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Targeted Total Marrow Irradiation Using Three-Dimensional Image-Guided Tomographic Intensity-Modulated Radiation Therapy: An Alternative to Standard Total Body Irradiation

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ABSTRACT

Total body irradiation (TBI) is an important part of bone marrow transplantation conditioning regimens. In TBI, dose escalation is difficult, because of associated normal organ toxicities. A method to deliver a more targeted dose of TBI preferentially to sites of greatest tumor burden is needed to reduce the dose to normal organs, reduce toxicities, and permit dose escalation. The purpose of this study was to evaluate, through a dosimetric analysis, the potential advantages and feasibility of selectively delivering targeted myeloablative doses of radiation to bone and marrow using a recently developed image-guided tomographic intensity-modulated radiation therapy delivery system (helical tomotherapy). Whole-body computed tomography datasets from 3 patients, age 5, 20, and 53 years, were used for treatment planning studies to evaluate 2 targeted TBI strategies: total marrow irradiation (TMI), in which the target region was defined as the skeletal bone, and total marrow and lymphoid irradiation (TMLI), in which the target regions were defined as bone, major lymph node chains, liver, spleen, and sanctuary sites, such as brain. Organ doses and dose distributions were compared with those in conventional TBI. A 1.7- to 7.5-fold reduction in median organ doses was observed with TMI and TMLI compared with conventional TBI. With this more targeted approach, a dose-volume histogram analysis predicted the potential to escalate the dose to bone (and containing marrow) up to 20 Gy, while maintaining doses to normal organs at lower levels than in conventional TBI to 12 Gy. Results were similar for the adult and pediatric patients, indicating that this form of targeted TBI will be applicable to most patients regardless of frame size. TMI to 10 Gy was delivered as part of a tandem transplant regimen to the 53-year-old patient with multiple myeloma. Clinical results confirmed the treatment planning predictions. After TMI, the patient experienced the expected blood count nadir, followed by successful engraftment. Grade 2 nausea and grade 1 emesis occurred only briefly on day 2 of TMI. Skin erythema, oral mucositis, esophagitis, and enteritis were not observed. This report demonstrates the feasibility and potential dosimetric advantages of selectively delivering myeloablative doses of radiation to bone and marrow using an image-guided tomographic intensity-modulated radiation therapy delivery system. Organ doses are substantially lower than those associated with standard TBI and predict the potential to significantly reduce associated toxicities and allow for dose escalation. The results also suggest that this form of targeted TBI may have potential advantages over other forms of targeted TBI, such as radioimmunotherapy or bone-seeking radionuclide therapy. Ongoing clinical trials will define the maximum TMI and TMLI doses achievable and define the potential advantages and limitations of this new approach for patients undergoing hematopoietic stem cell transplantation.

KEY WORDS

Total marrow irradiation • Total body irradiation • Helical tomotherapy • Multiple myeloma

INTRODUCTION

Total body irradiation (TBI) has played an important role in conditioning regimens for patients undergoing hematopoietic stem cell transplantation. The primary reasons for using TBI include tumor cell eradication and immunosuppression to allow for engraftment of donor marrow. In addition, TBI, acting as a form of "systemic radiotherapy," potentially complements high-dose systemic chemotherapy, providing therapy to sanctuary sites not easily reached by chemotherapy drugs and provides another mechanism of tumor cell kill against chemotherapy-resistant cell clones.

Historically, TBI has been primarily used as part of a dose-intensive myeloablative regimen. Clinical efforts to further intensify TBI dose have produced decreased relapsed rates in patients with myeloid leukemias undergoing allogeneic transplantation [1,2]. However, treatment-related morbidity and mortality have also increased, negating any potential advantage for survival. 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 and allow for further dose escalation [3].

Significant technological advances have recently been introduced in the radiation oncology clinic. By delivering therapy from multiple directions using multiple segmented or modulated beamlets, intensity-modulated radiation therapy (IMRT) allows for greater sculpting of radiation doses to fit the unique shape of each patient's tumor, optimizing radiation delivery to complex volumes and regions of the body. As a result, the dose to adjacent critical organs is minimized, reducing side effects and allowing for dose escalation to the tumor, thus improving outcomes [4].

Helical tomotherapy (HT) is a radiation therapy delivery device that represents an integration of technological advances in computed tomography (CT) image-guided radiotherapy and IMRT, permitting the delivery of image-guided IMRT in a helical tomographic fashion. The maximum target size possible is 60 cm wide $\times$ approximately 160 cm long [5]. The advent of HT therefore brings for the first time to the clinic the potential to deliver highly conforming dose distributions to large complex target shapes while simultaneously avoiding doses to critical normal organs [6-12], making it an attractive option for the delivery of conformal targeted TBI selectively to bone and marrow.

In this article we report studies demonstrating the feasibility and advantages of targeted TBI using HT over conventional TBI, with the goal of increasing dose conformity to anatomic areas of greatest tumor burden, reducing dose to normal organs, decreasing toxicities, and permitting dose escalation to tumors.

