



Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

The safety and efficacy of a novel hypo-fractionated total marrow and lymphoid irradiation before allogeneic stem cell transplantation for lymphoma and acute leukemia



Liu Shi ^{a,b,c,1}, Xuan Lu ^{d,1}, Di Deng ^{a,b,c}, Lijing Yang ^a, Hongli Zhao ^a, Jiuling Shen ^a, Xiaoyong Wang ^a, Conghua Xie ^{a,b,c}, An Liu ^e, Yang Cao ^{f,*}, Yu Xiong ^{a,b,c,*}

^a Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, Wuhan, China

^b Hubei Key Laboratory of Tumor Biological Behaviors, Zhongnan Hospital of Wuhan University, Wuhan, China

^c Hubei Clinical Cancer Study Center, Zhongnan Hospital of Wuhan University, Wuhan, China

^d Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China

^e Department of Radiation Oncology, City of Hope National Medical Center, Duarte, CA, USA

^f Department of Hematology & Cancer Biology Research Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

ARTICLE INFO

Article history:

Received 6 May 2020

Revised 7 November 2020

Accepted 8 November 2020

Available online 12 November 2020

Keywords:

Helical tomotherapy

Allogeneic hematopoietic cell transplantation

Lymphoma

Acute leukemia

Total marrow irradiation

ABSTRACT

Purpose: Total body irradiation (TBI) has been widely utilized as part of the conditioning regimen for hematopoietic stem cell transplantation (HSCT), but is associated with significant toxicities. Targeted TBI using helical tomotherapy allows precise and homogeneous tumor coverage and excellent sparing of organs at risk. The purpose of this study was to evaluate the clinical outcomes of a novel hypo-fractionation strategy for patients receiving total marrow and involved lymphoid irradiation (TMLI) as part of the conditioning regimen before HSCT.

Methods and Materials: 61 patients (7 acute myelogenous leukemia (AML), 33 acute lymphoblastic leukemia (ALL), 18 non-Hodgkin's lymphoma (NHL), 3 mixed acute leukemia (MAL)) received conditioning radiation treatment with TMLI (8 Gy to bone marrow, 10 Gy to involved field in 2 fractions per day) in conjunction with chemotherapy before transplantation.

Results: The median age of 61 patients with TMLI was 24 (4–54) years. The prescribed dose covered the entire bone and involved target volume, and the dose of organs at risk (OAR) was reduced by 28%–78% of the prescription dose. Grade 1–2 nausea and vomiting occurred in 12 patients and grade 1–2 pain in 6 patients during radiotherapy. Fatigue occurred in 16 patients. 2 patients had diarrhea, enteritis, and 1 patient had fever. None of patient had grade 3–4 non-hematologic adverse reactions. Late (30 days after HSCT) grade 2 toxicities including reversible enteritis occurred in 3 patients. 5 patients developed infectious pneumonia. The 2 years progression-free survival (PFS) was 64.1% (95% CI: 0.16–0.22) and overall survival (OS) was 74.7% (95% CI: 0.19–0.24) for the 61 patients who had received their planned HSCT. The 2-year non-relapse mortality was significantly reduced to 5% in this patient cohort.

Conclusions: This study demonstrates that hypo-fractionated TMLI (8 Gy to bone marrow, 10 Gy to involved field in a single day) as a conditioning regimen for lymphoma and acute leukemia was feasible and the clinical outcomes were acceptable.

© 2020 Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding authors at: Department of Hematology & Cancer Biology Research Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan 430030, China (Y. Cao). Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, China (Y. Xiong).

E-mail addresses: yangcao@tjh.tjmu.edu.cn (Y. Cao), yuxiong@whu.edu.cn (Y. Xiong).

¹ S.L. and L.X. contributed equally to this work.

1. Introduction

Total body irradiation (TBI) is an important part of conditioning regimens in patients undergoing hematopoietic stem cell transplantation (HSCT) [1]. A myeloablative regimen that includes TBI before HSCT resulted in higher survival rates compared to regimens without TBI [2]. In HSCT, TBI serves a dual purpose. One is cell killing, which contributes to eradication of malignant cells, potentially complements high-dose systemic chemotherapy. TBI

provides therapy to sanctuary sites not easily reached by chemotherapy drugs and provides another mechanism of tumor cell kill against chemotherapy-resistant cell clones. The other is immunosuppression to decrease the risk of graft versus host disease (GVHD) and to enable sustained engraftment [3,4]. However, treatment-related morbidity and mortality can increase, negating any potential advantage for survival [5,6]. A more targeted form of TBI is clearly needed to reduce the dose to normal organs relative to tumor, which would improve the therapeutic ratio of this important treatment modality.

