



# Allogenic Stem Cell Transplantation and Total Body Irradiation

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## SUMMARY

The clinical importance of bone marrow transplantation has increased considerably in recent decades. More than 450 centers for bone marrow transplantation now exist worldwide, performing more than 5000 transplantations per year. The number of transplant centers and patients has increased dramatically in Turkey in the last several years. When transplant donor and recipient are different individuals, hematopoietic graft is known as allogeneic graft. Total body irradiation (TBI) remains an important component of allogeneic hematopoietic stem cell transplant, with the goal of eradicating residual malignant cells and modulating the immune system of the transplant recipient. TBI is especially advantageous in allogeneic stem cell transplantation, since its biological effects can be exerted uniformly without sparing the “sanctuary” sites, such as nervous system or testicles. In this report, the role of TBI in allogeneic stem cell transplantation is reviewed.

**Keywords:** Allogenic stem cell transplantation; bone marrow donor; total body irradiation.

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Allogenic stem cell transplantation involves transferring the stem cells from a healthy person (the donor) to a patient (the recipient) following high-intensity chemotherapy and/or irradiation. The donor can be a relative of the patient or a stranger named as unrelated donor. The important thing is that the donor's immune system markers should closely matched to patients'. To find a HLA –matched sibling donor is not possible for 70% of the patients who need immediately an allogenic hematopoietic stem cell transplant.[1] To overcome this many countries developed regional or national bone marrow databases to find a matching donor. In Turkey the Turkkök Project (National Marrow Donor Program) has developed into a large national organization, allowing access to a large database of unrelated donors, where data of more than one million healthy persons stored. This has resulted increased chance of finding a

matching donor for patients of all races/ethnicities. The Turkkök Project has also developed programs and approaches that have successfully increased the efficiency of the search process, which has decreased the waiting time to transplant. It is also expected an increase in the feasibility of allogeneic stem cell transplantation and requirement of total body irradiation (TBI) applications in our country with this project.

Allogenic Stem Cell Transplantation, using human leukocyte antigen (HLA)-matched sibling or unrelated bone marrow donors has been used successfully to treat patients with high-risk or relapsed hematologic malignancies.[1,2] Some solid tumors are under the investigation of allogeneic transplantation (Table 1). Successful bone marrow transplantation with a combination of cyclophosphamide and total body irradiation as a conditioning regimen was first reported in the 1970s.[3]

**Table 1** Tumors which allogeneic transplantation using with total body irradiation is performed

Standard treatment	Under clinical investigation
Acute lymphoblastic leukemia, (ALL) Acute/chronic myelogenous leukaemia (AML/CML)	Neuroblastoma, Ewing sarcoma, High/low grade non-Hodgkin lymphoma, Multiple myeloma

TBI is an important component of hematopoietic stem cell transplant with the goal of eradicating residual malignant cells and modulating the immune system of the transplant recipient. TBI has several advantages over chemotherapy since its biologic effects can be exerted uniformly throughout the body without sparing of the “sanctuary” sites such as the nervous system or testis, which is evident for many chemotherapy drugs. However, there are always concerns with the use of irradiation regarding the long term sequelae, including cataracts, second malignancies, and developmental problems in pediatric cases specifically. Because of these concerns, chemotherapy regimens omitting total body irradiation have been studied extensively where busulfan replaced TBI.[4,5] Both TBI/Cyclophosphamide or Busulfan/Cyclophosphamide regimens have been accepted standard conditioning regimens since the 1980s. There are a few published papers comparing TBI/Cyclophosphamide versus Busulfan/Cyclophosphamide for stem cell transplantation and their long-term results for different leukaemia types (Table 2). In 2010, a meta-analysis compared the clinical results of different conditioning regimens for various leukaemias. In this metaanalysis, different studies were evaluated for therapeutic effects of TBI/CY or BU/CY regimens with assessment of engraftment, relapse patterns, complications, and disease-free survival.[6] A total of 3172 patients from 18 trials have been evaluated and TBI/CY regimen was reported to have similar

