

Review Article

Current Status and Perspectives of Irradiation-Based Conditioning Regimens for Patients with Acute Leukemia Undergoing Hematopoietic Stem Cell Transplantation

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ABSTRACT

Acute myeloid leukemia and acute lymphoblastic leukemia are the most common indications for allogeneic hematopoietic stem cell transplantation. Total body irradiation (TBI) is an important part of conditioning regimens. TBI-based regimens offer advantages in sanctuary sites but are associated with significant risks of early and late side effects, including pulmonary toxicity, growth retardation, and second malignancy. TBI is also associated with technical problems, such as dose heterogeneity. With evolving techniques in radiation oncology, it is possible to focus the dose to the entire skeleton while sparing the rest of the body. This technique is called total marrow irradiation (TMI). TMI is able to deliver the same or higher doses to bone marrow while reducing toxicity. With the success of TMI, we are moving toward ultra-personalized conditioning. We review the clinical role of the irradiation-based regimens currently in clinical use, emphasizing on their strengths and limitations. Novel technologies with targeted irradiation accompanied by the modern imaging techniques and increased knowledge of the disease process can help us achieve our goal of maximum response with minimum toxicity.

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1. INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the treatment of choice for many hematologic conditions. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are the most common indications for allo-HCT [1,2]. Transplantation must be preceded by administration of a conditioning regimen given to prevent graft rejection and leukemia relapse through the elimination of host T cells and reduction of the tumor burden. Conditioning may be based on either an irradiation and chemotherapy combination or chemotherapy alone. The purpose of this review is to summarize the most frequently used irradiation-based conditioning regimens, to discuss potential advantages and disadvantages of irradiation—compared to chemotherapy-based protocols in acute leukemia, and to present perspectives in this field.

2. TOTAL BODY IRRADIATION

As defined by the Center for International Blood and Marrow Transplant Research (CIBMTR) during the Bone Marrow

Transplantation Tandem Meeting in 2006, the regimens are classified by their intensity as myeloablative conditioning (MAC), reduced intensity conditioning (RIC), or nonmyeloablative conditioning (NMAC) [3]. MAC regimens contain high doses of alkylating agents with or without TBI, leading to complete ablation of bone marrow. NMAC regimens are those that do not require stem cell support and allow recovery of the patient's own marrow. Regimens that do not fit either criterion are called RIC. There is a wide spectrum of regimens that are used as RIC. Usually, it involves reduction of $\geq 30\%$ in TBI or chemotherapy myeloablative doses.

TBI is an integral part of many MAC regimens. TBI alone was first used in 1957 for acute leukemia [4]. The first successful use of TBI with cyclophosphamide (Cy/TBI) took place in 1979 [5]. The standard dose of TBI in a MAC conditioning is 12 Gy. Currently, various other TBI regimens are used, including a single fraction of 5–10 Gy, fractionated TBI of 10–14 Gy, hyperfractionated TBI up to 14–15 Gy, and other less common schedules. In addition to cyclophosphamide, various agents, such as cytarabine (AraC) [6], etoposide [7], melphalan [8], and busulfan (Bu) [9], have been combined with high-dose TBI. Due to the lack of randomized trials, there is currently no evidence suggesting that any of these combinations are superior to Cy/TBI.

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Table 1 | Irradiation-based conditioning regimens.

Regimen	Total Dose	Daily Dose	Route	Days
Myeloablative				
<i>Cy/TBI</i>				
Cyclophosphamide	120 mg/kg	60 mg/kg	i.v.	-6, -5
TBI	12 Gy	4 Gy (in 1 or 2 fractions)		-3, -2, -1
<i>TBI/Vep</i>				
TBI	12 Gy	4 Gy (in 1 or 2 fractions)		-6, -5, -4
Etoposide	60 mg/kg	60 mg/kg	i.v.	-3
<i>Mel/TBI</i>				
Melphalan	110–140 mg/m ²	110–140 mg/m ²	i.v.	-3
TBI	12 Gy	4 Gy (in 1 or 2 fractions)		-2, -1, 0
<i>Cy/Vep/TBI</i>				
Cyclophosphamide	120 mg/kg	60 mg/kg	i.v.	-6, -5
Etoposide	30 mg/kg	30 mg/kg	i.v.	-4
TBI	12 Gy	4 Gy (in 1 or 2 fractions)		-3, -2, -1
Reduced intensity				
<i>Flu/TBI</i>				
Fludarabine	120 mg/m ²	30 mg/m ²	i.v.	-6, -5, -4, -3
TBI	8 Gy	4 Gy (in 2 fractions)		-3, -2
Nonmyeloablative				
<i>Flu/TBI</i>				
Fludarabine	90 mg/m ²	30 mg/m ²	i.v.	-4, -3, -2
TBI	2 Gy	2 Gy		0
<i>Flu/Cy/TBI*</i>				
Fludarabine	150 mg/m ²	30 mg/m ²	i.v.	-6, -5, -4, -3, -2
Cyclophosphamide	29 mg/kg	14,5 mg/kg	i.v.	-6, -5
TBI	2 Gy	2 Gy		-1
<i>TLI/ATG</i>				
ATG	7,5 mg/kg	1,5 mg/kg	i.v.	-11, -10, -9, -8, -7
TLI	8 Gy	0,8 Gy		-11, -10, -9, -8, -7 -4, -3, -2, -1 ^{**}

Abbreviations: TBI: Total body irradiation; TLI: Total lymphoid irradiation; ATG: Anti-thymocyte globulin (Thymoglobulin, Sanofi); i.v.: intravenous.

* Mainly for transplantations from haploidentical donors with immunosuppressive protocols based on post-transplant use of cyclophosphamide

** Two 0.8 Gy fractions are used on day 1

With the development of NMA conditioning, a single dose of 2 Gy of TBI was successfully used as the Seattle protocol [10]. This protocol was associated with 20% nonfatal graft rejection, which was reduced to 3% by the addition of fludarabine at 90 mg/m² [11]. RIC regimens encompass a variety of protocols, including TBI administered at a total dose of 4 to 8 Gy, which allows for dose-adjustment according to patients' age and biological status on the one hand, and the risk of disease recurrence on the other. Finally, TBI-based RIC may be administered sequentially after cytoreductive chemotherapy (e.g., FLAMSA protocol) in patients with relapsed/refractory disease undergoing allo-HCT [12–14].

The most frequently used irradiation-based conditioning regimens are listed in Table 1.