Helical Tomotherapy (HT) as a new CT-image guided rotational intensity modulated radiotherapy can deliver highly conformal dose distributions [7,8]. To large complex target shapes while simultaneously avoiding doses to critical normal organs, making it an attractive option for the delivery of conformal targeted TBI [9]. Total bone marrow and involved lymphoid irradiation (TMLI) was designed to treat bone marrow and involved targets, including lymph node chains, liver, spleen, brain, spinal cord and testes [9,10]. The potential advantages, the acute toxicities, initial clinical experiences, and challenges of this approach were reported recently [10].

The optimal ablative dose or the fractionation scheme for FTBI has yet to be carefully explored [5]. The total myeloablative TMI dose used from literature search ranged from 6 to 12 Gy, with the most common total dose of 12 Gy delivered in 2 Gy fractions twice a day for 3 consecutive days [2]. Lin et al. reported that TMI with 8 Gy (2 Gy/day for 4 days) as a conditioning regimen for multiple myeloma was feasible and the outcomes were acceptable for the Asian patient population [11]. In this work, we present the treatment of a hypo-fractionated TMLI (8 Gy to bone marrow with concurrent 10 Gy to involved target delivered in 2 equal fractions in a single day) for lymphomas and acute leukemia in Asian patients as part of allogeneic HSCT regimen.

2. Materials and methods

2.1. Patients

61 consecutive patients treated with TMI/TMLI using HT at our institution between October 2016 and January 2019 were selected for this retrospective analysis.

TMLI was delivered at 4 Gy twice a day (BID) (minimum 6 h between fractions) to bone marrow for a total of 8 Gy, 5 Gy BID to the involved targets, including involved lymph nodes, liver, spleen, brain, spinal cord, testes, for a total of 10 Gy. 8 patients without involved target were treated with TMI, where bone marrow was the only target and received 4 Gy BID for a total 8 Gy. TMI/TMLI was performed on day -1. GVHD prophylaxis consisting of tacrolimus and sirolimus was also started on day -1. On Day 0, collected peripheral blood stem cells from HLA-matched related (45 patients) or matched unrelated donors (16 patients) was infused.

Standard anti-emetic regimens were used and palifermin was not administered.

2.2. Helical Tomotherapy planning

Immobilization: Patients were positioned using a dedicated immobilization system developed by our radiotherapy technicians' team to best fix the patients. Details of the technique have been previously published [9].

Computed Tomography (CT) Simulation: The patients were planned with head first supine position for upper torso and with feet first supine position for lower extremities. Image sets were scanned with 5.0 mm slice thickness for upper and lower body.

Contouring: All the CT images were sent to the Eclipse treatment planning system (Varian Medical System, Palo Alto, USA) for contouring. The clinical target volume (CTV) was defined as all skeletal bones while excluding the mandible. Considering the possible involuntary motion and setup error, the CTV was divided into three subvolumes: head, trunk, arms and legs [9]. These three subvolumes were enlarged of 3, 5 and 7 mm in three dimensions respectively, to generate the planning treatment volume (PTV-bone). Lymphatic sanctuary sites potentially including the major lymph node chains, liver, spleen, testes, and brain, with additional margin of 5 mm in three directions were contoured to generate PTV-lymph. The organs at risk (OARs) in the study included lens, eyes, optic nerves, parotid glands, oral cavity, lungs, heart, kidneys, stomach, small bowel, bladder and rectum.

Planning for TMLI: The prescription dose was 4 Gy BID for a total dose of 8 Gy to the PTV-bone, and 5 Gy BID for a total dose of 10 Gy to the PTV-lymph. For planning objective, at least 95% volume of PTV was the prescription dose. The dose volume histograms were calculated for the target and individual OARs. Toxicity of treatment was scored according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0).