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MATERIALS AND METHODS

For the initial studies, whole-body CT datasets from a 20-year-old adult female and a 5-year-old girl were used. Each patient had a diagnosis of acute myeloid leukemia (AML) and underwent CT scanning as part of a standard protocol at this institution for conventional TBI planning before hematopoietic stem cell transplantation. The following organs were contoured for treatment planning: lungs, liver, spleen, heart, small and large bowel, kidneys, orbits, lenses, brain, esophagus, bladder, parotid glands, oral cavity, stomach, breasts, ovaries, major lymph node chains, and bone.

Conventional TBI treatment at our institution is an adaptation of the method published by Shank et al. [13]. The patient is treated at an extended distance in the standing position. A total of 10 treatments of 1.2 Gy are delivered over 4 days, for a total of 12 to 13.2 Gy. On days 1, 2, and 3, the patient receives 3 treatments with a 4- to 5-hour interval between fractions. The remaining treatments are given on day 4. The lungs are shielded with 50% transmission blocks for all treatments, and the dose to the chest wall and rib cage underlying the block is supplemented with electron beam radiotherapy of appropriate energy to deliver 3 Gy per day, for a total of 6 Gy. For this study, conventional TBI dose distributions were simulated on the CMS XiO treatment planning system (St. Louis, MO).

TBI dose distributions using HT were simulated on the TomoTherapy Hi-Art treatment planning system. Two targeted TBI treatment strategies were evaluated. In the first strategy, *total marrow irradiation* (TMI), the target region is defined as the skeletal bone. The TMI approach is applicable as part of a conditioning regimen for multiple myeloma. The second targeted TBI strategy, *total marrow and lymphoid irradiation* (TMLI), defines the target regions as bone, major lymph node chains, liver, spleen, and sanctuary sites, such as brain. TMLI is of interest as part of a conditioning regimen for patients with myeloid and lymphoid leukemias, for example.

Details of the Hi-Art treatment planning system have been published previously [6]. For these studies, a 25-mm slice thickness and a pitch of 0.35 were used. The pitch is defined as the distance that the table travels in 1 gantry rotation divided by slice thickness. In all cases for this study, a minimum of 80% of the target volume was to receive the prescribed dose, with the primary objective being to reduce the normal organ D_{50} (median dose) and D_{90} (maximum dose of which 90% of the organ receives) to a minimum. Dose-volume histograms (DVHs) were obtained for all contoured organs and the target volumes.

DVH analysis was used to compare conventional TBI plans with TMI and TMLI plans. DVHs, which plot organ volume as a function of dose received, have

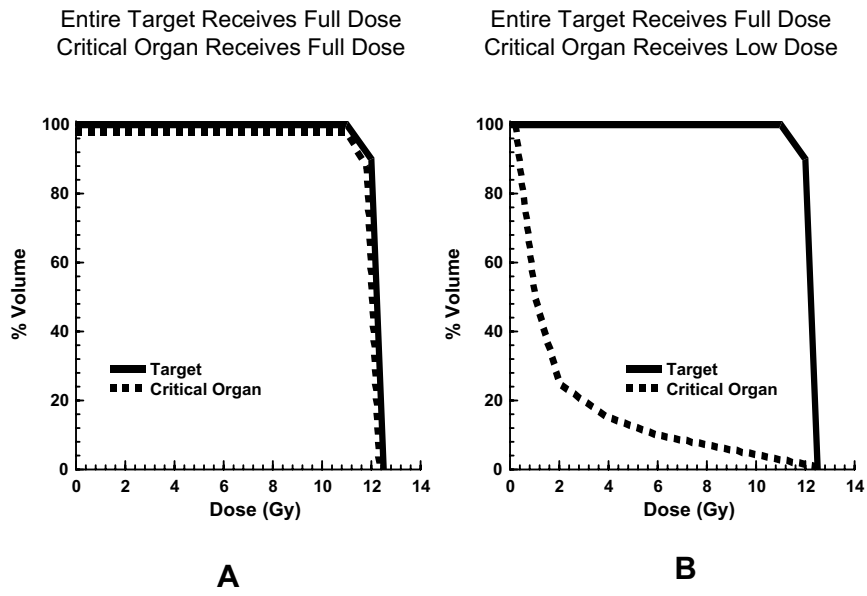

Figure 1. Hypothetical DVHs for tumor and normal organ. (A) The entire tumor target and critical normal organ receives the same full dose. This is comparable to conventional TBI. (B) DVHs for targeted RT to the tumor. The full dose is still delivered to the entire tumor; as a result, the tumor DVH is unchanged. However, the critical organ DVH is shifted to the left with lower doses to a large volume of the organ. In this case, only approximately 20% of the organ receives >2Gy.

been shown to be useful in predicting radiation toxicity [14]. For conventional TBI, DVHs for normal organs are nearly identical for the target region, as shown in Figure 1A. The goal of designing targeted TMI and TMLI using HT was to essentially shift the critical organ DVH down and to the left while maintaining the full dose to the entire target region, as shown in Figure 1B.