3. ADVANTAGES AND DISADVANTAGES OF TBI

TBI-based regimens have specific advantages over conditioning based on chemotherapy alone. Ionizing radiation can be delivered to sanctuary sites like brain or testes with the same efficiency as in lymph nodes or bone marrow. This is a considerable advantage over chemotherapy-based conditioning. There is no issue of cross-resistance. Application of ionizing radiation does not alter the response to chemotherapeutic agents and moreover, it usually

allows for effective elimination of neoplastic cells even in heavily pretreated patients. With the development of modern radiation planning, delivery techniques and the advantages of *in vivo*, on-line dose monitoring, the prescribed dose is homogeneously delivered to the whole body without creating cold- or hot spots. Finally, radiation treatment is not associated with the issues of medication metabolism and excretion, which can limit the utility of chemotherapeutic agents.

Unfortunately, TBI is associated with a significant risk of early and late side effects. The former may include nausea, vomiting, headache, mucositis, esophagitis, decreased appetite, indigestion, parotitis, mild erythema, and fatigue syndrome [15,16]. Late effects can be pulmonary toxicity, renal dysfunction, cataract, infertility, hypothyroidism, growth hormone deficiency (GHD) leading to growth retardation in children, and secondary malignancies. Long-term side effects may be irreversible and may affect the patient's lifespan and their quality of life [17–20].

The risk of late toxicities is particularly high in children. In a study of 129 pediatric patients who underwent TBI-based MAC for hematologic malignancies, 70.5% developed pulmonary toxicity [21]. Clinically, these patients present with the symptoms of fever, cough, hypoxia, and dyspnea. Chest radiographs often show bilateral diffuse shadowing, with pulmonary function tests showing a low diffusing capacity (DLCO) and a restrictive pattern. Pulmonary

toxicities can be acute or late in onset, and encompass several syndromes broadly divided into infectious and noninfectious categories. The exact pathophysiology of these conditions is still unclear and likely multifactorial. The TBI dose rate is significantly associated with pulmonary toxicity. Other factors like TBI total dose, dose per fraction, disease type, transplantation chemotherapy, the age of the patient, sex, and donor type did not significantly impact pulmonary toxicity in a recent study [21]. Adult survivors of childhood allo-HCT using TBI for ALL demonstrated reduced β -cell reserve and smaller pancreatic volume associated with reduced insulin sensitivity, leading to increased risk of diabetes and an exaggerated form of the metabolic syndrome with hypertriglyceridemia [22–25]. One German study, which included 110 ALL patients, showed that 15% suffered from pulmonary symptoms and lung fibrosis, 11% developed osteoporosis, 4.5% developed hypothyroidism, and 2 patients developed diabetes mellitus following TBI [26]. TBI also affected gonadal function leading to erectile dysfunction, infertility and postmenopausal syndrome [26].

It must be emphasized that the risk of developing some of the above-listed complications may be effectively reduced by attempts to spare the organs at risk (OAR). This can be achieved by a reduction in total dose, reduction in organ dose, fractionation, limiting the dose rate, and avoiding concomitant use of chemotherapy with similar side effect profile. Reduction in organ dose may be effectively achieved by organ shielding. This includes placement of blocks to reduce the irradiation dose to critical normal structures. Lung blocks are designed to include the pulmonary volumes identified on AP-PA films and to reduce the dose delivered to the mid-plane of the lungs. This has been shown to protect lung tissue and to improve overall survival (OS) after TBI in patients with compromised pulmonary function before allo-HCT. Lung shielding using lead alloy to reduce the radiation dose to the majority of the lung tissue is recommended during myeloablative-dose TBI, but not during low-dose TBI. It results in a reduction of the risk of radiation pneumonitis, particularly in patients with lung dysfunction [27]. Similarly, eye shielding and kidney blocks are also used. Despite this, many vital organs cannot be feasibly blocked during delivery of TBI, as this would also block areas of marrow and lymph nodes requiring treatment [28]. Other radio protective agents like Amifostine and Diindolylmethane (DIM) are under consideration, more studies are required to prove their efficacy [29,30]. Some other complications, such as veno-occlusive disease, may be more frequent after the use of alkylating agents than after irradiation. A meta-analysis of four randomized trials comparing Cy/TBI with busulfan combined with cyclophosphamide (BuCy) revealed an increased risk of cataract after Cy/TBI and increased risk of irreversible alopecia after BuCy [31]. With the median follow-up of seven years, the incidence of other late complications was comparable. Considering the risk of severe side effects, radiation-free, chemotherapy-based regimens have been developed and are commonly used.

4. TBI-BASED VERSUS CHEMOTHERAPY-BASED MYELOABLATIVE REGIMENS FOR AML

Evaluation of the efficacy and safety of myeloablative Cy/TBI in comparison with BuCy for patients with AML treated with

allo-HCT in first complete remission (CR1) was the goal of a prospective trial by a French group [32]. The outcome for Cy/TBI at 2 years was better for the probability of disease-free survival (DFS) (72% vs. 47%, $p < 0.01$), OS (75% vs. 51%, $p < 0.02$), relapse (14% vs. 34%, $p < 0.04$), and non-relapse mortality (8% vs. 27%, $p < 0.06$). A significant advantage of TBI-based compared to chemotherapy-based myeloablative regimens for patients with AML in CR1 was also demonstrated by a retrospective analysis performed on behalf of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) [33]. The use of TBI was associated with reduced risk of relapse (hazard ratio [HR] = 0.74, $p = 0.003$) and improved DFS (HR = 1.2, $p = 0.02$).

In recent years, an intravenous (IV) formulation of busulfan became available and is associated with more predictable pharmacokinetics compared with the oral counterpart. A retrospective analysis by the EBMT ALWP including patients with AML in CR1 or CR2 showed that the risk of relapse was reduced after the use of Cy/TBI compared to IV busulfan + cyclophosphamide (HR = 0.71, $p = 0.004$) but the effect on DFS and OS was not significantly different [34]. Another retrospective study by the CIBMTR compared IV busulfan-based conditioning with various TBI-based regimens in patients with myeloid malignancies undergoing matched sibling or unrelated allo-HCT [35]. Among patients with AML, the use of IV busulfan was associated with superior OS rate (57% vs. 46%, $p = 0.003$). However, the interpretation of the result is difficult due to lack of disease-oriented multivariate analyses and high heterogeneity of the AML stages, including patients in either CR or active disease.

