraction, 10 patients (47.6%) (p=0.090) were in grade 3 and higher leukopenia; in week 1 after TBI, 9 (42.9%) were in grade 3 and higher leukopenia (p=0.553) (Table 1, 2).

Basale grade 3 anemia was not found in any patient, and a week later, grade 3 anemia was found in 5 (23.8%) patients. The median basale Hb value was 9.9 g/dL (range 8.3–13.40); the median Hb value on week 1 following TBI was 10.1 g/dL (range 7.4–12.4). There was a Hb difference of 0.2 g/dL after TBI, which was not statistically significant (p=0.129).

Table 1. Demographics and treatment details of patients

Variables			Variables		
Gender			Mean (SE)	1.92	0.65
Male	14	66.7%	Median (range)	0.88	0-12.83
Female	7	33.3%	24 h after the first fraction grade 3 neutropenia		
Age			No	10	47.6%
Median (range)	11	2–17	Grades 3 and 4	11	52.4%
Primary			24 h after the first fraction LEU		
ALL	11	52.4%	Mean (SE)	2.11	0.74
AML	4	19%	Median (range)	0.95	0.1–14.55
TM	3	14.3%	24 h after the first fraction grade 3 leukopenia		
AA	2	9.5%	No	11	52.4%
ALCL	1	4.8%	Grades 3 and 4	10	47.6%
Basale NEU			Post TBI 1 w NEU		
Mean (SE)	1.09	0.20	Mean (SE)	0.11	0.03
Median (range)	0.77	0.01–3.15	Median (range)	0.045	0–0.5
Basale grade 3 neutropenia			Post TBI 1 w grade 3 neutropenia		
No	9	42.9%	No	0	0
Grades 3 and 4	12	57.1 %	Grades 3 and 4	21	100%
Basale LEU			Post TBI 1 w LEU		
Mean (SE)	2.25	0.46	Mean (SE)	0.25	0.10
Median (range)	2.46	0.3–8.62	Median (range)	0.09	0.01–2.08
Basale grade 3 leukopenia			Post TBI 1 w grade 3 leukopenia		
No	18	85.7%	No	12	57.1%
Grades 3 and 4	3	14.3%	Grades 3 and 4	9	42.9%
Basale HB			Post TBI 1 w platelet		
Mean (SE)	10.13	0.32	Mean (SE)	105.650	59.15
Median (range)	9.9	8.3–13.40	Median (range)	29000	10 000–998 000
Basale grade 3 anemia			Post TBI 1 w grade 3 thrombocytopenia		
No	21	100%	No	5	23.8%
Grade 3	0	0	Grades 3 and 4	16	76.2%
Basale platelet			Post TBI 1 w Hb		
Mean (SE)	175.230	0.70	Mean (SE)	9.86	0.33
Median (range)	134 000	16 000–759 000	Median (range)	10.1	7.4–12.4
Basale grade 3 thrombocytopenia			Post TBI 1 w grade 3 anemia		
No	16	76.2%	No	16	76.2%
Grades 3 and 4	5	23.8%	Grade 3	5	23.8%
24 h after the first fraction NEU			TBI-BMT (days)		
Mean (SE)	2.72	0.70	Mean (SE)	4.2	0.75
Median (range)	2.12	0–12	Median (range)	4	0–13
24 h after the first fraction grade 3 neutropenia			Total TBI doses		
No	11	52.4%	12 Gy	15	71.4 %
Grades 3 and 4	10	47.6%	4 Gy	1	4.8 %
24 h after the first fraction LEU			3 Gy	5	23.8%
Mean (SE)	2.9	0.81	NET		
Median (range)	2.26	0.01–14.89	Mean (SE)	13.9	2.85
24 h after the first fraction grade 3 leukopenia			Median (range)	14	10–20
No	13	61.9%	PET		
Grades 3 and 4	8	38.1%	Mean (SE)	22.1	8.30
48 h after the first fraction NEU			Median (range)	22	0–35

AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; TM: Thalassemia major; AA: Aplastic anemia; ALCL: Anaplastic large cell lymphoma; SE: Standard error; Hb: Hemoglobin; NEU: Neutrophil; LEU: Leukocyte; h: Hours; w: Week; RT: Radiotherapy; BMT: Bone marrow transplant; NET: Neutrophil engraftment time; PET: Platelet engraftment time.

