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IMAGE-GUIDED TOTAL-MARROW IRRADIATION USING HELICAL TOMOTHERAPY IN PATIENTS WITH MULTIPLE MYELOMA AND ACUTE LEUKEMIA UNDERGOING HEMATOPOIETIC CELL TRANSPLANTATION

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Purpose: Total-body irradiation (TBI) has an important role in patients undergoing hematopoietic cell transplantation (HCT), but is associated with significant toxicities. Targeted TBI using helical tomotherapy results in reduced doses to normal organs, which predicts for reduced toxicities compared with standard TBI.

Methods and Materials: Thirteen patients with multiple myeloma were treated in an autologous tandem transplantation Phase I trial with high-dose melphalan, followed 6 weeks later by total-marrow irradiation (TMI) to skeletal bone. Dose levels were 10, 12, 14, and 16 Gy at 2 Gy daily/twice daily. In a separate allogeneic HCT trial, 8 patients (5 with acute myelogenous leukemia, 1 with acute lymphoblastic leukemia, 1 with non-Hodgkin's lymphoma, and 1 with multiple myeloma) were treated with TMI plus total lymphoid irradiation plus splenic radiotherapy to 12 Gy (1.5 Gy twice daily) combined with fludarabine/melphalan.

Results: For the 13 patients in the tandem autologous HCT trial, median age was 54 years (range, 42–66 years). Median organ doses were 15–65% that of the gross target volume dose. Primarily Grades 1–2 acute toxicities were observed. Six patients reported no vomiting; 9 patients, no mucositis; 6 patients, no fatigue; and 8 patients, no diarrhea. For the 8 patients in the allogeneic HCT trial, median age was 52 years (range, 24–61 years). Grades 2–3 nausea, vomiting, mucositis, and diarrhea were observed. In both trials, no Grade 4 nonhematologic toxicity was observed, and all patients underwent successful engraftment.

Conclusions: This study shows that TMI using helical tomotherapy is clinically feasible. The reduced acute toxicities observed compare favorably with those seen with standard TBI. Initial results are encouraging and warrant further evaluation as a method to dose escalate with acceptable toxicity or to offer TBI-containing regimens to patients unable to tolerate standard approaches. © 2009 Elsevier Inc.

Helical tomotherapy, IMRT, Bone marrow transplantation, Multiple myeloma, Leukemia.

INTRODUCTION

Radiation therapy in the form of total-body irradiation (TBI) continues to be an important part of conditioning regimens in patients undergoing hematopoietic cell transplantation (HCT). Several randomized trials have shown superior outcomes using TBI compared with non–TBI-containing regimens (1–4). Randomized trials have also shown decreased relapse rates in patients with acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) with higher TBI doses (5, 6). However, overall survival was unchanged because of an increase in toxicities and treatment-related mortality rates. A more targeted form of TBI delivery therefore is needed to allow for dose escalation with acceptable toxicity and for the potential to improve outcomes. Rapid advances in the delivery of external beam radiotherapy using intensity-modulated radiation therapy coupled with image-guided radiation therapy now allow radiation oncologists to ''sculpt'' dose to the unique shape of each patient's tumor. These advances are being translated to large-field applications.

Recently, we reported on the concept of using helical tomotherapy (HT) to deliver a more targeted conformal form of TBI (7–9). Dosimetry studies showed lower organ doses and predicted for reduced toxicities. This report details the observed acute toxicities and initial clinical experience of

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patients undergoing HCT using this approach. The potential advantages and challenges of this approach are discussed.

METHODS AND MATERIALS

Patient characteristics

The first 21 patients treated from June 2005 to June 2007 with targeted TBI using HT on two separate studies are the subjects of this report. Both trials defined acute toxicities as those occurring in the first 30 days after targeted TBI using National Cancer Institute Common Toxicity Criteria Version 3 and were approved by the City of Hope Cancer Center (Duarte, CA) Institutional Review Board.