Image Guidance: Four MVCT scans for each patient were performed (three for the Plan-Upper delivery and one for Plan-Lower) in order to check the patient's whole body alignment. An automatic registration process of the kilovoltage planning CT with the MVCT was performed utilized three rigid translations in the left-right, superior-inferior, and anterior-posterior directions, as well as roll (rotation around the SI axis). After the automatic image registration, the attending physician verified the image fusion and alignment to ensure proper PTV coverage and normal organ sparing [9].

2.3. Supportive care

Intravenous fluid support, and anti-emetics were prescribed 2 h before TMLI treatment. Non-steroidal anti-inflammatory drugs were given to patients with fever after radiotherapy.

2.4. Analysis

Descriptive statistics were collected for patients and disease characteristics, treatment features and toxicity. All analyses were performed using the Statistical Package for the Social Sciences, version 12.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Patient population

61 consecutive patients between October 2016 and January 2019 were enrolled in this study. The patients' characteristics are shown in supplementary Table 1. The median age was 24 (range, 4–54). Patients were enrolled on this trial with a median of 6 months (range, 2–35 months) from diagnosis. 20 patients had refractory leukemia at transplant. 1 patient received left optical nerve radiotherapy (30 Gy / 15 Fractions) 9 months before TMI, 1 NK / T cell lymphoma patient had nasal cavity radiotherapy (56 Gy / 28 Fractions) 2 years before TMLI, 8 patients had Car t cell therapy with a median of 4 months (range, 1–8 months) before TMLI.

3.2. Toxicities

Grade 1–2 nausea and vomiting occurred in 12 patients and grade 1–2 pain in 6 patients during radiotherapy (Fig. 1). No nau-

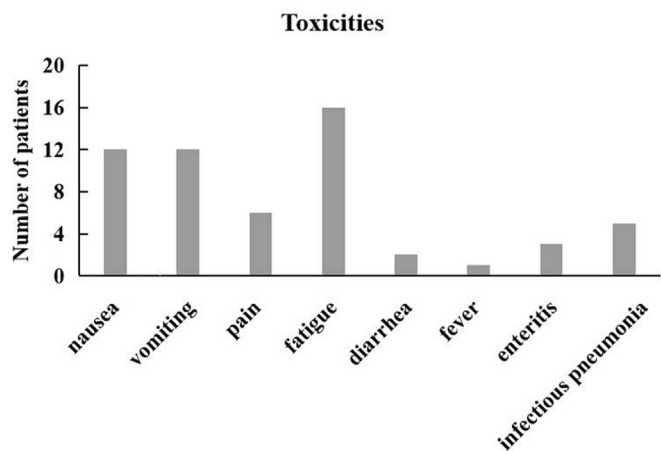


Fig. 1. Toxicities. All the toxicities were grade 1–2, none of the patients developed grade 3–4 adverse reactions.

sea or vomiting > grade 2 was observed. Grade 1–2 fatigue occurred in 16 patients. 2 patients had grade 1–2 diarrhea, and 1 patient had fever. None of the patients developed grade 3–4 non-hematologic adverse reactions. Late (30 days after HSCT) grade 2 toxicities including reversible enteritis occurred in 3 patients. 5 patients developed infectious pneumonia, mainly manifested as cough, expectoration and wheezing, which were confirmed by PET-CT. Among them, 4 patients improved after anti-infectious treatment, and 1 patient died because of poor infection control caused by persistent leukopenia.

For all TMI patients, the mean doses of the OARs were approximately 28–78% of the prescribed PTV dose, mostly below 5 Gy, except for the doses to the brain, for which the average dose was approximately 6.3 Gy. The lenses, with an average max dose of approximately 2.3 Gy, were the organs that received the least dose. Compared to the lower OARs doses of TMI group, the mean dose of gastrointestinal tract and brain in TMLI patients increased slightly as expected, approximately 72–90% of the prescribed 10 Gy to PTV_{lymph} (Fig. 2).

Fig. 3 showed the follow up clinical outcome following HSCT. The 2 year overall survival (OS) rate for the 61 patients enrolled was 74.7% (95% CI: 0.19–0.24) (Fig. 3A) and the 2 year progression-free survival (PFS) was 64.1% (95% CI: 0.16–0.22) (Fig. 3B). The relapse rate was 27% and the non-relapse mortality was 5%.