Table 2. Grade 3 and above leukopenia analysis on day 1 after basale and RT

	24 h after the first fraction leukopenia	n (%)	Grade 3 and above leukopenia	Total	OR (95% CI)	p
Basale grade 3 and above leukopenia	No	13 (72.2%)	5 (27.8%)	18 (100.0%)	0.278 (0.132–0.585)	0.042
	Grade 3 and above Leukopenia	0 (0%)	3 (100%)	3 (100%)		
Total		13 (61.9%)	8 (38.1%)	21 (100%)		

The Chi-squared test and Fisher's exact test results. OR: Odds ratio; CI: Confidence interval.

Basale grade 3 and higher thrombocytopenia was found in 5 patients (23.8%); on week 1 following RT, grade 3 or higher thrombocytopenia was found in 16 patients (76.2%). However, the difference was not statistically significant. Basale platelet value was median 134 000 (range 16 000–759 000), and the median platelet value was 29 000 (range 10 000–998 000) on week 1 following TBI (p=0.278).

Patient follow-up periods are at least 90 days. During this period, idiopathic or RP was not observed in the patient file or electronic system data. Only 1 (4.8%) patient was diagnosed with infectious pneumonia 6 months after TBI and then the patient died. This patient does not meet the appropriate criteria for RT-related pneumonia,[32,33] and the patient died due to COVID-related endemic pneumonia in radiological, hematologic, and clinical evaluation. In 2 (9.6%) patients, grade 2–3 enteritis responding to medical treatment was observed. One patient developed GVH disease (4.8%) (Table 3).

Discussion

In the current study, the 2D TBI was applied to the patients with a dose rate of 0.053 and an energy of 6 MV. According to our results, the suppression effect on bone marrow emerged from 24 h after the first fraction. In week 1 after TBI, all 21 (100%) patients were grade 3 and higher neutropenic. When analyzed according to basale, 24 h after the first fraction was 8 (38.1%). There was a 23.4% increase in grade 3 and higher leukopenia after TBI (p=0.042; OR (95% CI) 0.278 (0.132–0.585). The median NET time was 14 (range 10–20) days. The median PET was 22 (11–35) days. RP was not observed in any patients. GVH was observed in 1 patient (4.8%), while grade 2 enteritis was seen in 2 patients (9.5%). Our results demonstrate that we are able to provide effective bone marrow suppression with acceptable and manageable side effects with our technique.

TBI is a specialized treatment that is applied to large areas and has technical difficulties. In order to standardize and facilitate this difficult treatment, instructions are presented in the AAPM TG-29 report.[34] To perform dose calculations in accordance with these instructions, patient thickness and prescription point should usually be measured at the belly level. To be able to calculate RT doses in accordance with these instructions, patient thickness, prescription point, and belly level should be measured. This guide contains recommendations for parallel opposite fields and high-energy photon beams from 4 to 18 MV.[23,24] AAPM's TG-51 calibration protocol is an additional guide for dosimetry of high-energy photon beams.[35] Often, 6 or 10 MV energy is preferred for TBI in pediatric patients, and in this energy, there is no risk of additional neutron scattering for patients and personnel.[2] Although more homogeneous plans are obtained with energies of 10 MV or higher, these energy levels are not suitable for children who have low body mass.[36] In traditional TBI, in each treatment fraction, treatment is applied over two opposing areas in the form of AP/PA fields or left–right lateral fields or fields that are combined. Mostly, a single source of radiation is used, and the patient is rotated 180° and positioned between doses. Contrary to many treatment protocols, skin protection is not a goal in TBI.[1,2] The AP/PA fields should be preferred in the foreground over bilateral fields due to lower lung doses.[37]

With the widespread use of modern RT techniques, many techniques such as helical tomotherapy and dynamic arc-based technique have been tried for TBI to increase the homogeneity of radiation. In RT plans using modern techniques, there is a prolongation of treatment times, but there are many advantages: obtaining a more homogeneous dose distribution, better PTV coverage, and less acute.[38–41] Although tomotherapy and Varian are available in our clinic, it was deemed appropriate to apply TBI with 2D techniques. Finally, our physician and medical physics team have 2D experience. The reasons for our preference for 2D are primarily the significant prolongation of treatment times in IMRT plans. The number of patients who receive daily treatment on our devices is high. Prolonged fraction times may cause delays and pauses in clinical planning. In addition, the compliance of pediatric patients is impaired during prolonged treatment periods, and they can move. Patients with adjustment disorder during the