Phase I tandem autologous HCT trial of melphalan and targeted TBI in multiple myeloma

Patients with Stages I–III disease using the staging system by Durie and Salmon (10) who were less than 18 months from diagnosis were eligible for this trial. Previous radiotherapy was allowed if delivered to 20% or less of bone marrow–containing areas and 20 Gy or less, conventionally fractionated. Patients first underwent mobilization with cyclophosphamide (1.5 g/m^2) and filgrastim (10 μg/kg/d) followed by apheresis to collect a minimum of 4×10^6 CD34$^+$ cells/kg. This was followed by melphalan 100 mg/m^2/d for 2 days, followed by reinfusion of one half the collected peripheral stem cells.

A minimum of 6 weeks later, targeted TBI using HT was administered using the methods described next. Gross target volume (GTV) was defined as skeletal bone, and we have referred to this technique as total-marrow irradiation (TMI). As part of the Phase I portion of this study, TMI dose was escalated in cohorts of 3–6 patients according to standard Phase I trial design. Five dose levels were defined for this trial: 10, 12, 14, 16, 18, and 20 Gy delivered at 2 Gy daily to twice daily (minimum, 6 hours between fractions) over 5 days, followed by peripheral stem cell infusion. Dose-limiting toxicity was defined as Grade 3 or 4 nonhematologic toxicity (except fatigue) or Grade 4 leukopenia or thrombocytopenia for longer than 28 days.

Maintenance dexamethasone (40 mg/d $\times$ 4 days every 28 days) and thalidomide (50–200 mg/d) therapies were started a minimum of 30 days after TMI. Follow-up included serum protein electrophoresis every 3 months and bone x-rays and bone marrow biopsies at 3, 6, and 12 months post-TMI and yearly thereafter. Complete response was defined as the absence of serum and urinary M-protein and no more than 5% plasma cells on bone marrow. Very good partial response was defined as 90% or greater decrease in bone marrow plasma cells and blood M-protein levels. Partial response was defined as 50% or greater decrease in blood and bone marrow findings. Stable disease was defined as less than 25% decrease in blood and bone marrow findings for a minimum of 3 months. Progression was defined as greater than 25% increase in M-protein, greater than 25% increase in bone marrow plasma cells, or new bone lesions.

Pilot allogeneic HCT trial with targeted TBI combined with the reduced-intensity chemotherapy regimen of fludarabine and melphalan

Patients with advanced hematologic malignancies (AML, acute lymphoblastic leukemia [ALL], non-Hodgkin's lymphoma [NHL], and multiple myeloma [MM]), defined as either high-risk remission, less than 10% blasts in marrow, or 50% or greater decrease in marrow blasts after induction therapy, were eligible. Previous radiotherapy was allowed if delivered to 20% or less of bone marrow–containing areas and 20 Gy or less, conventionally fractionated. Patients older than 50 years or with comorbidities who may have benefited from HCT, but were not eligible for standard, full intensity, myeloablative, HCT-conditioning regimens, were eligible to enter this study.

Targeted TBI was delivered from Days –7 to –4 at 1.5 Gy twice daily (minimum 6 hours between fractions) for a total of 12 Gy, combined with fludarabine (25 mg/m^2/d $\times$ 5 on Days –7 to –3) and melphalan (140 mg/m^2 on Day –2). Graft-vs.-host disease prophylaxis consisting of tacrolimus and sirolimus was started on Day –1. On Day 0, collected peripheral-blood stem cells from HLA-matched related or matched unrelated donors was infused. For all patients, GTV was defined as skeletal bone, major lymph node chains, and spleen. Brain and testes were also included in the GTV for patients with ALL. We have referred to this technique as total marrow and lymphoid irradiation (TMLI). For the first 100 days after discharge, patients were followed up at least weekly with complete differential blood counts and comprehensive metabolic panel. Bone marrow biopsy was performed at approximately 100 days after stem cell infusion.

In both trials, standard antiemetic regimens were used, and palifermin was not administered.

Radiotherapy technique

Details of the technique have been published previously (8). All patients were initially scanned for treatment planning purposes on a large-bore (85-cm) computed tomography (CT) simulator with 60-cm field of view (Philips Medical System, Eindhoven, The Netherlands). The CT scans in 4-mm slices were obtained during shallow breathing, inspiration, and expiration to account for changes in position during respiration of the ribs, lungs, kidneys, spleen, and liver. A full-body Vac-lok bag (CIVCO Medical Systems, Kalona, IA) and thermoplastic mask over the head and neck were used as immobilization devices.

