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The Safety and Efficacy of Total Body Irradiation Before Allogeneic Stem Cell Transplantation for Lymphomas and Acute Leukemia Using Novel uRT-linac 506c Accelerator

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Abstract

Purpose: The conditioning strategy for Hematopoietic Stem Cell Transplantation (HSCT) has frequently included Total Body Irradiation (TBI), however this has serious toxicities. uRT-linac 506c 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 TBI using novel uRT-linac 506c accelerator before HSCT for lymphomas and acute leukemia.

Methods and Materials: 31 patients (4 Acute Myelogenous Leukemia (AML), 17 Acute Lymphoblastic Leukemia (ALL), 9 Non-Hodgkin's Lymphoma (NHL), 1 Mixed Acute Leukemia (MAL)) received conditioning radiation treatment with TBI (8 Gy to bone marrow, 10 Gy to total body, 12 Gy to involved field in 2 fractions per day) in conjunction with chemotherapy before transplantation.

Results: The median age of the 31 TBI patients was 27 (13 to 55) years. Median dose of Organs at Risk (OARs) was down-regulated by 39.2% to 85.7% of the prescription dose. The majority of the acute toxicity were grade 1 to 2. Six reported nausea and vomiting, 3 headaches, 5 fatigue, 3 oral mucositis, 2 parotitis, 1 temporary loss of taste, as well as 2 fever and 3 enteritis. Late toxicities include 6 infectious pneumonia and one cytomegalovirus infection. The 2-year Progression-Free Survival (PFS) and Overall Survival (OS) rates post-transplant were 84.8% (95% CI: - 0.039, 0.006) and 57.0% (95% CI: -0.075, -0.026), respectively.

Conclusion: This study demonstrates that TBI using novel uRT-linac 506c accelerator as a conditioning regimen for lymphoma and acute leukemia was feasible and the clinical outcomes were acceptable.

Keywords: Total body irradiation; Allogeneic hematopoietic cell transplantation; uRT-linac 506c; Lymphoma; Acute leukemia

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Introduction

Since it was first used in Bone Marrow (BM) transplantation, Total Body Irradiation (TBI) has been recognized as a crucial component of the conditioning regimen for Hematopoietic Stem Cell Transplantation (HSCT) for a variety of illnesses, including leukemia and lymphomas [1,2]. TBI promotes immunosuppression to prevent the rejection of donor hematopoietic stem cells and creates the necessary physical conditions for engraftment [3]. In sanctuary organs like the testis and the Central Nervous System (CNS), which chemotherapy medications cannot access, TBI is also employed to destroy cancerous cells [4]. The conventional TBI, however, has both short- and long-term toxicity and may have serious adverse effects on organs such the lung, liver, kidney, and intestine [5]. To lower the dosage to healthy organs compared to the tumor, a more targeted form of TBI is unquestionably required.

The uRT-linac 506c (United Imaging Healthcare Co., LTD., Shanghai) is a novel linear accelerator that combines diagnostic helical CT with a high dose rate intensity modulated accelerator

by locating a diagnostic CT behind the gantry sequentially with the same axis. This novel structure provides a possibility for high quality image verification, 4D image guided radiotherapy, online adaptive radiotherapy, and so on. The treatment couch on the uRT-linac 506c may act significantly differently from a typical one for the dose distribution during contemporary precision radiotherapy as a result [6]. Accordingly, the stepping depth of the treatment couch would be much longer than usual, which makes a unique radiation dosimetry effect of it [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 [5]. This presents a chance for TBI while preserving other organs, likely having an impact on recovery, toxicity, and prognosis.

The optimal ablative dose or the fractionation scheme for Fractionated-TBI (FTBI) has yet to be carefully explored [5]. The myeloablative TBI dose used from literature search ranged from 6 Gy to 12 Gy, with the most common total dose of 12 Gy delivered in 2 Gy Fractions (F) twice a day for 3 consecutive days [9]. In 2020, the uRT-linac 506c unit was installed and prepared for clinical operation. In this work, we present the treatment of a hypo-fractionated TBI (8 Gy to bone marrow, 10 Gy to total body with concurrent 12 Gy to involved target delivered in 2 equal fractions in a single day) using novel uRT-linac 506c for lymphomas and acute leukemia in Asian patients as part of allogeneic HSCT regimen.