In recent years, chemotherapy-based regimens incorporated thiotepea. According to a recent matched-pair analysis by the EBMT ALWP including patients with AML in CR1 treated with allo-HCT, the results after thiotepea-based and TBI-based conditioning were comparable in terms of OS, DFS, relapse rate, non-relapse mortality (NRM), as well as the incidence of chronic graft-versus-host disease (GVHD). There was a trend for reduced incidence of grade II-IV acute GVHD after thiotepea-based conditioning (25% vs. 35%, $p = 0.06$) [36]. In parallel to chemotherapy-based regimens, the TBI-based protocols are also evolving. The German study group performed a prospective, randomized trial comparing Cy/TBI 12 Gy with TBI 8 Gy combined with fludarabine. The authors revealed that the use of RIC was associated with comparable results in patients below 40 years of age while, among older adults (40–60 years), it was associated with reduced NRM and improved survival [37].

5. TBI-BASED VERSUS CHEMOTHERAPY-BASED MYELOABLATIVE REGIMENS FOR ALL

TBI is considered a standard basis for MAC in adults with ALL in CR1. Although it has never been prospectively evaluated, results of numerous retrospective analyses indicated its advantage over chemotherapy-based regimens mainly due to reduced risk of relapse. In a multivariate analysis by the EBMT ALWP restricted to patients treated in CR1 between the years 2008 and 2012, the use of TBI was associated with more than twice reduction of the risk

of relapse (HR = 0.48, $p = 0.004$) and treatment failure (HR = 0.63, $p = 0.02$) compared to irradiation-free conditioning [38]. Also, in patients with primary refractory ALL who fail to achieve a CR after ≥ 2 courses of chemotherapy, the use of TBI-based conditioning was found to be associated with improved OS (HR = 0.53, $p = 0.04$) and leukemia-free survival (HR = 0.44, $p = 0.01$) [39]. Mitsuhashi *et al.* showed that IV busulfan in combination with cyclophosphamide in ALL patients may be associated with results comparable to TBI. However, the limitation of that study is that the number of patients treated was relatively small ($n = 40$) and, therefore, further verification is needed [40]. Similar to AML, thiotepea-based conditioning regimens are being incorporated in the treatment of ALL. Promising results have been published based on a retrospective analysis, showing leukemia-free and OS at 2 years of 58.9% and 61.4%, respectively, for patients treated in CR1 [41].

For patients with ALL, TBI is most frequently combined with cyclophosphamide but, according to some retrospective analyses, the combination with etoposide may be at least equally effective. In a study by Marks *et al.* in patients treated with CR2, the use of TBI/etoposide was associated with reduced risk of relapse, treatment failure, and overall mortality compared to Cy/TBI 12 Gy [42].

6. HETEROGENEITY OF TBI TECHNIQUES

Conventional TBI treatment techniques can be classified into anteroposterior/poster-anterior (AP/PA) and parallel-opposed lateral (LAT) techniques. The AP/PA technique often provides a more homogeneous dose distribution than the LAT technique, because in this dimension (relative to the lateral dimension) the reference depth at which the dose is calculated is more uniform. However, due to the lower density of lung tissue (compared to the remainder of the body), the lungs can be overdosed. Hence, lung blocks are required with the AP/PA technique. Recent advances in radiotherapy allow performing TBI on the standard treatment table with dynamic techniques. Along with three-dimensional treatment planning, it allows for OAR sparing, without the need of casting individualized shields, and for controlling dose distribution in the body, without the risk of over- or under dosage. Consequently, the data concerning the frequency and severity of late adverse effects of TBI performed with older methods are becoming obsolete, and new evidence must be gathered in order to draw conclusions on the risk and effectiveness of radiation-based conditioning regimens as compared to chemotherapy-based regimens.

While administration of chemotherapy is relatively easy and uniform, TBI is associated with multiple technical issues. TBI is very heterogeneous in terms of the dosage, timing, other technical aspects and, therefore, insufficiently standardized at the international level. The EBMT performed a survey from February to July 2013 [43]. The questionnaires were sent to all 205 EBMT centers, out of which 57 responded. The survey showed that delivery of TBI varies significantly among centers, and the total dose of TBI used varied from 8 Gy to 14.4 Gy. The TBI fractions ranged from 1 to 8, and dose per fraction from 1.65 Gy to 8 Gy. The most commonly used fractionation was 6 fractions of 2 Gy each, delivered twice daily. Not only the dose but the dose rate also varied between 11 and 30 cGy/min. A total of 91.1% of the centers used linear accelerators, while 8.9% still used Cobalt-60 machines. Most of the treatment

centers used “patient in one field” with 2 fields per fraction and 2 patient positions per fraction technique. Lung was the most commonly shielded organ, but some centers also used shields for lenses, thyroid gland, larynx, kidneys, and/or salivary glands. German and American radiation oncology groups have published guidelines on the use of TBI. But the guidelines provide only general requirements and do not deal with specific details [44,45]

7. PERSONALIZED IRRADIATION-BASED CONDITIONING

Considering potential side effects and technical problems associated with TBI, various novel techniques are emerging in the field of HCT-related radiotherapy. The principle of TBI is to deliver a homogenous dose of radiation to the whole body. However, the distribution of residual malignancy may not necessarily be homogenous. Novel wide-field techniques allow more distinctive distribution of the dose, adjustment to the type of disease or even to individual patient’s needs. Such personalized approaches entail potential to escalate the dose and increase efficacy, while sparing organs not involved in the disease in order to reduce toxicity.

Intensity-modulated radiation therapy (IMRT) is a technology that allows for shaping of the isodoses, by changing positions of the leaves in the multileaf collimator (MLC) during irradiation. It results in the concentration of the high-dose regions within the target volume, while relatively sparing the surrounding normal tissues. It was first introduced in 1999, and has been shown to minimize acute treatment-related morbidity, making dose escalation feasible, which may ultimately improve local tumor control [46].

7.1. Total Marrow Irradiation

TMI focuses the dose to the entire skeleton, while sparing the rest of the body. This markedly reduces the toxicity of the treatment, while keeping the same or higher dose in the bone marrow as used in TBI. Introduction of TMI has allowed for dose escalation with acceptable toxicity, which cannot be achieved with traditional TBI techniques [47–53]. TMI can be delivered using either helical tomotherapy (HT), fixed-gantry angle linear accelerator-based IMRT, or volumetric modulated arc therapy (VMAT).