Target and avoidance structures were contoured on an Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). Avoidance structures contoured included lungs, heart, kidneys, liver, esophagus, oral cavity, parotid glands, thyroid gland, eyes, lens, brain, stomach, small bowel, rectum, bladder, and testes. The GTV for each trial was described previously. The mandible and maxillary bones were excluded from the GTV in an effort to minimize oral cavity dose and mucositis. Digital imaging and communications in medicine-radiation therapy (DICOM-RT) images were then transferred to the Hi-Art tomotherapy treatment planning system (Tomotherapy, Inc., Madison, WI). Plans were designed such that a minimum of 85% of the GTV received the prescribed dose (8).

Our current procedure involves initial laser alignment of the patient in a Vac-lok bag and thermoplastic mask. The mask is then removed and a megavoltage CT scan is obtained with fusion to the planning CT. The necessary couch shifts are then made, followed by initiation of treatment. A slice thickness of 2.5 mm, pitch of 0.3–0.45, and modulation factor of 2.5–3.0 were used for treatment, resulting in a beam-on time of approximately 50 minutes.

The current treatment table on the HT unit has a maximum travel length of approximately 150 cm. We chose to treat the lower extremities on a conventional C-arm linear accelerator through standard anteroposterior–posteroanterior (AP-PA) fields given the lack of sensitive organs in this area in this adult population. At the time of treatment planning, a radiopaque marker was placed in the thigh

region to define the lower border (50% isodose line) of the HT plan. The AP-PA fields were gapped to this border at midplane.

RESULTS

Twenty-one patients were treated with either TMI or TMLI. There were no delays in treatment delivery caused by toxicities, and all patients completed the planned dose and schedule with the exception of 1 patient on the autologous HCT myeloma trial, who received 12 Gy instead of the planned 14 Gy because of machine downtime. Most patients were treated without mask immobilization in place because of initial concerns of vomiting during treatment. However, to date, only 1 patient experienced nausea during the therapy, which required a brief treatment interruption.

Phase I tandem autologous HCT trial of melphalan and TMI in MM

Thirteen patients with MM, received TMI per protocol, with 3 patients at each dose level of 10, 12, 14, and 16 Gy, with the exception of a fourth patient added to the 14-Gy level for reasons stated previously. Median age was 54 years (range, 42–66 years). There were seven men and six women. Median time from diagnosis to receiving melphalan was 8 months (range, 4–13 months), and median number of prior chemotherapy regimens was two (range, one to four). No patient received prior radiotherapy. Median number of days between melphalan and TMI was 79 (range, 4 to 125 days).

Figure 1 shows a color wash of the first patient treated to 10 Gy. Figure 2 shows dose–volume histograms for major critical organs for the same patient, with substantial dose sparing relative to the GTV. Figure 3 shows median (D_{50}) doses averaged for each dose level for all major organs. As expected,

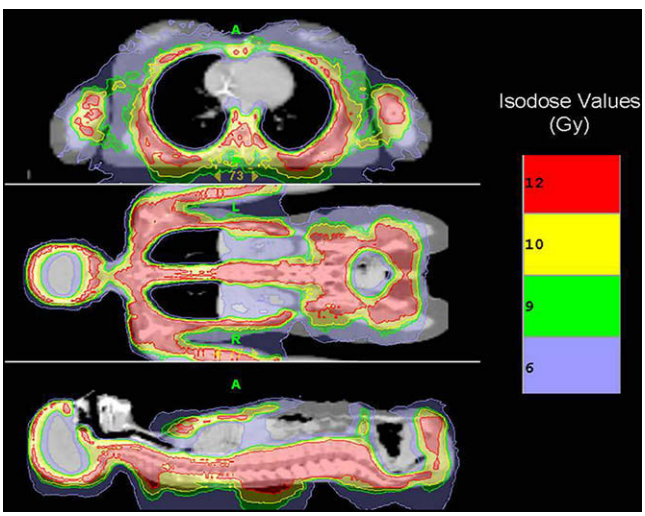


Fig. 1. Color wash shows dose distribution of the first patient treated with targeted total-body irradiation (TBI) using Tomotherapy. The target structure is skeletal bone. Reprinted from Biol Blood Marrow Transplant, vol. 12, Wong JYC, Liu A, Schultheiss T, et al. Targeted total marrow irradiation using three-dimensional image-guided tomographic intensity-modulated radiation therapy: An alternative to standard total body irradiation, pages 306–315. Copyright 2006, with permission from American Society for Blood and Marrow Transplantation.