Materials and Methods

Patients

Thirty-one consecutive patients treated from September 2020 to November 2021 with TBI using uRT-linac 506c are the subjects for this retrospective analysis. All the patients provided the written informed consent form regarding the free academic use of the treatment information.

TBI was delivered at 5 Gy twice a day (BID) (minimum 6 h between fractions) to total body for a total of 10 Gy, simultaneously augment dose to 6 Gy BID to the involved targets, including involved lymph nodes, liver, spleen, brain, spinal cord, testes, for a total of 12 Gy, decreased dose to 4 Gy BID to BM for a total of 8 Gy. TBI 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 (26 patients) or matched unrelated donors (5 patients) was infused.

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

uRT-linac 506c 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 [10,11].

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 uRT-linac 506c's control system, consisting of an integrated Treatment Planning System (TPS) and Oncology Information System (OIS) platform named uRT-TPOIS 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 sub-volumes: Head, trunk, arms and legs [11]. These three sub-volumes were enlarged of 3 mm, 5 mm and 7 mm in three dimensions respectively, to generate the Planning Treatment Volume (PTV-bone). Involved targets 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 TBI: The prescription dose was 4 Gy BID for a total dose of 8 Gy to the PTV-bone, 5 Gy BID for a total dose of 10 Gy to total body, and 6 Gy BID 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. The color-coded uRT-linac 506c TBI dose distribution of a patient irradiated with 8 Gy to 12 Gy is shown in Figure 1. 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 [11].

Supportive care

Venous fluid support, mannitol, and anti - emetic drugs were prescribed 2 h before the TBI. The patients after receiving the radiotherapy were administrated with non-steroidal anti-inflammatory drugs.

Analysis

Demographic, disease and treatment characteristics were generated with descriptive statistics. Non-Relapse Mortality (NRM) was determined from transplant to death from any cause other than disease relapse or disease progression. All analyses were conducted by employing the Statistical Package for the Social Sciences, version 12.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 31 TBI patients were analyzed. No toxicities were reported to have caused therapy delivery delays, and all patients finished the prescribed dose and schedule. The patients' characteristics are listed in Table 1. The median age was 27 years (range, 13 to 55). The median amount of time between diagnosis and TBI was 7.7 months (range, 1 to 30 months). At transplants, 4 individuals had refractory leukemia. One patient got testicular irradiation 2.5 years prior to TBI, two patients underwent Chimeric Antigen Receptor T-cell immunotherapy (CAR-T) 4 and 6 months prior to TBI, and one patient each underwent allo- and auto-HSCT 31 and 43 months prior to TBI.

Toxicities and survival

The majority of the acute toxicity were grade 1 to 2. There were 6 reports of nausea and vomiting, 3 of headache, 5 of exhaustion, 3

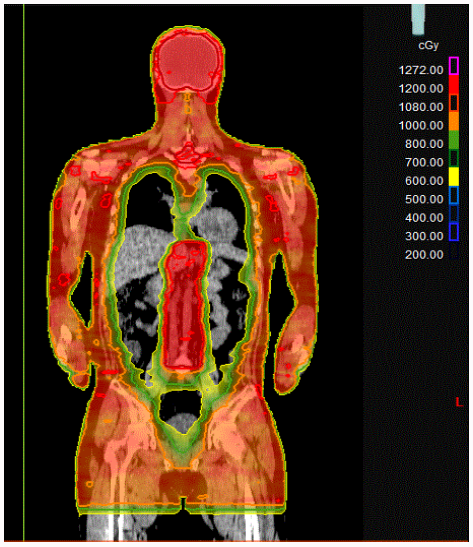

Figure 1: Color-coded Total Body Irradiation (TBI) plan shows dose to the targeted areas, with relative sparing of dose to critical organs. 10 Gy for TBI and simultaneously augment dose to 12 Gy for targeted dose boost to extramedullary disease sites, and decreased dose to 8 Gy to bone marrow.

Table 1: The characteristics of patient.