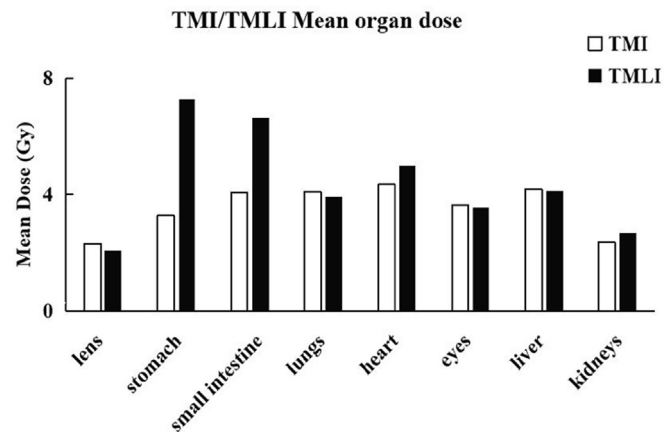


Fig. 2. The mean dose of organs at risk (OARs) of 8 total marrow irradiation (TMI) patients, 53 total marrow and involved lymphoid irradiation (TMLI) patients.

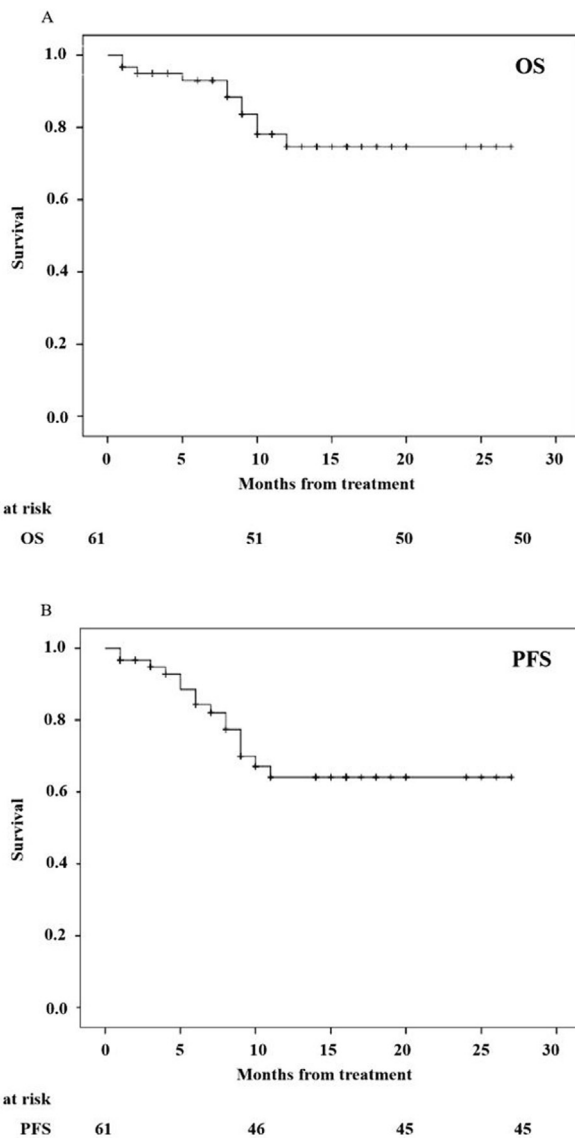


Fig. 3. Clinical outcomes. A: overall survival (OS) and B: progression-free survival (PFS).

4. Discussion

We are the first to report the clinical outcomes of a novel hypo-dose fractionation strategy of a myeloablative conditioning regimen including 61 patients of TMI (8 patients) / TMLI (53 patients) treated with 8 Gy to the bone marrow and 10 Gy to the involved targets as part of HSCT regimen. None of the patients had grade 3–4 non-hematologic adverse reactions. Comparing to conventional TBI, TMI and TMLI can reduce the doses to OARs significantly [12,13]. The doses to OARs as a percentage of the prescription dose of lens, stomach, small intestine, lungs, heart, eyes, liver, and kidneys in TMI were on average 21%, 27%, 33%, 47%, 36%, 33%, 33% and 20% of TBI. In TMLI, those numbers were on average 19%, 60%, 54%, 45%, 42%, 32%, 33% and 22%, respectively. By successfully reducing dose accumulation in the oral cavity, esophagus, stomach, and small bowel (the average reductions compared with 8 Gy TBI were 55%, 46%, 63%, and 60%, respectively), Hypo-fractionated TMLI in our study did not increase the toxicities in the entire treatment course and was as effective as conventional TBI treatment. Wong et al [14] and Hui et al [15] reported a substantial dose reduc-