occurrence of engraftment, acute and chronic graft-versus-host disease with BU/CY, but had higher rates of cataract, interstitial pneumonitis, later growth or developmental problems.[6] BU/CY regimen was related with more severe complications such as veno-occlusive disease of liver, hemorrhagic cystitis, and treatment-related mortality. The authors also concluded that different treatment regimens and leukaemia types may affect the complications and outcome.[6] The results of TBI containing regimens in acute lymphoblastic leukemia (ALL) is summarized in Table 2. The ideal conditioning regimen for leukaemia patients undergoing bone marrow transplantation still remains unknown and the results of current ongoing BFM trial will be the answer of this question in the near future.

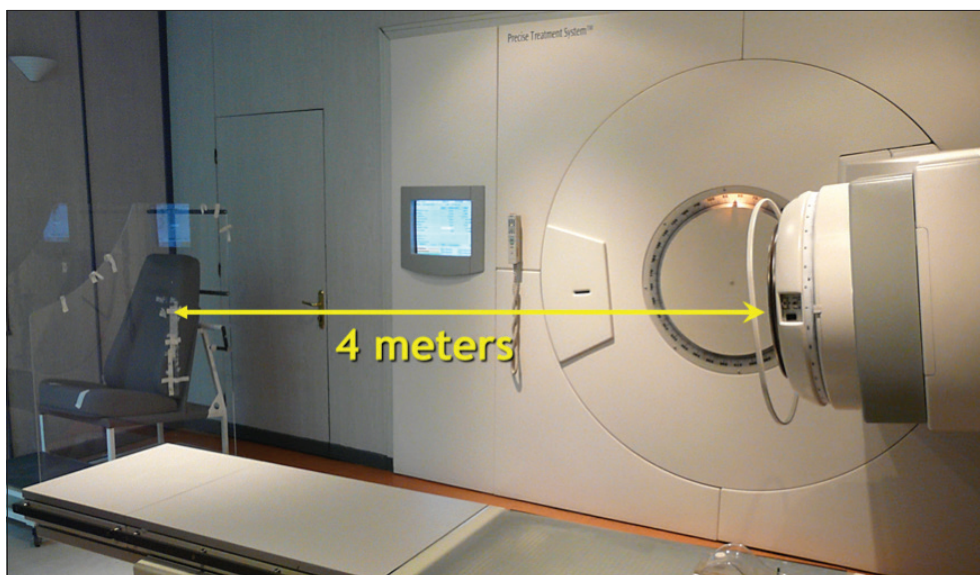
Numerous different techniques have been developed to deliver TBI.[7–10] The choice of a particular technique varies among institutes and depends on experience of the institute, the workload of the department, geometry of the treatment room, available infrastructure and equipment, and treatment protocol. In the majority of departments two treatment techniques or combination of both are used in practice. An antero-posterior posteroanterior (AP/PA) technique generally provides a better dose uniformity along the longitudinal body axis, but it is not possible to cover the whole body with a single field and use of multiple neighboring fields is always a challenge. Bilateral TBI (treating from the left and right side of the body) can be more comfortable to the patient if seated on a specially designed TBI Chair (Figure 1) but, presents greater variation in body thickness along the path of the beam. Thus compensators are required to achieve dose uniformity along the body axis.

The aims of designing a treatment technique for an individual department should be as follows: performing TBI within the department’s regular schedule, using the best possible technique requiring a short treatment time, providing a comfortable positioning to patients, improving and simplifying the lung shielding system to provide reproducible positioning of the patients. Therefore, the ideal treatment technique comprises the

**Table 2** The results of TBI containing regimens in acute lymphoblastic leukemia

Author	Regimen	Overall Survival
Bunin[5]	BU	67%
	TBI	47% 3 year
Davies[4]	CY/TBI	55%
	BU/CY	40% 3 year
Park J[15]	TBI/CY	64.3% 2 year
Kamer –unpublished results	TBI/CY	69% 2 year

BU: Busulfan; CY: Cyclophosphamide; TBI: Total body irradiation.