	TBI
Gender	9 Female, 22 Male
Age in years (range)	27 (13-55)
Disease	4 AML, 17 ALL, 9 NHL, 1 MAL
Refractory leukemia	4 patients
Median time from diagnosis to transplant in months (range)	7.7 (1-30)
Radiotherapy before TBI	1 patient
CAR-T before TBI	2 patients
HSCT before TBI	1 allo-HSCT, 1 auto-HSCT

ALL: acute Lymphoblastic Leukemia; allo-: allogenetic; AML: Acute Myelogenous Leukemia; auto-: autogenetic; CAR-T: Chimeric Antigen Receptor T-cell Immunotherapy; HSCT: Hematopoietic Stem Cell Transplantation; MAL: Mixed Acute Leukemia; NHL: Non-Hodgkin's Lymphoma; TBI: Total Body Irradiation

of oral mucositis, 2 of parotitis, 1 of momentary taste loss, 2 of fever, and 3 of enteritis (Figure 2). None of the patients experienced grade 4 non-hematologic adverse events, and all had successful engraftment. Late (30 days after HSCT) toxicities included one patient of cytomegalovirus infection and six patients of infectious pneumonia, which were mostly characterized by coughing, expectorating, and wheezing and were later verified by CT and biopsy. Graft-Versus-Host Disease (GVHD) struck 3 individuals, 2 of whom improved after receiving anti-rejection therapy, and 1 of whom died from unmanageable GVHD grade IV.

The average OAR doses for all TBI patients ranged from 14.3% to 60.8% of the prescribed PTV dose. The lens received the least amount of dose, with an average maximum dose of roughly 1.43 Gy. The organ receiving the highest dosage, the small intestine, had an average maximum dose of around 6.08 Gy (Figure 3).

Twenty patients (64.5%) were living after a median follow-up of 17.9 months (range 11 to 26 months), while 11 patients (35.5%) had died. Disease progression (4 patients, 13%), infection (6 patients, 19%), and chronic GVHD (1 patient, 3%), were the causes of mortality.

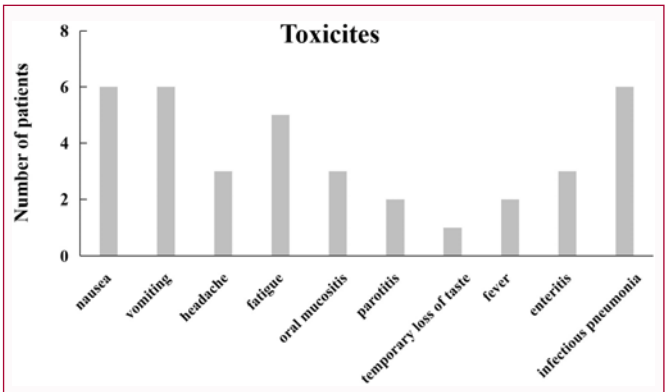

Figure 2: Toxicities. All the toxicities were grade 1 to 2, none of the patients developed grade 3 to 4 adverse reactions.

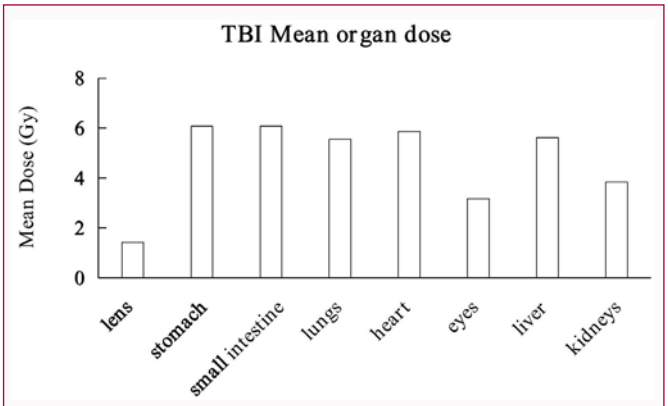

Figure 3: The mean dose of Organs at Risk (OARs) of 31 Total Body Irradiation (TBI) patients.

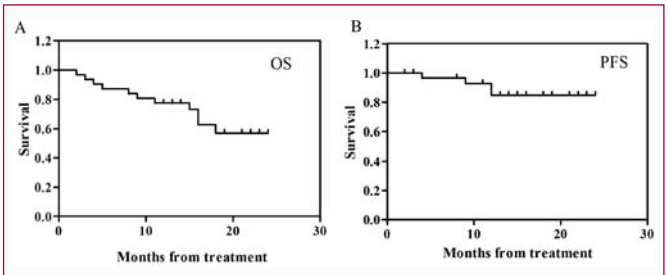

Figure 4: Clinical outcomes. A) Overall Survival (OS) and B) Progression-Free Survival (PFS).