RESULTS

TMI versus Conventional TBI

Initial analysis compared conventional TBI and TMI delivered by HT in the 20-year-old female with AML. Figure 2 shows the dose distribution color wash of this TMI plan and demonstrates sculpting of the full dose to skeletal bone/marrow with avoidance of

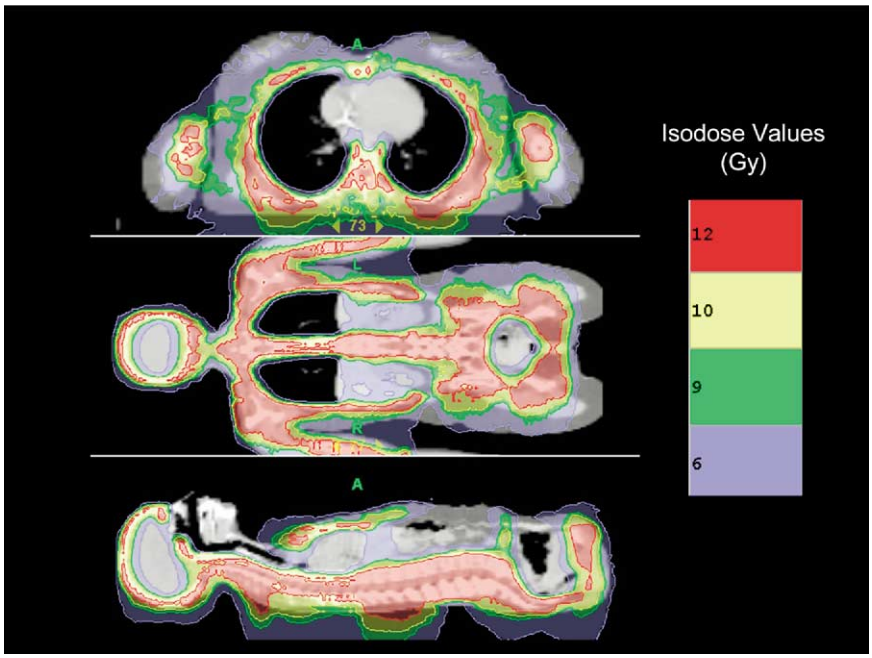

Figure 2. Color wash of a TMI tomotherapy plan to a prescribed dose of 12 Gy in a 20-year-old adult female. Relative sparing of dose to brain, oral cavity, thyroid, lungs, heart, soft tissue, and gastrointestinal tract is seen.

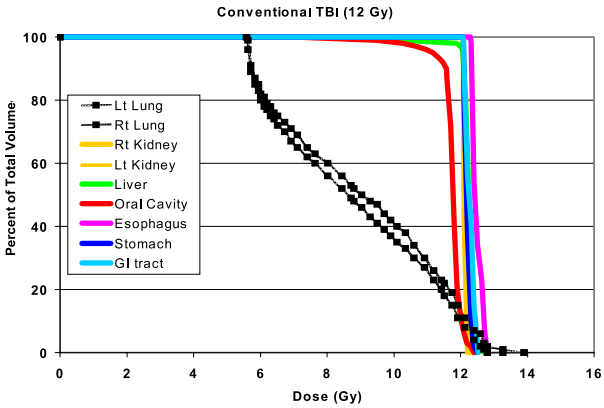

Figure 3. DVHs for major normal organs for the case of a 20-year-old female undergoing conventional TBI. Except for lung, the full dose is delivered to almost the entire normal organ. Partial blocking results in some dosage reduction to the lung.

lung, heart, gastrointestinal tract, thyroid, breast, and other soft tissues. Figure 3 shows organ DVHs for conventional TBI to 12 Gy. As expected, for all normal organs except lung, nearly the entire organ receives the full dose. With partial lung shielding, the DVHs for lung are shifted to the left, although approximately 40% of the lung volume still receives 10 Gy or more and 100% of the lung volume receives close to 6 Gy or more. For comparison, Figure 4 shows DVHs for the same patient receiving 12 Gy TMI. All normal organ DVHs are shifted to the left, while the target region continues to receive full dose. Table 1 reports median doses to normal organs for the 2 plans, showing that a 1.7- to 7.5-fold reduction in median dose is achieved with TMI compared with conventional TBI.

Table 1. *Comparison of Median Doses (Gy) to Normal Organs for TMI versus TBI to 12 Gy*

Organ	TMI 12 Gy	TBI 12 Gy	Ratio of TBI/TMI Median Doses
Lungs	4.3	8.8	2.1
Esophagus	3.9	12.4	3.2
Liver	6.0	12.3	2.1
Kidneys	5.6	12.2	2.2
Bowel	3.5	12.3	3.5
Bladder	7.0	12.4	1.8
Eyes	6.6	11.3	1.7
Parotids	3.9	11.8	3.0
Oral cavity	2.2	11.8	5.4
Stomach	3.1	12.2	3.9
Ovaries	4.3	12.3	2.9
Breasts	6.9	11.5	1.7
Heart	6.2	12.1	2.0
Thyroid	3.7	12.1	3.3
Brain	4.0	12.0	3.0
Lens	1.5	11.3	7.5

Dose Escalation of Targeted TMI to 20 Gy

To evaluate the potential for dose escalation using this approach, treatment plans for TMI to 20 Gy were next evaluated and compared with TMI to 12 Gy and conventional TBI to 12 Gy for the same 20-year-old female patient. Median organ doses for TMI 20 Gy are still less than for conventional TBI 12 Gy (Table 2). Because pneumonitis is a major dose-limiting toxicity of conventional TBI, lung DVH curves for the various plans were compared (Figure 5). The TMI 20 Gy curve shifts to the right of the TMI 12 Gy curve, but all portions of the TMI 20 Gy curve remain to the left of those for conventional TBI 12 Gy, indicating that lung doses are lower for TMI up to 20 Gy than for conventional TBI to 12 Gy.