Table 3. Details of the patients

Patient no.	Age, gender	Primary	TBI scheme	RT-BMT	Adverse effect	Engraftment time	Follow-up	Last status
1	13 y, M	AML	2Gy BID total 12 Gy	4 d	Grade 2 diarrhea	NET: 12 d PET: 14 d	FU: 3.2 mo	Alive
2	13 y, M	AA	3Gy × 1 fraction	1 d	None	NET: 15 d PET: –	9.3	Alive
3	10 y, M	ALL	2 Gy BID total 12 Gy	4 d	None	NET: 14 d PET: 16 d	4.63	Ex
4	17 y, M	ALL	2 Gy BID total 12 Gy	NS	None	NS	9.07 mo	Alive
5	14 , F	ALCL	200 BID total 4 Gy	1 d	None	NET: 12 d PET: 14 d	10.68	Alive
6	17 y, M	AML	2 Gy BID total 12 Gy	3 d	None	NET: 15 d PET: 20 d	6,74	Alive
7	8 y, M	ALL	2 Gy BID total 12 Gy	5 d	None	NET: 20 d PET: 27 d	1.87	GVH+ Ex
8	2 y, F	AA	3 Gy × 1 fraction	2 d	None	NET: 14 d PET: 17 d	9.4	Alive
9	10 y, M	ALL	2 Gy BID total 12 Gy	5 d	Anxiety during RT	NET: 15 d PET: 25 d	13.63	Alive
10	12 y, M	ALL	2 Gy BID total 12 Gy	5 d	None	NET: 12 d PET: 14 d	8.8	Alive
11	3 y, F	AML	2 Gy BID total 12 Gy	1 d	None	NET: 10 d PET: 12 d	8.18	Alive
12.	15 y, F	ALL	2 Gy BID total 12 Gy	5 d	None	NET: 15 d PET: 34 d	6.93	Ex (COVID pneumonia)
13	15 y, M	AML	2 Gy BID total 12 Gy	2 d	Grade 2 diarrhea	NET: 13 d PET: 31 d	3.38	Alive
14	11 y, F	TM	3 Gy × 1 fraction	13 d	None	NET: 16 d PET: 34 d	11.66	Alive
15	10 y, M	TM	3 Gy × 1 fraction	2 d	None	NET: 10 d PET: 12 d	3.2	Alive
16	16 y, M	ALL	2 Gy BID total 12 Gy	6 d	None	NET: 19 d PET: –	3.0	Ex
17	9 y, F	ALL	2 Gy BID total 12 Gy	5 d	None	NET: 16 d PET: 24 d	3.98	Alive
18	7 y, M	ALL	2 Gy BID total 12 Gy	4 d	None	NET: 11 d PET: 11 d	3.88	Alive
19	12 y, F	TM	3 Gy × 1 fraction	12 d	None	NET: 10 d PET: 12 d	11.7	Alive
20	5 y, M	ALL	2 Gy BID total 12 Gy	5 d	None	NET: 16 d PET: 35 d	9.2	Alive
21	9 y, M	ALL	2 Gy BID total 12 Gy	–	None	–	3	Ex

TBI: Total body irradiation; F: Female; M: Male; ALL: Acute lymphoblastic lymphoma; AML: Acute myeloblastic lymphoma; TM: Thalassemia major; AA: Aplastic anemia; ALCL: Anaplastic large cell lymphoma; RT: Radiotherapy; BID: Bis in die (twice a day); NET: Neutrophil engraftment time; PET: Platelet engraftment time; d: Day; mo: Months.

fractionation are treated with anesthesia. According to our clinical experience, children's compliance with short-term treatments is higher. The disadvantage of the 2D technique is that the doses of organs such as the lens, lung, and heart could not be calculated. Only dose values are controlled by an *in vivo* dosimeter. *In vivo* dosimeter is measured with a MOSFET dosimeter placed on the patient's surface during treatment and allows dose modification.[28]