tion magnitude of OARs comparing TMI versus TBI of 15–65% and 30–88%, respectively. Our results of 29–74% average reduction of OAR doses were comparable with others. For TMLI (8–10 Gy / 2 Fractions) regimen, the mean doses of the OARs were mostly lower than TMLI (12 Gy/8 Fractions) regimen.

Like any other radiation treatments, the total dose and fractionation for TBI have to be balanced between the relapse rate, side effects and complications [16–18]. Historically, TBI regimens differed widely in total dose, fractionation schedule, dose rate, patient positioning, and beam modifiers [19]. In the 1970 s, the most commonly used TBI schedule was a single fraction of about 10 Gy administered at a low-dose rate [20,21]. In the 1980 s, some researchers recommended fractionating the dose once daily or twice daily with the goal of improving the therapeutic ratio, reducing relapse rates, GVHD and toxicities, particularly to reduce treatment mortality [22]. Based on many clinical data supporting use of fractionation and reduced dose-rate, myeloablative regimens delivering 12 Gy, twice daily, over 3 days, in combination with chemotherapy were most commonly adopted [23]. TMI and TMLI are a new form of delivering myeloablative dose to target volume while significantly reducing dose to normal organs. Although it has been carried out for more than a decade clinically, there is no uniform standard on the optimal total dose and fractionation.

Shigematsu et al. reported that 1-year OS was 80.0% for fractionated-TBI (FTBI) 12 Gy/4–6 fractions[24]. Thomas et al. reported that the 2-year OS was 65% for the FTBI schedule, compared to 45% for the single fraction TBI (STBI) 10 Gy schedule for acute nonlymphoblastic leukemia in first remission ($p = 0.05$). No acute toxicity difference was observed between the two treatments[25]. However, in another large retrospective study in 21 French institutions, Socie et al. compared a STBI 10 Gy versus several fractionated schemes of FTBI 12 Gy, mainly 2 Gy BID for 3 days or 4 Gy once daily for 3 days[26]. The study did not demonstrate a significant difference in OS, but the fractionation significantly reduced the incidence of chronic GVHD. In order to improve the OS, Clift et al. conducted two randomized studies on patients with myeloid leukemia, one cohort with standard TBI of 12 Gy and the other with dose escalated to 15.75 Gy. It was discovered that disease recurrence decreased significantly in the higher dose group. However, the toxicity to the liver and lungs increased. Because of the treatment related mortality, there was no difference in the OS of patients in the two groups[27,28]. Our study is the first one to demonstrate that a hypo-fractionated TMLI (Single day treatment of 8 Gy to bone marrow, 10 Gy to involved target delivered in 2 fractions) on Tomotherapy as a conditioning regimen for lymphoma and acute leukemia was feasible and the outcomes were acceptable. The 2 years PFS and OS are 64.1% and 74.7% for the 61 patients, with a better OS than commonly employed FTBI 12 Gy / 6 Fractions (74.7% versus 65%[25]). Although the comparison is preliminary, there are several possible explanations why our study had a slightly better OS and worth further investigation: 1. the dosage: according to time dose fractionation formula, the biological equivalent dose of 8 Gy in 2 fractions BID approximates that of 12 Gy in 6 fractions[9], the therapeutic ratios were similar. 2. the fractionation: The delivery of TMLI in 1 day probably reduces treatment mortality. The 2 years non-relapse mortality was 5% in our study, which was lower than 20.4% seen in FTBI 12 Gy delivered 4–6 fractions regimens [29]. In our study, a hypo-fractionation concept was used to deliver myeloablative dose in a single day. The biological effective dose was kept equivalent, by giving an overall lower total dose, but higher radiation dose in each fraction. The increased dose per fraction may offer a clinical benefit for TMI [17], which was supported by Hui et al. [17] in the radiation escalation strategies. Given the favorable clinical outcome, hypo-fractionation TMI/TMLI scheme should be explored as an alternative conditioning regimen for HSCT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the Fundamental Research Funds for the Central Universities (2042018kf0183). The authors acknowledge the radiotherapy technicians, especially Jian G, Dapeng Z and Haiyang L, for their dedication, and the physicians team lead by Hui L, for their support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2020.11.004>.