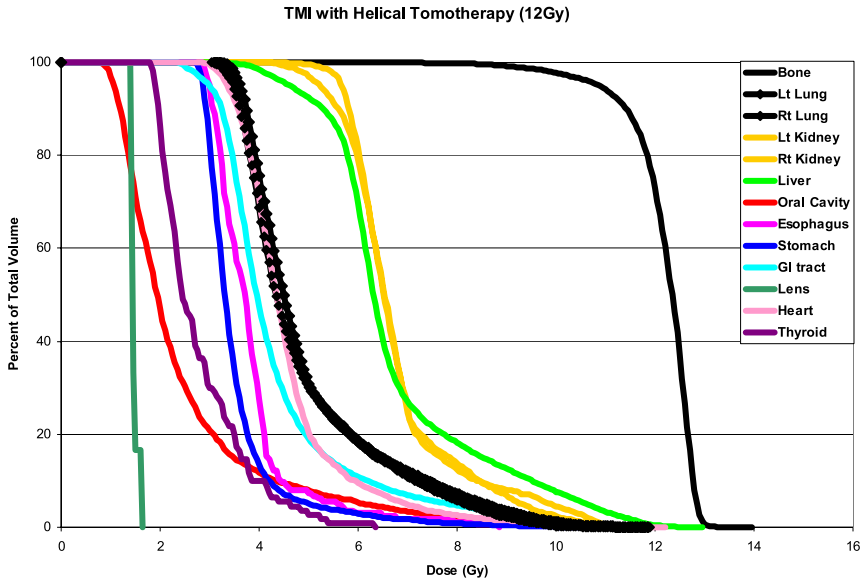

Figure 4. DVHs for major normal organs for the case of a 20-year-old female undergoing TMI delivered by HT. The DVHs for all major organs are shifted to the left of the target (bone) DVH and to the left of the DVHs for conventional TBI (Figure 3), indicating lower doses to a large volume of each normal organ.

Table 2. *Median Doses (Gy) to Normal Organs for TMI to 12 Gy, TMI to 20 Gy, and TBI to 12 Gy*

Organ	TMI 12 Gy	TMI 20 Gy	TBI 12 Gy
Lungs	4.3	6.8	8.84
Esophagus	3.9	5.6	12.4
Liver	6.0	8.7	12.3
Kidneys	5.6	8.7	12.2
Bowel	3.5	5.0	12.3
Bladder	7.0	7.4	12.4
Eyes	6.6	7.0	11.3
Parotids	3.9	4.8	11.8
Oral cavity	2.2	3.0	11.8
Stomach	3.1	5.0	12.2
Ovaries	4.3	6.0	12.3
Breasts	6.9	8.7	11.5
Heart	6.2	6.4	12.1
Thyroid	3.7	4.9	12.1
Brain	4.0	7.9	12.0
Lens	1.5	1.9	11.3

TMLI versus Conventional TBI

Treatment plans were also developed for the same 20-year-old female patient treated with TMLI, where the target region was expanded to include not only skeletal bone/marrow, but also liver, spleen, major lymph node chains, and sanctuary sites such as brain. Figure 6 displays median doses to normal organs for TMLI to 13.2 Gy compared with TMI to 13.2 Gy and conventional TBI to 13.2 Gy. Also shown are organ doses for a plan in which just the skeletal bone/marrow compartment is treated to 15.8 Gy while the dose to liver, spleen, and brain remains at 13.2 Gy. Adding liver, spleen, and brain as target regions with TMLI does not significantly increase median organ doses compared with TMI, and median doses remain well below those of conventional TBI to 13.2 Gy.

Dose Escalation of TMLI to 20 Gy

Finally, treatment plans were developed for the same 20-year-old patient treated with TMLI, with the TMI compartment escalated to 20 Gy while liver, spleen, and brain were treated to 12 Gy and all other organs were treated as avoidance structures. Figure 7 displays DVH curves for critical organs treated by these 2 plans. For this TMLI plan, all DVH curves remain well to the left of conventional TBI DVH curves, predicting the ability to deliver up to 20 Gy to the marrow compartment with comparable or reduced risks of mucositis, esophagitis, enteritis, pneumonitis, nephropathy, and cardiomyopathy.