with escalation of the prescribed GTV dose, median doses for all organs increased, but still remained less than that for standard TBI. At our institution, standard TBI is delivered through AP-PA fields to 12 or 13.2 Gy with 50% lung transmission blocks and electron boost of 6 Gy to the underlying rib cage, resulting in a lung D_{50} of approximately 9 Gy (7).

The relative degree of organ dose sparing seen with each patient was similar despite differences in patient size and body habitus. Table 1 lists the average and range for D_{50} organ doses for all 13 patients with organ doses normalized to a GTV dose of 12 Gy for comparison purposes. The D_{50} doses to lens and oral cavity were less than 25% of the prescribed GTV dose; to lungs, heart, gastrointestinal tract, and thyroid, approximately 35–50%; and to kidneys, liver, brain, bladder, and eyes, approximately 50–65%.

The observed acute toxicities appeared to be consistent with the reduced organ doses predicted from treatment plans (Table 2). No Grade 4 toxicities were observed. Grade 3 toxicities were infrequent, with 2 patients reporting fatigue and 1 patient reporting anorexia. All patients reported Grades 1–2 nausea, but 6 experienced no vomiting, 8 experienced no diarrhea, 9 experienced no mucositis, and 12 experienced no erythema. All patients who achieved successful engraftment with a median time to independence from platelet transfusions of 8 days (range, 6–11 days) and a median time to absolute neutrophil count of 1,000/μl or greater of 10 days (range, 9–12 days).

With a median follow-up of 13 months (range, 5–25 months), 5 patients remain in complete remission (the longest is 25 months); 1 patient, in very good partial remission; 4 patients, in partial remission; and 2 patients, with stable disease. One patient who received 10 Gy experienced progression at 9 months and died of disease at 13 months. Eight patients remain on maintenance thalidomide and Decadron (Dexamethasone, Roxane Labs Inc., Columbus, Ohio) therapy. Although follow-up is limited, radiation pneumonitis was not observed.

Pilot allogeneic HCT trial with TMLI combined with the reduced-intensity chemotherapy regimen of fludarabine and melphalan

Eight patients have been treated on this trial, 5 with a diagnosis of AML, 1 with ALL, 1 with MM, and 1 with non-Hodgkin's lymphoma. Two were in first remission, 1 was in first relapse, 4 were induction failures, and 1 had progressive disease. Median age was 52 years (range, 24–62 years). There were three men and five women. Four patients received hematopoietic stem cells from an HLA-identical sibling donor, and 4 patients, from a matched unrelated donor. No patient had received previous radiotherapy.

Organ D_{50}s with TMLI were similar to those seen with TMI on the MM trial (Table 1), with the exception of slightly higher doses to the parotids and thyroid because of lymph nodes included in the GTV. Acute toxicities were primarily Grades 2–3. Grade 3 nausea, vomiting, mucositis, and diarrhea occurred in 6, 2, 6, and 3 patients, respectively. No Grade 4 nonhematologic acute toxicity was observed. All