References

- [1] Kim D-Y, Kim IH, Yoon S-S, Kang HJ, Shin HY, Kang H-C. Effect of dose rate on pulmonary toxicity in patients with hematolymphoid malignancies undergoing total body irradiation. *Radiat Oncol* 2018;13(1). <https://doi.org/10.1186/s13014-018-1116-9>.
- [2] Ishibashi N, Soejima T, Kawaguchi H, et al. National survey of myeloablative total body irradiation prior to hematopoietic stem cell transplantation in Japan: survey of the Japanese Radiation Oncology Study Group (JROSG). *J Radiat Res*. 2018; 59: 477–483.
- [3] Kawa-Iwanicka A, Łobodziec W, Dybek M, Nenko D, Iwanicki T. Dose distribution homogeneity in two TBI techniques—Analysis of 208 irradiated patients conducted in Stanisław Leszczyński Memorial Hospital, Katowice. *Rep Pract Oncol Radiother* 2012;17(6):367–75. <https://doi.org/10.1016/j.rpor.2012.07.013>.
- [4] Stephens SJ, Thomas S, Rizzieri DA, Horwitz ME, Chao NJ, Engemann AM, Lasserer M, Kelsey CR. Myeloablative conditioning with total body irradiation for AML: Balancing survival and pulmonary toxicity. *Adv Radiat Oncol* 2016;1(4):272–80. <https://doi.org/10.1016/j.adro.2016.07.001>.
- [5] Studinski RCN, Fraser DJ, Samant RS, et al. Current practice in total-body irradiation: results of a Canada-wide survey. *Curr Oncol*. 2017; 24: 181–186.
- [6] Baron F, Zachée P, Maertens J, et al. Non-myeloablative allogeneic hematopoietic cell transplantation following fludarabine plus 2 Gy TBI or ATG plus 8 Gy TLI: a phase II randomized study from the Belgian Hematological Society. *J Hematol Oncol*. 2015;8:4.
- [7] Mabuchi Y, Takiguchi Y, Yahata T, et al. Short term outcomes of helical tomotherapy during concurrent chemoradiotherapy for advanced cervical cancer. *Mol Clin Oncol*. 2019; 10: 382–386.
- [8] Piotrowski T, Skórska M, Jodda A, Ryczkowski A, Kaźmierska J, Adamska K, Karczewska-Dzionk A, Żmijewska-Tomczak M, Włodarczyk H. Tomotherapy – a different way of dose delivery in radiotherapy. *wo* 2012;1:16–25. <https://doi.org/10.5114/wo.2012.27332>.
- [9] Bao Z, Zhao H, Wang D, Gong J, Zhong Y, Xiong Yu, Deng Di, Xie C, Liu An, Wang X, Liu H. Feasibility of a novel dose fractionation strategy in TMI/TMLI. *Radiat Oncol* 2018;13(1). <https://doi.org/10.1186/s13014-018-1201-0>.
- [10] Stein A, Palmer J, Tsai NC, et al. Phase I trial of total marrow and lymphoid irradiation transplant conditioning in patients with relapsed/refractory acute leukemia. *Biol Blood Marrow Transplant*. 2017;23:618–24.
- [11] Lin S-C, Hsieh P-Y, Shueng P-W, Tien H-J, Wang L-Y, Hsieh C-H. Total Marrow Irradiation as Part of Autologous Stem Cell Transplantation for Asian Patients with Multiple Myeloma. *Biomed Res Int* 2013;2013:1–7. <https://doi.org/10.1155/2013/321762>.
- [12] Schultheiss TE, Wong J, Liu An, Olivera G, Somlo G. Image-guided total marrow and total lymphatic irradiation using helical tomotherapy. *International Journal of Radiation Oncology*Biophysics* 2007;67(4):1259–67. <https://doi.org/10.1016/j.ijrobp.2006.10.047>.
- [13] Rosenthal J, Wong JY, Stein A, et al. Phase 1/2 trial of total marrow and lymph node irradiation to augment reduced-intensity transplantation for advanced hematologic malignancies. *Blood*. 2011; 117, 309–315.
- [14] Wong JY, Rosenthal J, Liu A, et al. Image-guided total-marrow irradiation using helical tomotherapy in patients with multiple myeloma and acute leukemia undergoing hematopoietic cell transplantation. *Int J Radiation Oncology Biol Phys*. 2009;73:273–9.
- [15] Hui SK, Verweris MR, Higgins P, et al. Helical tomotherapy targeting total bone marrow—first clinical experience at the University of Minnesota. *Acta Oncol*. 2007;46:250–5.
- [16] Wilke C, Holtan SG, Sharkey L, DeFor T, Arora M, Premakanthan P, Yohe S, Vagge S, Zhou D, Holter Chakrabarty JL, Mahe M, Corvo R, Dusenbery K, Storme G, Weisdorf DJ, Verweris MR, Hui S. Marrow damage and hematopoietic recovery following allogeneic bone marrow transplantation for acute