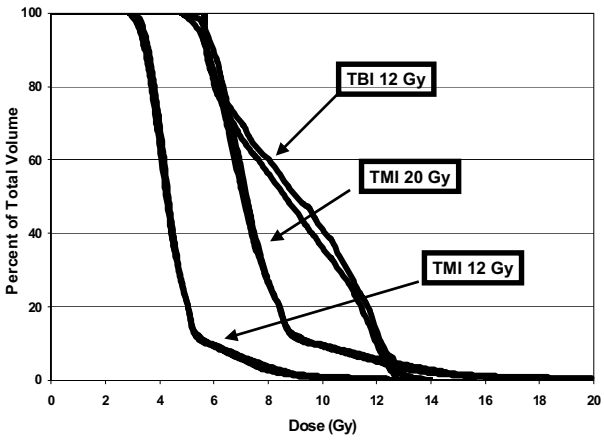

Figure 5. Lung DVHs for the case of a 20-year-old female treated with TMI 12 Gy, TMI 20 Gy and conventional TBI 12 Gy. The DVHs for TMI 12 or 20 Gy remains to the left of TBI 12 Gy, predicting potentially less pulmonary toxicity compared with TBI.

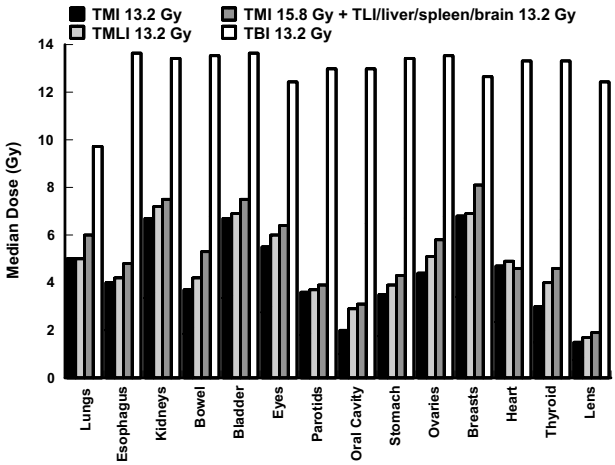

Figure 6. Median organ doses for TMLI versus TMI and conventional TBI in a 20-year-old female. TMLI results in median doses that are slightly higher than those for TMI but still substantially lower than for conventional TBI.

TMLI in a Pediatric Patient

TMLI treatment plans were also developed using a CT dataset from a 5-year-old girl. This patient demonstrated similar shifting of DVH curves for all critical organs well to the left of that for the target regions (data not shown), indicating that targeted TBI with HT will also be feasible in a pediatric population.

Delivery of TMI to a Patient with Multiple Myeloma

Based on the foregoing results supporting the advantages of TMI, a phase I clinical trial evaluating TMI in patients with multiple myeloma was initiated at our institution. Details of this ongoing trial will be the subject of a separate publication. Briefly, patients with stage I–III multiple myeloma who demonstrate response or stable disease after chemotherapy undergo tandem high-dose therapy with peripheral blood progenitor cell (PBPC) support. The first high-dose therapy consists of melphalan, followed a minimum of 6 weeks later by TMI. In this trial, the initial dose level of TMI is 10 Gy, delivered at 2 Gy/day over 5 consecutive days, with

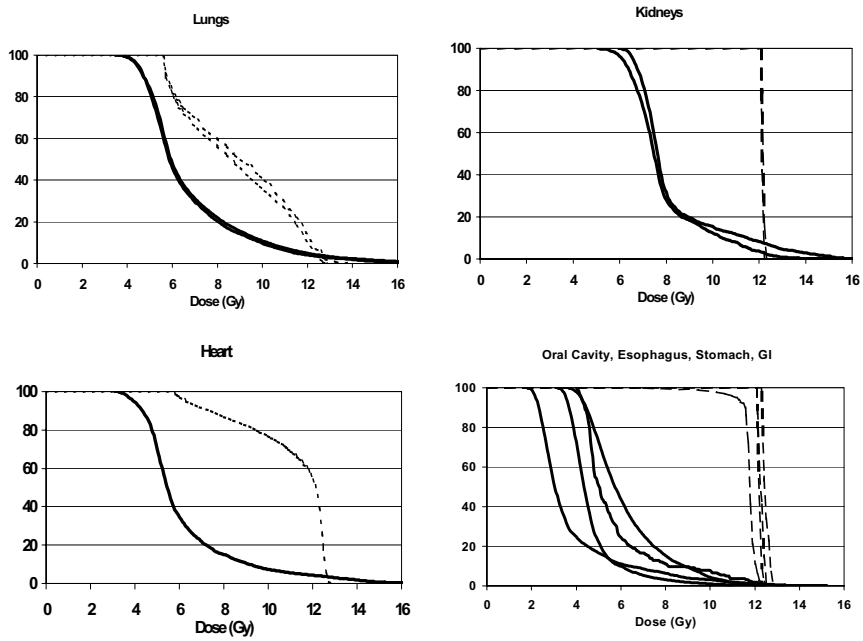

Figure 7. DVHs for critical normal organs in a 20-year-old female treated with TMLI (20 Gy to bone/marrow compartment and 12 Gy to brain, skull, liver, ribs, spleen, and major lymph node chains) compared with conventional TBI to 12 Gy. DVHs for TMLI remain well to the left of those for TBI, predicting that the marrow compartment can be escalated to 20 Gy with no significant increase in organ toxicity.

plans to escalate TMI dose for each cohort of patients in accordance with a conventional phase I trial design.