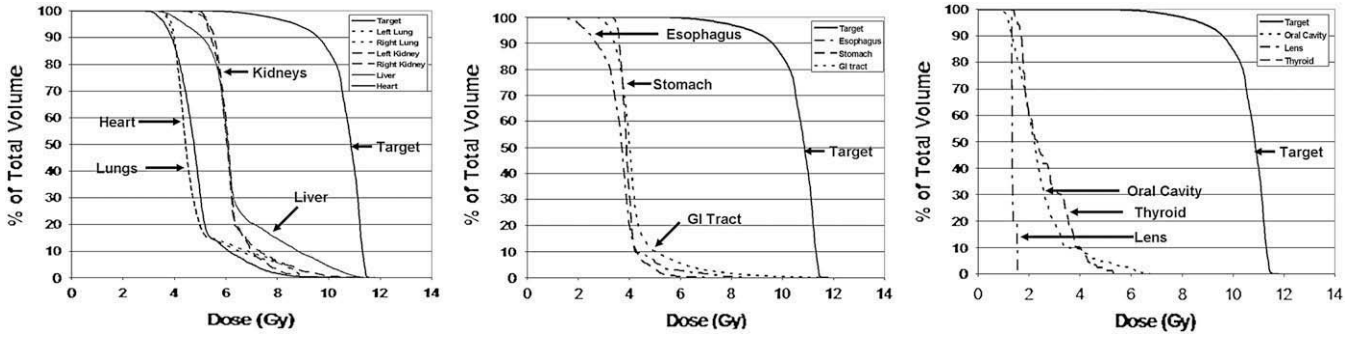


Fig. 2. Major organ and target (gross target volume) dose–volume histogram curves of first patient with multiple myeloma treated with total-marrow irradiation.

patients achieved successful engraftment, with a median time to absolute neutrophil count of 1,000/μl or greater of 15 days (range, 11–21 days) and platelet count of 20,000/μl or greater of 15 days (range, 10 to 18 days). With a median follow-up of 4.6 months (range, 1.6–12.0 months), 7 of 8 patients are alive and remain in remission, the longest for 12 months. To date, 3 patients have undergone bone marrow biopsies at Day 100 that showed no evidence of disease and 100% donor chimerism. One patient died of influenza type A pulmonary infection. Acute graft-vs.-host disease occurred in 6 patients.

DISCUSSION

The TBI has an important role in patients undergoing HCT to eradicate malignant cells and in those undergoing allogeneic HCT as a means of immunosuppression to prevent rejection of donor hematopoietic cells. The TBI has distinct advantages over chemotherapy. Unlike chemotherapy, delivery of radiation therapy to target sites is not dependent on blood supply; not influenced by interpatient variability in drug absorption, metabolism, biodistribution, or clearance kinetics; and can reach potential sanctuary sites, such as testes and brain. Some randomized studies have shown an advantage in relapse, disease-free survival, and overall survival rates with TBI-containing over non–TBI-containing high-dose conditioning regimens, particularly in patients with acute leukemias (1–4).

Several groups have attempted to escalate TBI doses in an effort to improve outcomes. The group from Fred Hutchinson Cancer Center carried out two randomized trials comparing Cytoxan (Cyclophosphamide, Roxane Labs Inc, Columbus, Ohio) combined with 12 Gy at 2 Gy/d or 15.75 Gy at 2.25 Gy/d. In a trial of 116 patients with CML in chronic phase, the higher dose resulted in a significantly lower relapse rate (0% vs. 25%; $p = 0.008$), but higher treatment-related mortality rate (24% 12 Gy and 34% 15.75 Gy; $p = 0.13$), and as a result, no significant change in overall survival (5). In a separate trial of 71 patients with AML in first remission, the relapse rate also decreased with the higher dose (14% vs. 39%; $p = 0.06$), but these gains were offset by an increase in nonrelapse mortality (38% vs. 19%; $p = 0.05$), resulting in no difference in overall survival between the two arms (6). Therefore,