- leukemias: Effect of radiation dose and conditioning regimen. *Radiother Oncol* 2016;118(1):65–71. <https://doi.org/10.1016/j.radonc.2015.11.012>.
- [17] 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 Transpl* 2017;23(7):1110–6. <https://doi.org/10.1016/j.bbmt.2017.04.002>.
- [18] Magome T, Froelich J, Holtan SG, et al. Whole-body distribution of leukemia and functional total marrow irradiation based on FLT-PET and dual-energy CT. *Mol Imaging*. 2017; 16: 1536012117732203.
- [19] Thomas ED, Storb R, Clift RA, Fefer A, Johnson FL, Neiman PE, Lerner KG, Glucksberg H, Buckner CD. Bone-Marrow Transplantation: (First of Two Parts). *N Engl J Med* 1975;292(16):832–43. <https://doi.org/10.1056/NEJM197504172921605>.
- [20] Altschuler C, Resbeut M, Blaise D, et al. Fractionated total body irradiation and bone marrow transplantation in acute lymphoblastic leukemia. *Int J Radiation Oncology Biol Phys* 1990;19:1151–4.
- [21] Gale RP, Butturini A, Bortin MM. What does total body irradiation do in bone marrow transplants for leukemia?. *Int J Radiation Oncology Biol Phys* 1991;20:631–4.
- [22] Inoue T, Shibata H, Masaoka T. Role of total body irradiation based on the comparative study of preparation regimens for allogeneic bone marrow transplantation for acute leukemia in first remission (Meeting abstract). *Int Congress of Radiat Oncol, Kyoto, Japan, 1993*: 169.
- [23] Paix A, Antoni D, Waissi W, et al. Total body irradiation in allogeneic bone marrow transplantation conditioning regimens: a review. *Crit Rev Oncol Hematol* 2018;123:138–48.
- [24] Shigematsu A, Ozawa Y, Onizuka M, et al. A safety and efficacy study of medium-dose etoposide, cyclophosphamide and total body irradiation conditioning before allogeneic stem cell transplantation for acute lymphoblastic leukemia. *Transplant Direct* 2015;1:e8.
- [25] Thomas ED, Clift RA, Hersman J, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission using fractionated or single-dose irradiation. *Int J Radiation Oncology Biol Phys* 1982;8:817–21.
- [26] Socie G, Devergie A, Girinsky T, et al. Influence of the fractionation of total body irradiation on complications and relapse rate for chronic myelogenous leukemia. The Groupe d'Etude des greffes de moelle osseuse (GEGMO). *Int J Radiation Oncology Biol Phys* 1991;397–404.
- [27] Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: a randomized trial of two irradiation regimens. *Blood* 1991;77:1660–5.
- [28] Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. *Blood* 1990;76:1867–71.
- [29] Shigematsu A, Ozawa Y, Onizuka M, et al. A safety and efficacy study of medium-dose etoposide, cyclophosphamide and total body irradiation conditioning before allogeneic stem cell transplantation for acute lymphoblastic leukemia. *Transplant Direct* 2015;1(2):e8.