The first patient in this study was a 53-year-old woman who presented with stage I-A IgGκ multiple myeloma. After responding to decadron and thalidomide therapy, the patient then received intravenous melphalan 100 mg/m^2 on days −2 and −1, with reinfusion of PBPC cells on day 0. The white blood cell count nadir was at day 5, and absolute neutrophil counts recovered to >500/μL by day 13. Platelet nadir was at day 8, with cessation of platelet transfusions reached by day 9. Twelve weeks later TMI was performed, delivering 2 Gy/day from days −6 through −2, for a total of 10 Gy. Treatments were provided with the patient maintained in the supine position using standard immobilization techniques. The current HT treatment table has a maximum travel of 1.6 m; therefore, anterior and posterior (AP/PA) open fields on a conventional linear accelerator were matched to the inferior border of the HT field to treat the lower extremities. The approximate duration of the TMI treatment was 50 minutes of beam-on time to deliver a 2-Gy fraction.

Median organ doses for this patient's TMI therapy are given in Table 3. Figure 8 displays target and critical organ DVHs (A) and dose distribution color washes (B), which are comparable to those seen in the preclinical studies. On day 0, PBPCs were reinfused. White blood cell count nadir (<0.2 K/μL) was at day 3, and absolute neutrophil counts recovered to >500/μL by day 10. Platelet nadir (14 K/μL) was at day 5, with cessation of platelet transfusions reached by day 11. The patient experienced only a single brief episode of grade 2 nausea and grade 1 emesis on day 2 of TMI, which was controlled with antiemetics. She experienced no further nausea during the rest of the week while receiving prophylactic antiemetics. At 2 weeks, she experienced partial alopecia. Skin erythema, oral mucositis, esophagitis, and diarrhea were not observed.

Table 3. *Median Organ Doses Determined From Treatment Plans for the 53-Year-Old Female With Multiple Myeloma Treated With 10-Gy TMI*

Organ	TMI 10 Gy	TBI 10 Gy	Ratio of TBI/TMI Median Doses
Lungs	4.4	8.3	1.89
Esophagus	3.7	10.2	2.76
Liver	6.0	10.2	1.70
Kidneys	6.0	10.0	1.67
Bowel	4.0	10.4	2.60
Bladder	6.0	10.3	1.72
Eyes	5.4	10.0	1.85
Parotids	3.8	10.5	2.76
Oral cavity	2.2	10.4	4.73
Stomach	3.8	10.0	2.63
Ovaries	5.3	10.3	1.94
Breasts	6.1	10.3	1.69
Heart	4.8	9.9	2.06
Thyroid	2.3	10.4	4.52
Brain	4.7	10.3	2.19
Lens	1.3	9.0	6.92

TMI organ doses are compared with median doses from a 10-Gy standard TBI plan in the same patient.