The biological RT effect of TBI on cells and tissues depends on factors such as total dose, fraction dose, total treatment duration, fraction time, dose homogeneity, patient and tumor characteristics, presence of simultaneous systemic treatment, and dose rate.[2] The dose rate is a measure of the amount of radiation given in unit time. When TBI was first used, it was applied with cobalt devices, and the dose rate of these devices was <5 cGy/min. The dose rate can be increased up to 50 cGy/min with linear accelerators that are later put into use. The dose rate is effective not only on the therapeutic efficacy of TBI but also on its side effects. The dose rate is an important radiobiological parameter that is directly related to acute and chronic side effects. Although there is more than one variable in RT-related damage to organs such as lungs and kidneys, one of the important parameters to consider is the dose rate. Low dose rates (<10 cGy/min) should be preferred in patients who will be treated with TBI.[24] However, the use of excessively low dose rate values due to side effects may limit the therapeutic efficacy of TBI. Scarpati et al.[42] showed that leukemia relapses increased in patients given TBI doses 8.4–12.5 Gy in 3 days with a dose rate of ≤0.04 Gy/min. In addition, dose rates >0.3 Gy/min do not have an additional effect on hematopoietic cells.[43] In radiobiological studies, the majority of which are old-dated, the effect of dose rate on side effects decreased with fractionation. With fractionation, the toleration of normal tissues to ionized radiation increases, and this provides a decrease in side effects. In addition, the dose rate was assessed in terms of in-treatment changes, and it has been shown that the average dose rate is more important than the instantaneous dose rate.[2] The dose rate value calculated in our study is 0.053 Gy/min and is compatible with the literature data.

The most important concerns for TBI are long-term morbidities, but acute side effects can cause problems in the treatment process by causing disruption in treatment protocols. The main acute side effects of TBI are parotitis, nausea, vomiting, diarrhea, xerostomia, mucositis, esophagitis, skin erythema, headache, alopecia, loss of appetite, and fatigue. These side effects are usually moderate and respond to symptomatic treatment. IV fluids and antiemetics, pain medication, and skincare can be applied depending on the symptom in side effect management. In the subacute and chronic period, endocrinopathy, cataracts, hepatotoxicity, nephrotoxicity, cardiovascular, and neurocognitive side effects may occur.[1,2]

Neutropenia is common acute toxicity in patients receiving CT or irradiated red bone. Neutropenia is frequently observed in patients undergoing TBI due to combined cytotoxic treatments. In Pearlman's paper published in 2021, neutropenia (grade 3–5) was observed from 23% to 41.2%. In our study, all patients received CT before TBI and 57.1% of the patients before TBI had grade 3 and 4 neutropenia, and 14.3% of the patients before TBI had grade 3 and 4 leukopenia. Deepening of neutropenia and leukopenia was observed after TBI. This condition, which requires close follow-up, is also an expected clinical reflection of the myelosuppressive effect of TBI. In addition, vital follow-up is important in this patient group. In an animal experiment conducted by Capitano et al.,[44] it was reported that the body temperature, which increases physiologically up to 39.5°C after TBI, can be the response to neutropenia with G-CSF-, IL-17-, and IL-1-dependent mechanism. These patients should be closely monitored for frequent hemograms and vital signs after TBI.

Idiopathic interstitial pneumonitis/pneumonia syndrome is a fatal RT side effect that can occur days or months after TBI. The most common dates of pulmonary toxicity are 60–90 days after KIT.[2] After single-fraction TBI, IP occurred more frequently than fractionated TBIs, and the risk of incidence could be up to 60% and the mortality up to 50%.[45] However, in the articles presented after TBI using fractionated regimens, the incidence of IP in children ranges from 0% to 35%, and its mortality is lower than 20%.[28,46–50] A complex mechanism that includes alveolar epithelial damage, cell aging, oxidative stress, and local inflammation underlies RT-related pulmonary complications. Subacute fibrosis may occur as a result of fibroblast cumulation and collagen accumulation following acute damage and followed by chronic pulmonary fibrosis. RP can be seen at different rates depending on treatment technique, primary malignancy, patient, and dose, but the overall incidence is 10.3%–45%.[51–53] In the study conducted by Oertel et al.,[54] in which 335 patients were monitored for a median of 85 months, pulmonary toxicity was observed in 24.8% of the patients. The most common side effects are RT-associated pneumonia (13.4%) and pulmonary obstruction (6.0%). To prevent this mortal complication, lowering the doses in the lungs has been tried. In addition, lung doses of 8 Gy and higher are associated with significantly lower OS. When we examine this in terms of treatment techniques, significantly higher lung doses were detected in other lateral areas compared with AP/PA. The mean lung dose was 818 cGy (SD 220 cGy) in patients who were applied TBI with AP/PA. It is 1139 cGy (SD 103 cGy) in patients who underwent opposite lateral treatment.[28] Thus, it can be said that the AP/PA technique is more suitable for lung doses. In the retrospective analysis of Beyzadeoglu et al.,[22] 105 patients who underwent TBI with 12 Gy 6 fraction were evaluated. During a median 12-month follow-up period, 9.5% of pa-