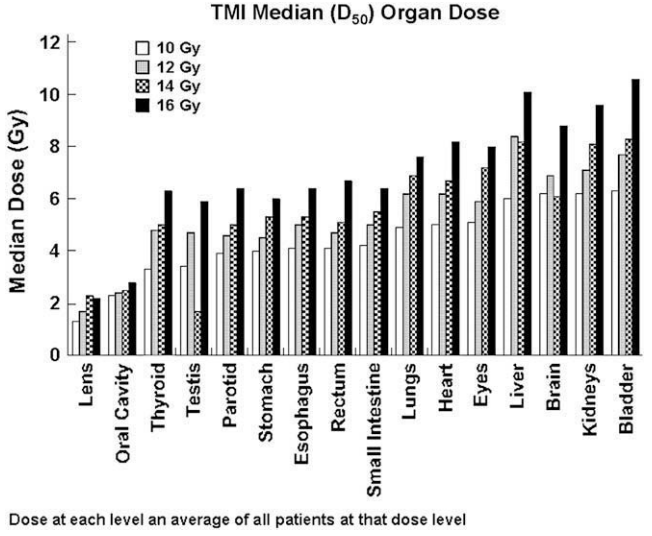


Fig. 3. Median (D_{50}) organ doses for each dose level. TMI = total-marrow irradiation.

Table 1. Organ D_{50}s for 13 patients with multiple myeloma treated with TMI (doses normalized assuming a gross target volume dose of 12 Gy) and 8 patients treated with TMLI to 12 Gy

	TMI	TMI	TMLI	TMLI
Organ	Mean D_{50} (Gy) (n = 13)	Range D_{50} (Gy)	Mean D_{50} (Gy) (n = 8)	Range D_{50} (Gy)
Lens	1.7	1.4–3.1	2.5	1.3–3.0
Oral cavity	2.3	1.6–2.9	3.0	2.8–3.2
Thyroid	4.4	2.8–5.5	5.2	4.6–6.4
Parotids	4.6	3.7–5.0	5.3	4.4–5.6
Stomach	4.6	4.0–5.2	4.5	4.0–5.0
Rectum	4.7	4.2–5.5	4.8	4.3–5.6
Esophagus	4.8	4.3–5.6	4.9	4.4–5.4
Small intestine	4.8	4.5–5.3	4.8	4.6–5.2
Lungs	5.9	5.3–6.7	5.7	4.9–6.8
Eyes	6.0	5.3–6.5	6.2	5.8–6.9
Heart	6.0	5.6–6.6	6.2	6.0–6.8
Brain	6.4	4.7–8.8	5.2	4.1–6.2
Testes	6.5	5.8–7.3	6.6	5.0–9.5
Kidneys	7.2	6.7–7.7	6.7	6.0–7.4
Bladder	7.5	6.8–8.4	7.5	6.8–8.2
Liver	7.5	6.6–9.7	9.2	7.8–11.2

Abbreviations: TMI = total-marrow irradiation; TMLI = total marrow and lymphoid irradiation; D_{50} = median dose.

Table 2. Acute toxicities in 13 patients with multiple myeloma treated with TMI

Age (y)	54	42	49	54	66	53	56	54	61	52	60	49	62
Sex	F	M	M	F	M	M	F	M	F	F	M	F	M
TMI dose (Gy)	10	10	10	12	12	12	12*	14	14	14	16	16	16
Nausea	2†	1	2	2	2	1	1	2	1	1	2	1	1
Vomiting	1	2		1	1			2			2	1	
Anorexia													3
Fatigue	1	3	1	1	1			1	1	2	3		
Erythema	2												
Diarrhea	1				1		1		1		2		
Esophagitis	1												
Oral mucositis			2		2						2	1	

Abbreviation: TMI = total-marrow irradiation.
* Total of 12 Gy delivered over 7 days.
† Toxicities graded using National Cancer Institute Common Toxicity Criteria Version 3.

escalation of TBI dose has been challenging. Gains in disease control are associated with an increase in regimen-related toxicities and nonrelapse mortality, resulting in no improvement in overall survival. New more targeted strategies are clearly needed to allow further dose escalation without an associated increase in short- and long-term side effects.

Biologically guided systemic radiotherapy using radiolabeled antibodies (11) or such bone-seeking radiopharmaceuticals as ^{166}Ho-1, 4, 7, 10-tetraazacyclododecan-1, 4, 7, 10-tetramethylene-phosphonate (12) are currently undergoing evaluation as part of HCT conditioning regimens. A limitation with these approaches is the inability to completely control the radiation dose to tumor or normal organ for a given patient. Dose distribution is dictated by multiple factors, such as tumor size, tumor burden, antigen expression, tumor microenvironment, clearance kinetics, and *in vivo* stability of the agent. These factors can lead to low unpredictable doses to a given tumor or higher than expected doses to critical organs. Tumor doses using biologically guided systems in general have been less than those achievable by using external beam radiotherapy (13).