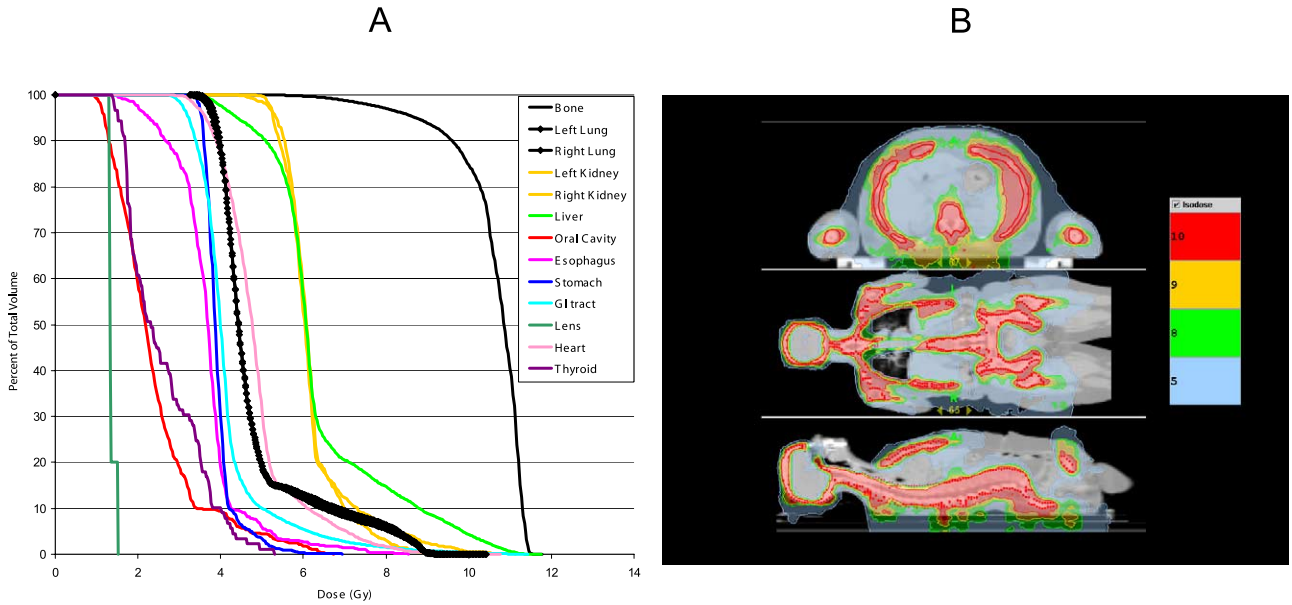

Figure 8. (A) DVHs for major normal organs for the first patient treated with TMI delivered by HT. Target dose was 1000 cGy. The DVHs for all major organs are shifted to the left of the target (bone) DVH, comparable to what is seen with the initial simulated case (Figure 4). (B) Dose distribution color wash of the same patient.

DISCUSSION

TBI remains a critical aspect of conditioning regimens for patients undergoing hematopoietic stem cell transplantation for hematologic malignancies. The benefits of TBI are well documented and can include tumoricidal effects and immunosuppression to facilitate engraftment of donor marrow. Toxicities from TBI, which is often delivered with chemotherapy, are also well described and include mucositis, esophagitis, xerostomia [15], nausea, vomiting, enteritis [16], pneumonitis [17,18], veno-occlusive disease [19], hypothyroidism [20], nephropathy [21], and cataract formation [22].

To improve outcomes, 2 randomized trials have evaluated the effects of increasing the dose of fractionated TBI. A total of 71 patients with AML in first remission were randomized to cyclophosphamide and 12 Gy (2 Gy/day × 6) or 15.75 Gy (2.25 Gy/day × 7) of TBI. The group receiving the higher TBI dose had a 3-year relapse rate of 12%, significantly lower than the 35% rate for the group receiving the lower TBI dose ($P = .06$) [2]. The same group of investigators carried out a similar randomized study of 57 patients with chronic myeloid leukemia in the chronic phase. The 15.75-Gy group had a 4-year relapse rate of 0%, compared with a rate of 25% for the 12-Gy group ($P = .008$) [1]. However, in both studies survival was not improved with higher TBI doses, because of an increase in treatment-related mortality. These studies suggest that modest increases in TBI dose can result in a clinically important reduction in relapse rate, but the feasibility of this strategy is limited by an associated increase in toxicities. This has prompted efforts to develop a more targeted form of TBI that can reduce toxicities and allow for dose escalation [3].

Rapid technologic advances have resulted in the ability to deliver radiotherapy with greater precision at lower doses to adjacent critical organs. HT (commercially available as the TomoTherapy HiArt system) is an FDA-approved radiation therapy delivery device that represents an integration of technological advances in CT image-guided radiotherapy and IMRT. Specifically, a 6-MV linear accelerator is mounted on a CT ring gantry and rotates around the patient as the patient translates through the ring. The 40-cm-wide treatment fan beam is segmented using a 64-leaf binary collimator. The minimum beamlet size is 5 × 6 mm; the maximum couch travel is 160 cm. The maximum target size possible is approximately 60 cm wide × approximately 160 cm long [5]. This is substantially greater coverage than that afforded by linear accelerator–based IMRT systems, which have a maximum target length of approximately 15-20 cm. Thus HT allows the delivery of highly conforming dose distributions to large complex target shapes while simultaneously avoiding doses to critical normal organs [6-12], making it an attractive option for the delivery of conformal targeted TBI. Additional dose conformality is achieved by having beamlets target from 360 degrees, compared with the 5-9 beam angles used by traditional IMRT systems.

In this study, median organ dose and dose volume histograms were used to compare different TBI scenarios, because the likelihood of radiation toxicity for a given organ is a function of both the total dose [23] and the volume of the organ receiving that dose [14,24-26].

Therefore, toxicity can be substantially reduced by limiting the volume of each organ receiving tolerance doses. DVHs have been shown to be a predictive tool for radiation-related toxicity [14,24-26].

Results from these studies clearly illustrate the feasibility and potential advantages of targeted TBI using HT. Compared with conventional TBI, TMI and TMLI treatment plans using the same total dose resulted in substantially lower median doses to all major organs. DVHs demonstrated reduced doses to almost the entire volume of each organ. These data predict that treatment-related morbidity will be significantly reduced with this form of targeted TBI, providing a compelling reason to evaluate this strategy as part of myeloablative conditioning regimens. For example, DVH dosimetric analysis demonstrated that lung doses were substantially lower for TMI than for conventional TBI, predicting for the ability to escalate the TMI dose to 20 Gy without incurring any additional risk of pneumonitis.

The 53-year-old patient with multiple myeloma reported here represents the first case treated with TMI using HT (TomoTherapy, personal communication). Multiple myeloma presents an appropriate clinical setting to begin evaluation of this novel form of targeted TBI. Attempts to improve overall response and response duration have focused on using myeloablative therapies [27]. Conventional TBI has been part of these strategies, but it results in significant side effects when combined with high-dose chemotherapy [28]. A more targeted TBI strategy is needed to reduce associated side effects, thereby permitting dose escalation in this highly radiosensitive disease.