**Fig. 1.** TBI set-up at the Ege University Hospital. Bilateral irradiation is used with an SSD of 4 meters. Patient is seated on a specially designed chair. Plexiglas beam screens are used to increase the surface dose. Reference dose is measured by 0.6 cc ion chamber taped on the plexiglas screen.

requirements of dose homogeneity, lung sparing and dose prescription, accuracy of treatment, reproducibility and reliability of treatment set-up, comfort for patient and staff. The technique of TBI has evolved in parallel with an increase in the knowledge of the biologic response to ionizing radiation and improvements in radiation dosimetry and treatment delivery. Recently, new advanced techniques using helical tomotherapy and VMAT (volumetric modulated arc therapy) were implemented for TBI.[9] VMAT dose distribution was better than conformal techniques but total treatment time was unacceptably longer (treatment time was 2 hours per day) for daily use especially for small kids. Longer treatment times were also reported with helical tomotherapy.[7] Another disadvantage of helical tomotherapy is the limited treatment length of the longitudinal axis, allowing a maximum PTV length of 145 cm. Patients exceeding 145 cm body length require another complex plan for lower part of the body, which extends the total treatment time further.

The best total radiotherapy dose and dose rate are other unanswered questions in clinical practice. Several authors tried to find a relationship between the total dose of TBI and treatment outcome. Although some of them reported a higher overall survival with increasing TBI dose,[10] others reported opposite.[11] Vriesendorp et al.[12] reported that the results of TBI is related with dose, fraction size and endpoint selection and

that different TBI procedures could not be compared without radiobiological “normalization”. This normalization will also be different for various endpoints. Relapse rates were significantly lower in the TBI schedules using higher doses but disease-free survival and treatment-related mortality were significantly different in various trials.[13]

Acute and especially long term side effects are the major concern for TBI protocols.[14] Most centres use fractionated TBI to reduce acute side effects such as nausea and vomiting, and late effects such as cataracts. Shielding of the lungs to keep the total lung doses under 10 Gy is also widely used to prevent severe radiation pneumonitis. In Europe, most centres do not irradiate children below the age of 2 years due to the harmful effects on the developing brain. The biggest risks for children who received TBI are the secondary malignancies, growth retardation (especially if irradiated below 10 years) and infertility (most common after irradiation during or after puberty).

To date, it has not been shown that TBI in the conditioning regimen for childhood ALL can be replaced by chemotherapy. Davies et al. compared outcomes of HLA-identical sibling transplants for ALL in children who received cyclophosphamide CY/TBI (n=451) versus those who received Bu/CY (n=176) for pre-transplant conditioning. The 3-year probabilities of survival were 55% with TBI/CY and 40% (95% CI 32% to 48%)

with Bu/CY (univariate  $p=0.003$ ). In a multivariate analysis, the risks of relapse were similar in the two groups (relative risk [RR], 1.30 for Bu/CY v CY/TBI;  $p=0.1$ ). Treatment related mortality was higher in the Bu/CY group (RR, 1.68;  $p=0.012$ ). Death and treatment failure (relapse or death, inverse of leukaemia-free survival (LFS)) were more frequent in the Bu/CY group (RR, 1.39;  $p=0.017$  for death; RR, 1.42;  $p=0.006$  for treatment failure).[4] Bunin et al. performed a randomized trial of oral Bu vs. TBI in children with ALL. There was no significant difference between Bu and TBI for patients who received stem cells from related donors (36% vs 58%). However, for unrelated donors, EFS was 20% for Bu and 57% for TBI. Relapse was similar in both arms. [5] The available reports did not clarify whether all allogeneic stem cell transplant patients need a TBI containing regimen.[14,15]

In conclusion, TBI has been used most frequently for allogeneic transplantation in patients with acute leukaemia before HSCT. The main drawbacks of allogeneic transplantation are early transplant-related mortality and late complications with the latter impacting both quality of life and patient outcomes. At present, there are a lot of unanswered questions about TBI techniques, indications and dose. Developing national protocols will improve TBI procedures in our country.

### Disclosure Statement

The authors declare no conflicts of interest.

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