Clinically, there are multiple advantages of TMI as compared to TBI. For patients with advanced leukemia (relapsed, refractory, high risk), TMI offers a chance to escalate the dose of irradiation, therefore potentially increasing the efficacy compared to TBI, with yet acceptable toxicity. Hui *et al.* conducted a phase 1 trial in high-risk leukemia patients undergoing allo-HCT. The conditioning regimen included TMI + fludarabine + Cy. The TMI dose escalation to 15 Gy and 18 Gy resulted in 42% 1-year probability of OS and 22% DFS rate. This study demonstrated that TMI dose escalation is feasible with acceptable toxicity [48]. In another study by Wong *et al.* including relapsed/refractory AML, TMI was used in combination with etoposide 60 mg/kg and Cy 100 mg/kg. The TMI dose was escalated up to 13.5 Gy and 15 Gy resulting in acceptable toxicity [54]. Other study used 9 Gy TMI in combination with sequential fludarabine and busulfan to treat AML patients at high risk of relapse [55] (see Table 2).

Table 2 Dose escalation studies with TMI.

Author	N	Disease	Median Age	Chemotherapy Dose	TMI Dose	Conclusions
Hui <i>et al.</i> 2017 [48]	16	Acute leukemia, Allo-HCT, MUD, or UCB High-risk-disease*	4 P 8 A	Flu25 mg/m ² × 3 days Cy 60 mg/kg/day i.v. × 2 days	15 (3 Gy /# daily) for 6 pt and 18 (3 Gy /# daily) for 6 pt Gy	1 year OS 42% DFS 22% RR 36 NRM 42% TMI dose escalation to 15 Gy is feasible with acceptable toxicity
Wong <i>et al.</i> 2013 [54]	12	AML ALL advanced refractory Allo-HCT, MUD, or UCB	33	VP 60 mg/kg on -5 Cy 100 mg/kg on -3	TMI -10 to -6 12 Gy (3 pt) 13.5 Gy (3 pt) 15 Gy (3 pt) 1.5 Gy BID	Comparable acceptable toxicity NRM in 100 days -8% Total NRM 17%
	20	AML ALL advanced refractory	41	VP 60 mg/kg on -3 Bu -12 to -8 and dose 800 uM/min	-8 to -4 12 Gy (12 pt) 13.5 Gy (2 pt)	TMI of 13.5 with BU and VP associated with dose limiting toxicity
Wong <i>et al.</i> 2009 [53]	8	AML ALL, NHL, MM Allo-HCT, MUD, or UCB for patients >50 or co-morbidities	52	Flu 25 mg/m ² × 5 days HDM 140 mg/m ² × 1 day	TMI TLI splenic RT to 12 Gy (1.5 Gy BID)	Acceptable toxicity
Rosenthal <i>et al.</i> 2011 [51]	33	All hematologic malignancies with age >50 or compromised organ function	55.2	Flu 25 mg/m ² × 5 days HDM 140 mg/m ² × 1 day	TMI, total 12 Gy to 150 cGy/# BID TLI 2 Gy/# daily	1 year OS 75% EFS 65% NRM 19% No increase in toxicity
Stein <i>et al.</i> 2017 [60]	51	Relapsed/refractory AML or ALL and resistant to salvage conventional chemotherapy regimens	34	VP16-60 mg/kg CY 100 mg/kg	TMLI, ranging from 1200 cGy to 2000 cGy, BID over 4 or 5 days**	NRM 3.9% at day +100 NRM 8.1% at 1 year The TMLI/CY/VP16 conditioning regimen is well tolerated at TMLI doses up to 2000 cGy, no increase in GVHD
Patel <i>et al.</i> 2014 [55]	14	High-risk AML/All, relapsed refractory AML, ALL, CML refractory to TKI, MM relapsed after Auto HSCT	52	Flu 40 mg/m ² on days 8 to 5 Bu 4800 mM* minute given on days 4 to 1	3 Gy n = 3, 6 Gy n = 3 9 Gy n = 6, 12 Gy n = 2 1.5 Gy/fraction, BID	9 Gy TMI in combination with sequential FluBu in patients at high risk of relapse was acceptable side effects

Abbreviations: N: Number of patients; TMI: Total marrow irradiation; Allo-HSCT: Allogenic hematopoietic stem cell transplantation; MUD: Matched unrelated donor; UCB: Umbilical cord blood; MRD: Minimum residual disease; OS: Overall survival; DFS: Disease-free survival; P: Pediatric; A: Adults; RR: Relapse rate; HDM: High-dose melphalan; VP-60: Etoposide; Cy: Cyclophosphamide; Bu: Busulphan; GVHD: Graft-versus host disease; TMLI: Total marrow lymphoid irradiation; EFS: Event-free survival; TLI: Total lymphoid irradiation; BID: twice a day; BM: Bone marrow; CML: Chronic myeloid leukemia; TKI: Tyrosine kinase inhibitors; MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma; AML: Acute myeloid leukemia; ALL: Acute lymphoid leukemia; Flu: Fludarabine; NRM: Non-relapse mortality

*Not achieving remission with standard induction and salvage chemotherapy or who had evidence of pre-transplantation MRD

**In the case of BM, major lymph node chains and testes involvement, the dose was escalated up to 2000 cGy; and of with liver, portal hepatitis, and brain, up to 1200 cGy

For patients with early-stage acute leukemia (CR1) undergoing allo-HCT, TMI doses equivalent to those of TBI may be equally effective, while much less toxic [56]. This may be of particular importance for older patients and those with comorbidities considered ineligible for myeloablative TBI.

7.2. TMI Combined with Total Lymphoid Irradiation

Total lymphoid irradiation (TLI) has been used for a long time to produce long-lasting lymphoid depletion and immunosuppression for solid organ transplantation [57]. The first use of TLI combined with cyclophosphamide for allo-HCT in aplastic anemia patients took place in 1980 [58]. Lowsky *et al.* described a non-myeloablative, chemotherapy-free protocol containing TLI

in combination with anti-thymocyte globulin, which was associated with very low risk of GVHD, and the results were enhancing especially for patients with lymphoma [59]. For treatment of acute leukemia, there are current attempts to combine TLI with TMI (TMLI). Such combinations are expected to reduce the risk of graft failure compared to TMI alone. In the case of ALL, it should also increase the efficacy of eliminating disease that may reside in lymphoid tissue. Stein *et al.* conducted a phase-1 trial of TMLI dose escalation to 20 Gy along with Cy and etoposide in patients with high-risk leukemia undergoing allo-HCT. The study showed a 3.9% incidence of NRM at day +100 and 8.1% at 1 year. The TMLI/Cy/etoposide conditioning regimen was well tolerated at TMLI doses up to 20 Gy with no increase in GVHD [60]. Two studies by Wong *et al.* and Rosenthal *et al.* have successfully used 12 Gy of TMI and TLI along with

fludarabine and high-dose melphalan in patients over 50 years of age with multiple comorbidities, and compromised organ function [51,53].