tients developed RP. In this patient group, the median total lung dose was 9.6 Gy (range 8.8–10.9), and the relationship between total lung dose and RP was not significant. Significantly less RP was seen in patients with a low dose rate (0.04). Lung shields can be used to reduce the risk of pulmonary toxicity. It is possible to reduce lung doses with lung shields. Metallic blocks or multileaf collimators in IMRT treatments can be used as lung shields. However, the bone marrow in the ribs or mediastinal lymph nodes is actually the target tissue for TBI before BMT. The effectiveness of TBI should not be reduced while reducing lung doses. For these target volumes, it is possible to apply additional doses and modify TBI with electron boost fields and mediastinal photon fields.[55–57] In such treatment plans, scattered doses should be meticulously calculated.[58,59] In our study, RP was not observed in any of our patients in the treatment schemes applied with a dose rate of 0.053 Gy/min. One of our patients died 7 months after the end of TBI due to pneumonia. Patient file notes noted that the patient died due to infectious pneumonia. The file notes and the radiological and hematologic parameters of this patient were retrospectively assessed. Patient's CT report showed infection with COVID-19. RT-related pneumonia was not considered in the patient as the criteria for the diagnosis of RT pneumonia have not been met.[32]

Diarrhea and enteritis are common abdominal acute complications of RT during irradiation. Damage to RT-sensitive enteral cells occurs due to crypt abscess and inflammation. It usually starts within days after RT, and the initial treatment is hydration. Concomitant use of CT causes worsening of GIS toxicity. In Pearlman et al.'s[59] analysis, grade 3 diarrhea was observed in 2.1% of the patients. In our patient group, RT-related grade 2 enteritis was observed in two of our patients (9.6%), and clinical improvement was achieved with supportive treatment.

In our study, GVH disease was observed in 1 (4.8%) patient and the patient deceased. Different results have been obtained in studies comparing the success of BMT and GVH rates of regimens with and without TBI. In a study conducted by Styczynski et al.[60] on patients undergoing allo-HCT for ALL, it was reported that regimens with TBI provide better transplant results than regimens without TBI. In their study, Dandoy et al.[61] reported higher acute GVH (56% vs 27%, p<0.0001) and even higher endocrine morbidity (24% vs 8%, p<0.001) in the treatment of AML (treatments with TBI compared with the protocols without TBI). There is no difference in renal, cardiac, and pulmonary long-term side effects. In Yalcin et al.'s study,[62] protocols with and without TBI in ALL patients were compared, and acute graft versus host disease grades 2 to 4, veno-occlusive disease, capillary leakage syndrome, thrombotic microangiopathy, bloodstream infection, hemorrhagic cystitis, and posterior reversible encephalopathy syndrome were found to be similar. Additionally, neutrophil and PET were evaluated, and significantly higher NET was reported in regimens with TBI (17.5 vs 13 d, p=0.001). In our study, there was no patient arm that received only chemotherapy and did not include TBI. We only analyzed patients who underwent TBI. Our median NET was 14 (range 10–20) days, and the median PET was 22 (0–35) days.

The long-term side effects of TBI are especially pronounced in the <3-year-old group, and TBI is not preferred in this age group. TBI, adding side effects in the long term, significantly increases the risk of endocrinopathy, cognitive disorders, and secondary malignancies.[63] One of the most important long-term morbidities of TBI is hormonal problems followed especially in patients whose long survival is expected.[61] In the follow-up of TBI patients, remission in height and gonad functions was detected. Therefore, careful evaluation of percentile curves, GH plasma FSH, and inhibin B measurements are recommended.[64] Prospective randomized studies are required in this regard, but having looked at the current literature, it is clear that patients who are applied TBI should be closely monitored in terms of secondary malignancy, height–weight monitoring, and endocrine assessment (DM, GH, and inhibin). In this study, long-term side effects were not assessed.

The most important limitation of the study is that it is a single-centered retrospective study. In addition, the number of patients is 21, and the follow-up time is short. There is no long-term side effect assessment. However, our treatment technique, which is easily performed and will not disrupt clinical operations with a short treatment time, has been explained in detail.

Conclusion

TBI, applied with a dose rate of 0.053 Gy/min and 2D technique using LINAC at 6 MV energy in the pediatric patient's arm, is an effective treatment with acceptable acute side effects.

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