Recent technological advances in the delivery of external beam radiotherapy now allow for the delivery of a more targeted form of TBI. The HT (commercially available as the Tomotherapy HiArt System) integrates CT image-guided radiotherapy and intensity-modulated radiation therapy in a single device. 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 field is shaped by a binary multileaf collimator. The maximum target size possible is approximately 60 cm wide by approximately 160 cm long. The HT therefore allows for the delivery of highly conforming dose distributions to large complex target shapes while simultaneously reducing dose to critical normal organs (14), making it suited for the delivery of conformal targeted TBI.

Results from the two trials reported show the clinical utility of using HT to deliver targeted TBI. Organ D_{50}s were approximately 15–65% of the prescribed GTV dose. With dose escalation to 16 Gy, organ D_{50}s still remained less than that for standard TBI to 12 Gy, which predicted for reduced acute toxicities compared with TBI. Dose escalation continues on this Phase I trial.

Acute toxicities observed on the tandem autologous transplantation MM trial were modest and compare favorably with results from a Phase I tandem autologous HCT trial of similar design reported by Zaucha *et al*. (15). In this study, patients with MM or breast cancers or sarcomas with primarily bone metastases were first treated with busulfan, melphalan, and thiotepa, followed a median of 105 days later by modified TBI to 12, 13.5, or 15 Gy using 5% transmission blocks over the lungs and liver. Grades 1–2 mucositis was seen in 100% and diarrhea was seen in 34% of patients using the Bearman toxicity scale (16), which is similar to Grades 2–3 toxicity by using the National Cancer Institute Common Toxicity Criteria (Death from pulmonary toxicity was observed in 3 of 17 patients treated at 15 Gy).

Acute toxicities observed with the combination of TMLI, fludarabine, and melphalan were also acceptable, with Grades 2–3 and no Grade 4 toxicities observed. This compares favorably to a trial by Petropoulos *et al*. (17), who evaluated 9-Gy TBI (3 Gy/d) combined with fludarabine (120 mg/m^2) and melphalan (140 mg/m^2), which, although tolerated in a pediatric population, was not tolerated in adults because of mucositis, forcing study closure.

Interstitial pneumonitis is an associated toxicity with TBI. Lung D_{80}, D_{50}, and D_{10} are listed in Table 3 for the 13 patients with MM on the Phase I MM dose-escalation trial. For comparison, average lung D_{80}, D_{50}, and D_{10} values are listed for standard TBI plans to 12 Gy, which were generated using previously published methods (8) and used planning CT data sets from the first 3 patients. Further dose escalation

Table 3. Lung D_{80}, D_{50}, and D_{10} values for 13 patients with multiple myeloma on the TMI dose escalation trial

	TBI 12 Gy	TMI 10 Gy	TMI 12 Gy	TMI 14 Gy	TMI 16 Gy
D_{80}	7.0	4.5	5.6	6.4	6.9
D_{50}	9.4	4.9	6.2	6.9	7.6
D_{10}	12.3	6.8	8.4	9.4	10.9

Abbreviations: TMI = total-marrow irradiation; D_x = x% of dose level.

Values are an average for patients at each dose level. Lung D_{80}, D_{50}, and D_{10} values for standard TBI 12 Gy are shown for comparison.

to greater than 16 Gy may be associated with pneumonitis risks similar to 12-Gy TBI. Although the D_{50} for 16-Gy TMI is less than that for 12-Gy TBI, D_{80} values are similar. We are currently evaluating methods to further reduce lung dose on the Tomotherapy Hi-Art system as we continue to dose escalate.