8. ULTRA-PERSONALIZED IRRADIATION-BASED CONDITIONING

The whole skeleton is the target for TMI. However, the distribution of leukemic cells within bones is not homogenous. Therefore, more selective techniques focusing irradiation on particular bone marrow compartments are being considered. The bone marrow has 3 primary components: 1) trabeculae-rich osseous matrix, 2) hematopoietic active red marrow with increased affinity for cancer cells and vascular endothelium, 3) fat-rich yellow marrow with minimal hematopoiesis and scarce vasculature. The principal mechanism of action by which radiation works is by creating oxygen free radicals leading to damage to the DNA. As yellow marrow has a scarcity of vasculature, this part of the marrow is characterized by hypoxia and is more radio-resistant. Some studies have reported survival of leukemia cells in this part of the bone marrow, which was associated with leukemia resistance and/or relapse [61–64]. Modern imaging techniques like whole-body dual-energy CT (DE CT) lead to better differentiation of marrow composition [65]. This can help with more selective irradiation of bone marrow compartments. A recent study evaluating irradiation of functional bone marrow included delivering high dose to the red and yellow marrow, and lower doses to the remaining skeleton [66]. This study was conducted on 7 cadavers and 6 leukemia patients. Seven cadavers were scanned with DECT and the treatment planning was simulated to target irradiation. The dose of 18 Gy was planned for red and yellow marrow, while 12 Gy was planned to the entire skeleton. While treating functional marrow with higher doses, this method reduced the dose to OAR compared to standard TMI. Such strategy can further increase the efficacy of conditioning. However, the limitation of the study was that it was a preclinical study on cadavers and we need further clinical studies.

9. SUMMARY

Acute leukemias are highly radiosensitive. Allo-HCT offers a chance to deliver myeloablative doses of irradiation with high antileukemic activity and therefore TBI is still widely used as a part of conditioning for both AML and ALL. In the latter case, it remains a standard of care. Novel technologies allow for very precise dose delivery to organs affected by leukemia, in particular to the bone marrow. Such targeted irradiation may further be enhanced by modern imaging techniques accompanied by increasing knowledge of the disease biology. These new techniques may represent a new era of the use of irradiation as a part of conditioning regimens emerging for prospective, clinical trials.

CONFLICTS OF INTEREST

All authors declared no conflicts of interest.

REFERENCES

- [1] Passweg, JR, Baldomero, H, Bader, P, Bonini, C, Cesaro, S, Dreger, S, Duarte, RF, Dufour, C, Kuball, J, Farge-Bancel, D, Gennery, A, Kroger, N, Lanza, F, Nagler, A, Sureda, A, Mohty, M. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant* 2016;51(6);786–92.
- [2] Potdar, R, Varadi, G, Fein, J, Labopin, M, Nagler, A, Shouval, R. Shouval, prognostic scoring systems in allogeneic hematopoietic stem cell transplantation: where do we stand? *Biol Blood Marrow Transplant* 2017;23(11);1839–46.
- [3] Giralt, S, Ballen, K, Rizzo, D, Bacigalupo, A, Horowitz, M, Pasquini, M, Sandmaier, B. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant* 2009;15(3);367–69.
- [4] Atkinson, JB, Mahoney, FJ, Schwartz, IR, Hesch, JA. Therapy of acute leukemia by whole-body irradiation and bone marrow transplantation from an identical normal twin. *Blood* 1959;14(3);228–34.
- [5] Thomas, ED, Buckner, CD, Clift, RA, Fefer, A, Johnson, FL, Neiman, PE, Sale, GE, Sanders, JE, Singer, JW, Shulman, H, Storb, R, Weiden, PL. Marrow transplantation for acute non-lymphoblastic leukemia in first remission. *N Engl J Med* 1979;301(11);597–99.
- [6] Riddell, S, Appelbaum, FR, Buckner, CD, Stewart, P, Clift, R, Sanders, J, Storb, R, Sullivan, K, Thomas, ED. High-dose cytarabine and total body irradiation with or without cyclophosphamide as a preparative regimen for marrow transplantation for acute leukemia. *J Clin Oncol* 1988;6(4);576–82.
- [7] Horning, SJ, Chao, NJ, Negrin, RS, Hoppe, RT, Kwak, LW, Long, GD, Stallbaum, B, O'Connor, P, Blume, KG. The Stanford experience with high-dose etoposide cytoreductive regimens and autologous bone marrow transplantation in Hodgkin's disease and non-Hodgkin's lymphoma: preliminary data. *Ann Oncol* 1991;2 Suppl 1;47–50.
- [8] Moreau, P, Facon, T, Attal, M, Hulin, C, Michallet, M, Maloisel, F, Sotto, JJ, Guilhot, F, Marit, G, Doyen, C, Jaubert, J, Fuzibet, JG, François, S, Benboubker, L, Monconduit, M, Voillat, L, Macro, M, Berthou, C, Dorvaux, V, Pignon, B, Rio, B, Matthes, T, Casassus, P, Caillot, D, Najman, N, Grosbois, B, Bataille, R, Harousseau, JL. Intergroupe Francophone du Myélome. Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *blood* 2002;99(3);731–35.
- [9] Scott, B, Deeg, HJ, Storer, B, Chauncey, T, Petersdorf, S, Slattery, J, Appelbaum, F. Targeted busulfan and cyclophosphamide as compared to busulfan and TBI as preparative regimens for transplantation in patients with advanced MDS or transformation to AML. *Leuk Lymphoma* 2004;45(12);2409–17.
- [10] McSweeney, PA, Niederwieser, D, Shizuru, JA, Sandmaier, BM, Molina, AJ, Maloney, DG, Chauncey, TR, Gooley, TA, Hegenbart, U, Nash, RA, Radich, J, Wagner, JL, Minor, S, Appelbaum, FR, Bensinger, WI, Bryant, E, Flowers, ME, Georges, GE, Grumet, FC, Kiem, HP, Torok-Storb, B, Yu, C, Blume, KG, Storb, RF. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 2001;97(11);3390–400.