Results from this first case demonstrate the feasibility of using HT to deliver targeted TBI and confirms the ability of HT to deliver a myeloablative dose selectively to skeletal bone and bone marrow. Organ doses were comparable to those from the initial preclinical studies and predicted reduced toxicities compared with standard TBI. Although more patients and longer follow-up are needed, the fact that the first patient experienced minimal nausea and vomiting and no diarrhea, skin erythema, mucositis, or esophagitis while still achieving the expected count nadirs is very encouraging.

Other potential advantages of this approach are also evident from this study. The total dose to each compartment can be individualized, with a given organ compartment or target region receiving a minimum dose, a partial dose, or a maximum tolerated dose. For example, areas of recurrent or residual disease that may be resistant to chemotherapy can receive a simultaneous boosted dose with TMI or TMLI; sanctuary sites, such as the central nervous system, can be selectively targeted; and areas that were previously irradiated can be outlined and the dose minimized or only a partial dose delivered while the rest of the target region receives the intended full dose.

Some questions are not addressed by the results of this study and can be evaluated only through clinical trials. The TMI and TMLI treatment strategies presented in this report deliver the full dose to a user-defined anatomic target region felt to harbor a significant percentage of the tumor burden. In addition, with TMLI, major lymphoid regions are targeted to provide sufficient immunosuppression in the allograft setting. However, unlike conventional TBI, these targeted TBI approaches deliver reduced doses (approximately 1.7- to 7.5-fold less) to malignant cells that are in circulation or lie outside the defined target region. This may result in an increase in relapse rate [29]. However, this possible disadvantage may be outweighed by the potential advantage of intensifying systemic chemotherapy delivered with targeted TBI because of reduced radiation-related side effects.

Targeted TBI can potentially reduce acute graft-versus-host disease in the allogeneic transplantation setting, which some feel is triggered by normal tissue damage and induction of inflammatory cytokines set into play from dose-intensive conditioning regimens. Although this should translate into reduced treatment-related morbidity and mortality, there could also be a second-order effect from decreased graft-versus-disease effects. The ultimate impact of this variable on overall survival and outcome remains to be determined.

The importance of the higher radiation dose rate in HT compared with conventional TBI is unknown. Instantaneous dose rates for conventional TBI range from approximately 4 to 20 cGy/minute, compared to a maximum of 8 Gy/minute for HT TMI. The full impact of dose rate on marrow stroma and engraftment remains to be determined, although the patient reported here demonstrated no problems with engraftment.

Other methods of targeted TBI, including bone-seeking radionuclide therapy and antibody-guided radiation therapy (or radioimmunotherapy), are being actively evaluated in clinical trials as part of conditioning regimens for patients undergoing transplantation. Clinical results using these biologically targeted forms of TBI are encouraging, but also demonstrate several potential limitations. Tumor doses from radiolabeled antibodies are generally lower than can be achieved with targeted external-beam radiotherapy, with median or mean doses ranging from 240 to 1700 cGy at nonmyeloablative-administered activities [30]. Even at myeloablative administered activities, the estimated doses to marrow are lower than those achievable by targeted TMI or TMLI. In addition, interpatient and intrapatient variation of doses to tumor sites and normal organs exist because of individual variations in antibody clearance rates and biodistribution that cannot be easily

controlled for. Finally, normal organ uptake and clearance of these agents can result in radiation-induced toxicities [31-33]. These factors are not seen with TMI or TMLI.

But rather than competing strategies, these different forms of targeted TBI may be best used in combination, because each complements the other. HT-targeted TBI has the potential to deliver additional doses to tumor sites and to create dose- avoidance regions where needed, with the dose and dose regions potentially tailored to complement the unique radionuclide dose distribution of a given patient. HT-targeted TBI can also deliver additional dose to sanctuary sites likely underdosed by systemically administered radionuclide. Finally, systemic-targeted radionuclide therapy, such as radioimmunotherapy, complements HT-targeted TBI by targeting the dose to malignant cells in circulation that are not treated to full dose with HT. Combination targeted TBI strategies will likely prove feasible, because several trials that have combined conventional TBI and radioimmunotherapy have demonstrated engraftment with cumulative marrow doses of up to approximately 40 Gy [34].

In summary,results from this study demonstrate the feasibility and potential advantages to selectively deliver myeloablative doses of radiation to bone and marrow using an image-guided tomographic intensity-modulated radiation therapy delivery system. Organ doses are substantially lower than those associated with standard TBI and predict the potential to significantly reduce associated toxicities and allow for dose escalation. Given the available data, it is likely that there will be further room for dose escalation to the bone marrow before nonengraftment is observed. Results also suggest that this form of targeted TBI may have potential advantages over other forms of targeted TBI, such as radioimmunotherapy or bone-seeking radionuclide therapy. Clinical trials are currently underway to define the maximum TMI and TMLI doses achievable, characterize associated toxicities, and define the potential advantages and limitations of this new approach for patients undergoing hematopoietic stem cell transplantation.

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