Several questions arise using this approach. For example, does organ sparing also spare cancer cells or reduce the immunosuppression needed for allogeneic HCT? Organ sparing appears at this time to not be an adverse factor, but this will eventually have to be substantiated through clinical trials. However, it is important to note that most avoidance structures received approximately 35–65% of the target dose, and similar to a shrinking field concept, areas with lower tumor burden may require lower dose than areas with higher tumor burden, such as bone marrow. In addition, if a dose-escalation strategy is pursued, the maximum tolerated dose will likely be at a level at which most major organs receive a dose similar to standard TBI. The end result would be dose distribution similar to standard TBI with concomitant boost to areas of greatest tumor burden. Chemotherapy, which is often part of the conditioning regimen, adds to the therapeutic effect in avoidance areas. Finally, to date, there is no evidence of compromised immunosuppression, with all patients having achieved successful engraftment and 100% donor chimerism documented in all 3 patients who underwent follow-up Day 100 bone marrow biopsies.

The dose-rate used with this technique (~400 cGy/min) is higher than that used with standard TBI (~5–30 cGy/h), which may have greater effects on normal tissues. However, the available data show that higher dose-rates may not be as significant a factor. We have seen no evidence of graft failure at this dose-rate. The reduced acute toxicities observed suggest that reductions in dose and volume of organ receiving a given dose probably outweigh any dose-rate effects. Dose-rate effects appear to be clinically relevant only if less than 5–10 cGy/h (18, 19). Finally, dose-rate effects are probably outweighed by other factors, such as fractionation, which was used in this trial. Sampath *et al*. (20), in a multivariate logistic regression analysis of TBI in 1,090 patients from 20 published studies, found an inverse correlation with interstitial pneumonitis incidence and fractionation, but no dose-rate effect. A preclinical study by Tarbell *et al*. (21) reported a higher radiation-related mortality rate in mice receiving single-fraction TBI at high-dose-rate (80 cGy/min) compared with single-fraction TBI at low-dose-rate (5 cGy/min). Dose-rate effects were not seen with twice-daily or thrice-daily fractionation schedules, suggesting that fractionation was a greater factor in normal organ sparing than dose-rate effects.

The TMI and TMLI using HT, with its potential to reduce short- and long-term toxicities compared with conventional TBI approaches, has the potential to improve outcomes and broaden the scope of how TBI is used. Regimens using standard TBI are difficult to administer to older patients or those with comorbidities, with many centers excluding patients older than 50 years from these regimens. Reduced-intensity chemotherapy-alone regimens, such as fludarabine/melphalan, are better tolerated, but may not provide the needed tumoricidal activity in patients with more aggressive high-risk disease. For this reason, groups have attempted to combine TBI with these reduced-intensity regimens, which has been challenging because of associated toxicities (17). Results from this study show the feasibility of combining TMLI with an established reduced-intensity chemotherapy regimen, with patients older than 60 years tolerating the regimen.

These results also show the feasibility of combining 12-Gy targeted TMLI with high-dose melphalan (140 mg/m^2). A previous randomized Phase III trial showed no advantage and increased toxicity with 8-Gy TBI (2 Gy/d) and melphalan (140 mg/m^2) compared with melphalan alone (200 mg/m^2) in patients with MM (22). Using TMLI now provides an opportunity to reexplore the combination of melphalan and TBI at higher doses with acceptable toxicities.

Attempts to decrease relapse rates and improve outcomes with TMI- or TMLI-containing regimens through dose escalation may now be possible and should be explored in clinical trials. Although the maximum tolerated doses of targeted TBI with HT remains to be defined for each clinical regimen and setting, even modest increases in TBI doses to approximately 15.75 Gy have resulted in statistically significant decreases in relapse rates in patients with AML (6). Selective conformal boost doses to areas of greater tumor burden with simultaneous TMI or conformal dose avoidance to areas previously irradiated may also be possible with this approach.

In summary, TMI/TMLI using HT is feasible and shows promise as a way to deliver TBI with reduced toxicity without compromising dose to areas of greatest tumor burden. Reduced doses to major normal organs were predicted from treatment plans. The acute toxicities observed are consistent with these dose predictions and compare favorably with those seen using standard TBI regimens. Initial results are encouraging and warrant further evaluation in clinical trials as a method to dose escalate with acceptable toxicity and offer TBI-containing regimens to patients unable to tolerate standard approaches. Further evaluation is also needed to better characterize long-term toxicities and to assess the impact this new approach will have on disease control.

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