- [11] Baron, F, Sandmaier, BM. Current status of hematopoietic stem cell transplantation after nonmyeloablative conditioning. *Curr Opin Hematol* 2005;12(6);435–43.
- [12] Schmid, C, Schleuning, M, Ledderose, G, Tischer, J, Kolb, HJ. A sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome. *J Clin Oncol* 2005;23(24);5675–87.
- [13] Schmid, C, Schleuning, M, Hentrich, M, Markl, GE, Gerbitz, A, Tischer, J, Ledderose, G, Oruzio, D, Hiddemann, W, Kolb, HJ. High antileukemic efficacy of an intermediate intensity conditioning regimen for allogeneic stem cell transplantation in patients with high-risk acute myeloid leukemia in first complete remission. *Bone Marrow Transplant* 2008;41(8);721–27.
- [14] Schmid, C, Schleuning, M, Schwerdtfeger, R, Hertenstein, B, Mischak-Weissinger, E, Bunjes, D, Harsdorf, SV, Scheid, C, Holtick, U, Greinix, H, Keil, F, Schneider, B, Sandherr, M, Bug, G, Tischer, J, Ledderose, G, Hallek, M, Hiddemann, W, Kolb, HJ. Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. *Blood* 2006;108(3);1092–99.
- [15] Buchali, A, Feyer, P, Groll, J, Massenkeil, G, Arnold, R, Budach, V. Immediate toxicity during fractionated total body irradiation as conditioning for bone marrow transplantation. *Radiother Oncol* 2000;54(2);157–62.
- [16] Keklik, M, Kaynar, L, Yildirim, A, Sivgin, S, Eroglu, C, Cingoz, S, Pala, C, Eser, B, Cetin, M, Unal, A. An acute transverse myelitis attack after total body irradiation: a rare case. *Case Rep Hematol* 2013;2013;523901.
- [17] Leiper, AD. Late effects of total body irradiation. *Arch Dis Child* 1995;72(5);382–85.
- [18] Bolling, T, Kreuziger, DC, Ernst, I, Elsayed, H, Willich, N. Retrospective, monocentric analysis of late effects after Total Body Irradiation (TBI) in adults. *Strahlenther Onkol* 2011;187(5);311–15.
- [19] Omorim, M, Yamashita, H, Shinohara, A, Kurokawa, M, Takita, J, Hiwatari, M, Nakagawa, K. Eleven secondary cancers after hematopoietic stem cell transplantation using a total body irradiation-based regimen in 370 consecutive pediatric and adult patients. *Springerplus* 2013;2;424.
- [20] Davis, NL, Stewart, CE, Moss, AD, Woltersdorf, WW, Hunt, LP, Elson, RA, Cornish, JM, Stevens, MC, Crowne, EC. Growth hormone deficiency after childhood bone marrow transplantation with total body irradiation: interaction with adiposity and age. *Clin Endocrinol (Oxf)* 2015;83(4);508–17.
- [21] Abugideiri, M, Nanda, RH, Butker, C, Zhang, C, Kim, S, Chiang, KY, Butker, E, Khan, MK, Haight, AE, Chen, Z, Esiashvili, N. Factors influencing pulmonary toxicity in children undergoing allogeneic hematopoietic stem cell transplantation in the setting of total body irradiation-based myeloablative conditioning. *Int J Radiat Oncol Biol Phys* 2016;94(2);349–59.
- [22] Wei, C, Thyagarajan, M, Hunt, L, Cox, R, Bradley, K, Elson, R, Hamilton-Shield, J, Stevens, M, Crowne, E. Reduced beta-cell reserve and pancreatic volume in survivors of childhood acute lymphoblastic leukaemia treated with bone marrow transplantation and total body irradiation. *Clin Endocrinol (Oxf)* 2015;82(1);59–67.
- [23] Wei, C, Thyagarajan, MS, Hunt, LP, Shield, JP, Stevens, MC, Crowne, EC. Reduced insulin sensitivity in childhood survivors of haematopoietic stem cell transplantation is associated with lipodystrophic and sarcopenic phenotypes. *Pediatr Blood Cancer* 2015;62(11);1992–99.
- [24] Rajendran, R, Abu, E, Fadl, A, Byrne, CD. Late effects of childhood cancer treatment: severe hypertriglyceridaemia, central obesity, non alcoholic fatty liver disease and diabetes as complications of childhood total body irradiation. *Diabet Med* 2013;30(8);e239–42.
- [25] Mayson, SE, Parker, VE, Schutta, MH, Semple, RK, Rickels, MR. Severe insulin resistance and hypertriglyceridemia after childhood total body irradiation. *Endocr Pract* 2013;19(1);51–58.
- [26] Marnitz, S, Zich, A, Martus, P, Budach, V, Jahn, U, Neumann, O, Arnold, R. Long-term results of total body irradiation in adults with acute lymphoblastic leukemia. *Strahlenther Onkol* 2014;190(5);453–58.
- [27] Shank, B, Simpson, L. The role of total body irradiation in bone marrow transplantation for leukemia. *Bull N Y Acad Med* 1982;58(9);763–77.
- [28] Hill-Kayser, CE, Plastaras, JP, Tochner, Z, Glatstein, E. TBI during BM and SCT: review of the past, discussion of the present and consideration of future directions. *Bone Marrow Transplant* 2011;46(4);475–84.
- [29] Kouvaris, JR, Kouloulias, VE, Vlahos, LJ. Amifostine: the first selective-target and broad-spectrum radioprotector. *Oncologist* 2007;12(6);738–47.
- [30] Zhang, C, Lin, J, Cui, J, Li, B, Liu, C, Wang, J, Gao, F, Cai, J. Radioprotection of bone marrow hematopoiesis by CpG-oligodeoxynucleotides administered to mice after total-body irradiation. *J Radiat Res* 2011;52(6);828–33.
- [31] Blaise, D, Maraninchi, D, Michallet, M, Reiffers, J, Jouet, JP, Milpied, N, Devergie, A, Attal, M, Sotto, JJ, Kuentz, M, Ifrah, N, Dauriac, C, Bordigoni, P, Gratecos, N, Guilhot, F, Guyotat, D, Gluckman, E, Vernant, JP. Long-term follow-up of a randomized trial comparing the combination of cyclophosphamide with total body irradiation or busulfan as conditioning regimen for patients receiving HLA-identical marrow grafts for acute myeloblastic leukemia in first complete remission. *Blood* 2001;97(11);3669–71.
- [32] Blaise, D, Maraninchi, D, Archimbaud, E, Reiffers, J, Devergie, A, Jouet, JP, Milpied, N, Attal, M, Michallet, M, Ifrah, N, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytosan versus Cytosan-total body irradiation as preparative regimen: a report from the group d'Etudes de la Greffe de Moelle Osseuse. *Blood* 1992;79(10);2578–82.
- [33] Giebel, S, Labopin, M, Ehninger, G, Beelen, D, Blaise, D, Ganser, A, Bacigalupo, A, Czerw, T, Holowiecki, J, Fagundes, EM, Nowara, E, Frassoni, F, Rocha, V, Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Association of Human Development Index with rates and outcomes of hematopoietic stem cell transplantation for patients with acute leukemia. *Blood* 2010;116(1);122–28.
- [34] Nagler, A, Rocha, V, Labopin, M, Unal, A, Ben Othman, T, Campos, A, Volin, L, Poire, X, Aljurf, M, Masszi, T, Socie, G, Sengelov, H, Michallet, M, Passweg, J, Veelken, H, Yakoub-Agha, I, Shimoni, A, Mohty, M. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning

- regimen—a report from the acute leukemia working party of the European group for blood and marrow transplantation. *J Clin Oncol* 2013;31(28);3549–56.
- [35] Bredeson, C, LeRademacher, J, Kato, K, Dipersio, JF, Agura, E, Devine, SM, Appelbaum, FR, Tomblyn, MR, Laport, GG, Zhu, X, McCarthy, PL, Ho, VT, Cooke, KR, Armstrong, E, Smith, A, Rizzo, JD, Burkart, JM, Pasquini, MC. Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation. *Blood* 2013;122(24);3871–78.
- [36] Eder, S, Labopin, M, Arcese, W, Or, R, Majolino, I, Bacigalupo, A, de Rosa, G, Volin, L, Beelen, D, Veelken, H, Schaap, NP, Kuball, J, Cornelissen, J, Nagler, A, Mohty, M. Acute Leukemia Working Party. Thiotepa-based versus total body irradiation-based myeloablative conditioning prior to allogeneic stem cell transplantation for acute myeloid leukaemia in first complete remission: a retrospective analysis from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Eur J Haematol* 2016;96(1);90–97.
- [37] Bornhauser, M, Kienast, J, Trenscher, R, Burchert, A, Hegenbart, U, Stadler, M, Baurmann, H, Schafer-Eckart, K, Holler, E, Kroger, N, Schmid, C, Einsele, H, Kiehl, MG, Hiddemann, W, Schwerdtfeger, R, Buchholz, S, Dreger, P, Neubauer, A, Berdel, WE, Ehninger, G, Beelen, DW, Schetelig, J, Stelljes, M. Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. *Lancet Oncol* 2012;13(10);1035–44.
- [38] Giebel, S, Labopin, M, Socie, G, Beelen, D, Browne, P, Volin, L, Kyrz-Krzemien, S, Yakoub-Agha, I, Aljurf, M, Wu, D, Michallet, M, Arnold, R, Mohty, M, Nagler, A. Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica* 2017;102(1);139–49.
- [39] Pavlum, J, Labopin, M, Zoellner, AK, Sakellari, I, Stelljes, M, Finke, J, Fanin, R, Stuhler, G, Afanasyev, BV, Bloor, AJ, Anagnostopoulos, A, Mohty, M, Giebel, S, Nagler, A. Allogeneic hematopoietic cell transplantation for primary refractory acute lymphoblastic leukemia: a report from the Acute Leukemia Working Party of the EBMT. *Cancer* 2017;123(11);1965–70.
- [40] Mitsuhashi, K, Kako, S, Shigematsu, A, Atsuta, Y, Doki, N, Fukuda, T, Kanamori, H, Onizuka, M, Takahashi, S, Ozawa, Y, Kurokawa, M, Inoue, Y, Nagamura-Inoue, T, Morishima, Y, Mizuta, S, Tanaka, J. Adult Acute Lymphoblastic Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation. Comparison of Cyclophosphamide Combined with Total Body Irradiation, Oral Busulfan, or Intravenous Busulfan for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Lymphoblastic Leukemia. *Biol Blood Marrow Transplant* 2016;22(12);2194–200.
- [41] Eder, S, Beohou, E, Labopin, M, Sanz, J, Finke, J, Arcese, W, Or, R, Bonifazi, F, Aljurf, M, Socie, G, Passweg, J, Giebel, S, Mohty, M, Nagler, A. Thiotepa-based conditioning for allogeneic stem cell transplantation in acute lymphoblastic leukemia—A survey from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Am J Hematol* 2017;92(1);18–22.
- [42] Marks, DI, Forman, SJ, Blume, KG, Perez, WS, Weisdorf, DJ, Keating, A, Gale, RP, Cairo, MS, Copelan, EA, Horan, JT, Lazarus, HM, Litzow, MR, McCarthy, PL, Schultz, KR, Smith, DD, Trigg, ME, Zhang, MJ, Horowitz, MM. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. *Biol Blood Marrow Transplant* 2006;12(4);438–53.
- [43] Giebel, S, Miszczyk, L, Slosarek, K, Moukhtari, L, Ciceri, F, Esteve, J, Gorin, NC, Labopin, M, Nagler, A, Schmid, C, Mohty, M. Extreme heterogeneity of myeloablative total body irradiation techniques in clinical practice: a survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Cancer* 2014;120(17);2760–65.
- [44] Quast, U. Whole body radiotherapy: a TBI-guideline. *J Med Phys* 2006;31(1);5–12.
- [45] Wolden, SL, Rabinovitch, RA, Bittner, NH, Galvin, JM, Giap, HB, Schomberg, PJ, Rosenthal, SA, American College of Radiology, American Society for Radiation Oncology. American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) practice guideline for the performance of total body irradiation (TBI). *Am J Clin Oncol* 2013;36(1);97–101.
- [46] Teh, BS, Woo, SY, Butler, EB. Intensity modulated radiation therapy (IMRT): a new promising technology in radiation oncology. *Oncologist* 1999;4(6);433–42.
- [47] Einsele, H, Bamberg, M, Budach, W, Schmidberger, H, Hess, CF, Wormann, B, Meisner, C, Straka, C, Hebart, H, Trumper, L, Kroger, N, Zander, AR, Hegewisch-Becker, S, Hossfeld, DK, Schmidt, H, Muller, P, Schlimok, G, Hertenstein, B, Peest, D, Metzner, B, Frickhofen, N, Kanz, L, Bensinger, WI. A new conditioning regimen involving total marrow irradiation, busulfan and cyclophosphamide followed by autologous PBSCT in patients with advanced multiple myeloma. *Bone Marrow Transplant* 2003;32(6);593–99.
- [48] Hui, S, Brunstein, C, Takahashi, Y, DeFor, T, Holtan, SG, Bachanova, V, Wilke, C, Zuro, D, Ustun, C, Weisdorf, D, Dusenbery, K, Verneris, MR. Dose escalation of total marrow irradiation in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2017;23(7);1110–16.
- [49] Hui, SK, Kapatoes, J, Fowler, J, Henderson, D, Olivera, G, Manon, RR, Gerbi, B, Mackie, TR, Welsh, JS. Feasibility study of helical tomotherapy for total body or total marrow irradiation. *Med Phys* 2005;32(10);3214–24.
- [50] Hui, SK, Verneris, MR, Froelich, J, Dusenbery, K, Welsh, JS. Multimodality image guided total marrow irradiation and verification of the dose delivered to the lung, PTV, and thoracic bone in a patient: a case study. *Technol Cancer Res Treat* 2009;8(1);23–28.
- [51] Rosenthal, J, Wong, J, Stein, A, Qian, D, Hitt, D, Naem, H, Dagsis, A, Thomas, SH, Forman, S. Phase 1/2 trial of total marrow and lymph node irradiation to augment reduced-intensity transplantation for advanced hematologic malignancies. *Blood* 2011;117(1);309–15.
- [52] Schultheiss, TE, Wong, J, Liu, A, Olivera, G, Somlo, G. Image-guided total marrow and total lymphatic irradiation using helical tomotherapy. *Int J Radiat Oncol Biol Phys* 2007;67(4);1259–67.
- [53] Wong, JY, Rosenthal, J, Liu, A, Schultheiss, T, Forman, S, Somlo, G. Image-guided total-marrow irradiation using helical