Figure 4 showed the post-HSCT clinical follow-up results. For the 31 patients included, the 2-year OS rate was 57.0% (95% CI: -0.075, -0.026) (Figure 4A), and the 2-year Progression-Free Survival (PFS) rate was 84.8% (95% CI: -0.039, 0.006) (Figure 4B). Relapse rates were 13% and NRMs were 22%. Three patients (10%) had Extramedullary (EM) relapses, either with or without BM relapses. One of these individuals experienced concurrent BM and EM relapses. One patient (3%), had a BM recurrence without an EM relapse, while two patients (7%), had an EM relapse without a BM recurrence.

Discussion

We are the first to report the clinical outcomes of TBI using novel uRT-linac 506c accelerator before allogeneic HSCT as a myeloablative conditioning regimen. None of the patients had grade 3 to 4 non-hematologic adverse reactions. Comparing to conventional TBI, TBI using novel uRT-linac 506c can reduce the doses to OARs. The

dosages to OARs were, on average, 14%, 61%, 61%, 56%, 59%, 32%, 56%, and 39% of the prescribed doses to the lens, stomach, small intestine, lungs, heart, eyes, liver and kidneys in TBI.

The total dosage and fractionation for TBI must be adjusted, like any other radiation therapy, between the risk of recurrence, adverse effects, and complications [12-14]. The most common TBI regimen in the 1970s was administering a single fraction of around 10 Gy at a modest dose rate. Several publications recommended administration once or twice a day in the 1980s to improve the rate of treatment, particularly to lower treatment mortality [15]. Despite decades of clinical use, there is no agreed-upon standard for a number of the major issues (e.g., the optimal dosage of TBI and segmentation). TBI giving 12 Gy/6 F in combination with chemotherapy was most frequently used in the second half of the 20th century [2]. In a recent research, hypo-fractionated Total Marrow Irradiation (TMI) (8 Gy to 10 Gy/2 F) was shown to be practicable as a pretreatment plan for lymphoma and acute leukemia [11], with a superior OS than typical fractionated-TBI (12 Gy/6 F) (74.7% against 65%) [11], however a 27% recurrence rate persisted. While TMI offers HSCT patients a more precisely targeted radiation therapy than TBI, organ sparing may put the patient at a higher risk for EM relapse than TBI, particularly recurrence in skin or soft tissue [16]. Reductions in recurrence rates and toxicities, particularly pulmonary pneumonitis, were necessary to improve the results of the TBI regimen.

For conventional TBI, shields are frequently utilized to reduce the mean dosage to vital organs like the lungs. However, lung shielding has been shown to be ineffective in decreasing the dosage to the lungs and to potentially underdose the BM at the manubrium and ribs [17]. uRT-linac 506c allow a highly conformal dose distribution to be provided to large complex target shapes, while sparing other organs, thereby probably affecting recovery, toxicity and outcome [6-8]. In this work, we presented a novel conditioning regimen using the uRT-linac 506c to deliver 10 Gy for TBI and simultaneously augment dose to 12 Gy for targeted dose boost to EM disease sites in order to reduce the chance of EM relapse, while simultaneously decreasing dose to 8 Gy to BM in order to protect the hematopoiesis as a pretreatment scheme before HSCT. Our work is the first to show that TBI using uRT-linac 506c as a conditioning regiment for lymphoma and acute leukemia was possible and the results were acceptable. Relapse rates were substantially lower than with TMI (8 Gy to 10 Gy/2 F) (13% *vs.* 27%) [11]. 5% to 20% of individuals who undergo TBI in advance of HSCT may experience an EM recurrence [18,19]. Our 10% relapse rate for EM was similar to other studies' findings. The 2 years OS, however, was 57.0%. When compared to TMI (8 Gy to 10 Gy/2 F), the reduced recurrence rate did not enhance survival (OS, 57.0% *vs.* 74.7%) [11]. Due to a 22% rise in NRM brought on by infection, there was no OS benefit in our study. In our research, 1 patient died with unmanageable chronic GVHD grade IV (3%), while 6 patients died from infectious complications without recurrence (19%). After HSCT, infectious problems continue to be a serious issue that significantly increases mortality [20].

TBI and targeted dosage increase employing new uRT-linac 506c as a conditioning regimen for lymphoma and acute leukemia was possible with tolerable toxicity and an encouragingly low recurrence risk. Higher doses of TBI, however, resulted to a significantly reduced recurrence rate that was hindered by a worse incidence of NRM, leading to the conclusion that it did not provide survival advantages.

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