- tomotherapy in patients with multiple myeloma and acute leukemia undergoing hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys* 2009;73(1);273–79.
- [54] Wong, JY, Forman, S, Somlo, G, Rosenthal, J, Liu, A, Schultheiss, T, Radany, E, Palmer, J, Stein, A. Dose escalation of total marrow irradiation with concurrent chemotherapy in patients with advanced acute leukemia undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys* 2013;85(1);148–56.
- [55] Patel, P, Aydogan, B, Koshy, M, Mahmud, D, Oh, A, Saraf, SL, Quigley, JG, Khan, I, Sweiss, K, Mahmud, N, Peace, DJ, DeMasi, V, Awan, AM, Weichselbaum, RR, Rondelli, D. Combination of linear accelerator-based intensity-modulated total marrow irradiation and myeloablative fludarabine/busulfan: a phase I study. *Biol Blood Marrow Transplant* 2014;20(12);2034–41.
- [56] Hui, SK, Verneris, MR, Higgins, P, Gerbi, B, Weigel, B, Baker, SK, Fraser, C, Tomblyn, M, Dusenbery, K. Helical tomotherapy targeting total bone marrow - first clinical experience at the University of Minnesota. *Acta Oncol* 2007;46(2);250–55.
- [57] Sutherland, DE, Ferguson, RM, Simmons, RL, Kim, TH, Slavin, S, Najarian, JS. Total lymphoid irradiation. *Urol Clin North Am* 1983;10(2);277–88.
- [58] Slavin, S, Strober, S. Mechanisms of transplantation tolerance to allogeneic bone marrow cells following total lymphoid irradiation (TLI). *Haematol Blood Transfus* 1980;25;323–31.
- [59] Lowsky, R, Takahashi, T, Liu, YP, Dejbakhsh-Jones, S, Grumet, FC, Shizuru, JA, Laport, GG, Stockerl-Goldstein, KE, Johnston, LJ, Hoppe, RT, Bloch, DA, Blume, KG, Negrin, RS, Strober, S. Protective conditioning for acute graft-versus-host disease. *N Engl J Med* 2005;353(13);1321–31.
- [60] Stein, A, Palmer, J, Tsai, NC, Al Malki, MM, Aldoss, I, Ali, H, Aribi, A, Farol, L, Karanes, C, Khaled, S, Liu, A, O'Donnell, M, Parker, P, Pawlowska, A, Pullarkat, V, Radany, E, Rosenthal, J, Sahebi, F, Salhotra, A, Sanchez, JF, Schultheiss, T, Spielberger, R, Thomas, SH, Snyder, D, Nakamura, R, Marcucci, G, Forman, SJ, Wong, J. Phase I trial of total marrow and lymphoid irradiation transplantation conditioning in patients with relapsed/refractory acute leukemia. *Biol Blood Marrow Transplant* 2017;23(4); 618–24.
- [61] Kode, A, Manavalan, JS, Mosialou, I, Bhagat, G, Rathinam, CV, Luo, N, Khiabani, H, Lee, A, Murty, VV, Friedman, R, Brum, A, Park, D, Galili, N, Mukherjee, S, Teruya-Feldstein, J, Raza, A, Rabadan, R, Berman, E, Kousteni, S. Leukaemogenesis induced by an activating beta-catenin mutation in osteoblasts. *Nature* 2014;506(7487);240–44.
- [62] Konopleva, MY, Jordan, CT. Leukemia stem cells and microenvironment: biology and therapeutic targeting. *J Clin Oncol* 2011;29(5);591–99.
- [63] Scheller, EL, Doucette, CR, Learman, BS, Cawthorn, WP, Khandaker, S, Schell, B, Wu, B, Ding, SY, Bredella, MA, Fazeli, PK, Khoury, B, Jepsen, KJ, Pilch, PF, Klibanski, A, Rosen, CJ, MacDougald, OA. Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues. *Nat Commun* 2015;6;7808.
- [64] Schepers, K, Pietras, EM, Reynaud, D, Flach, J, Binnewies, M, Garg, T, Wagers, AJ, Hsiao, EC, Passegue, E. Myeloproliferative neoplasia remodels the endosteal bone marrow niche into a self-reinforcing leukemic niche. *Cell Stem Cell* 2013;13(3);285–99.
- [65] Arentsen, L, Hansen, KE, Yagi, M, Takahashi, Y, Shanley, R, McArthur, A, Bolan, P, Magome, T, Yee, D, Froelich, J, Hui, SK. Use of dual-energy computed tomography to measure skeletal-wide marrow composition and cancellous bone mineral density. *J Bone Miner Metab* 2017;35(4);428–36.
- [66] Magome, T, Froelich, J, Takahashi, Y, Arentsen, L, Holtan, S, Verneris, MR, Brown, K, Haga, A, Nakagawa, K, Holter Chakrabarty, JL, Giebel, S, Wong, J, Dusenbery, K, Storme, G, Hui, SK. Evaluation of functional marrow irradiation based on skeletal marrow composition obtained using dual-energy computed tomography. *Int J Radiat Oncol Biol Phys* 2016;96(3); 679–87.