Phase 1/2 trial of total marrow and lymph node irradiation to augment reduced-intensity transplantation for advanced hematologic malignancies

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This phase 1/2 study assessed the augmentation of reduced-intensity conditioning (RIC) with total marrow and lymph node irradiation (TMLI), for peripheral blood stem cell transplantation, in patients with advanced hematologic disease. The regimen consisted of fludarabine 25 mg/m² per day for 5 days, melphalan 140 mg/m² for one day, and TMLI radiation at 150 cGy/fraction in 8 fractions over 4 days. Eligible patients were over 50 years old and/or had compromised organ function. Median age of the 33 evaluable patients was 55.2 years. Eighteen events of nonhematologic grade III or higher toxicities occurred in 9 patients. Day 30 and day 100 mortalities were 3% and 15%, respectively. Patients achieved myeloid and platelet engraftment at a median of 14 days after transplantation. Long-term toxicities occurred in 2 patients: hypokalemia and tremor, both grade III, on days 370 and 361 after transplantation. Fourteen patients died, 7 of relapse-related causes and 7 of non–relapse-related causes. With a median follow-up for living patients of 14.7 months, 1-year overall survival, event-free survival, and non–relapse-related mortality were 75%, 65%, and 19%, respectively. Addition of TMLI to RIC is feasible and safe and could be offered to patients with advanced hematologic malignancies who might not otherwise be candidates for RIC. (*Blood*. 2011;117(1):309-315)

Introduction

Myeloablative therapy followed by allogeneic hematopoietic cell transplantation (HCT) is a curative treatment modality in patients with advanced hematologic malignancies. Several randomized trials have shown superior outcomes using fractionated total body irradiation (TBI) compared with non–TBI-containing regimens.[1-4] Higher TBI doses are associated with reduced relapse rate; however, outcome was offset by increased toxicity in patients with acute myelogenous leukemia (AML) and chronic myelogenous leukemia.[5-7] In these studies, there was no survival advantage because of TBI-related toxicities with increased risks of organ injury, including pulmonary, cardiac, renal, endocrine, and ophthalmologic damage.[8-12] In addition, TBI has been associated with an increased risk of secondary malignancies.[13-15] The concept of reduced-intensity conditioning (RIC) was developed in an effort to reduce transplantation-related morbidity and mortality in older patients or those with chronic organ failure.[16-19] A large retrospective study in 285 patients showed that long-term survival and disease control can be obtained with HCT after RIC conditioning; however, patients with advanced disease at the time of transplantation do poorly and may require alternate approaches.[20] Attempts to improve outcome by augmenting RIC with TBI at 900 cGy have shown that the regimen, although well tolerated in children, was too toxic in older patients and the study had to be discontinued.[21]

Intensity-modulated radiation therapy has opened a new era in radiation oncology. By delivering therapy from multiple directions using segmented or modulated beamlets, one can design radiation doses to fit the unique shape of the radiation target, optimizing radiation delivery to complex volumes and regions of the body. The Helical Tomotherapy (HT) Hi-Art System (Tomotherapy) is a marriage of spiral computed tomography (CT) and intensity-modulated radiation therapy technology. 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 treatment fan beam is segmented using a 64-leaf collimator. By rapid opening and closing of leaves as a function of gantry angle while the patient slides trough the ring, HT provides unprecedented ability to "sculpt" radiation doses to large complex-shaped target regions up to 150 to 160 cm in length while simultaneously reducing doses to normal organs.[22] Recently, we reported on the concept of HT to deliver a more targeted conformal TBI. In these studies, we investigated the use of HT as a more targeted form of delivery of total marrow and lymph node irradiation (TMLI) to allow for escalation of the dose-intensity with acceptable toxicity and for the potential to improve outcomes.[23-25] We report our clinical experience in the use of RIC with TMLI in patients undergoing HCT for advanced hematologic malignancies. The feasibility, toxicity, potential advantages, and challenges of this approach are discussed.

Methods

Eligibility criteria

This prospective pilot study accrued patients from July 2006 to March 2009 and was approved by the City of Hope Institutional Review Board. The protocol used an RIC regimen consisting of fludarabine (FLU) and melphalan (MEL) augmented by TMLI. All patients provided written informed consent before enrollment according to the Declaration of Helsinki.

The study was designed to determine the toxicity and feasibility of TMLI at 1200 cGy with FLU and MEL. Eligible patients were required to

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be greater than 50 years of age or have evidence of chronic organ failure, rendering them ineligible for myeloablative conditioning regimens. Eight patients (40%) in this cohort were previously reported,[24] with a shorter follow-up. Patients were eligible if diagnosed with AML, myelodysplastic syndrome with intermediate- or high-risk disease, granulocytic sarcoma (chloroma) with or without bone marrow involvement, mixed lineage leukemia, acute lymphoblastic leukemia, non-Hodgkin lymphoma, or multiple myeloma. Patients with advanced disease status were eligible if marrow blasts were less than 10% or if they showed a 50% or greater decrease in the marrow blast percentage, with no circulating blasts compared with the most recent marrow evaluation. The protocol required that patients have the ability to lie supine in a full body cast for approximately 30 minutes, the anticipated duration of each treatment session.

Patients were excluded if diagnosed with acute undifferentiated leukemia (ie, no lymphoid or myeloid markers, Fanconi anemia, major medical, or psychiatric disorders that would seriously compromise patient tolerance of this regimen): HIV infection, evidence of hepatitis B or C infection, evidence of cirrhosis, or uncontrolled or recent viral, bacterial, or fungal infection. Patients with a history of previous radiation therapy to more than 20% of bone marrow-containing areas or to any area exceeding 2000 cGy were excluded from this study.

Transplantations occurred between August 2006 and May 2009. Patients received transplantations from human leukocyte antigen (HLA)-compatible related donors or unrelated donors, matched for HLA-A, -B, and -DRB1 by high-resolution molecular methods. Grafts were depleted of erythrocytes as indicated for ABO incompatibility, but no patient received a T cell-depleted transplantation.

Preparative regimen

The conditioning regimen consisted of FLU 25 mg/m^2 for 5 days, MEL 140 mg/m^2 for 1 day. TMLI was delivered by HT over 4 consecutive days (day −7 to day −4) at 1.5 Gy per fraction, delivering 2 fractions per day with a minimum of 6 hours between fractions. All fields were treated with each fraction.

Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and sirolimus, except for one patient who received cyclosporine and methotrexate. For both tacrolimus and sirolimus, doses were adjusted to maintain blood levels of 5 to 10 ng/dL during the first 30 days after transplantation. Both were tapered as indicated depending on donor type, presence or absence of GVHD, and degree of donor cell chimerism.

TMLI

Details of the technique have been published previously.[24,25] Briefly, patients were initially scanned for treatment planning purposes on a large-bore (85-cm) CT simulator with 60-cm field of view (Philips Medical System). The CT scans 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 (95% CIVCO Medical Systems) 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). 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 gross target volume was defined as skeletal bone, major lymph node chains, and spleen. The mandible and maxillary bones were excluded from the gross target volume in an effort to minimize oral cavity dose and mucositis. Digital imaging and communications in medicine-radiation therapy images were transferred to the Hi-Art tomotherapy treatment planning system (Tomotherapy). Plans were designed such that a minimum of 85% of the gross target volume received the prescribed dose.[25]

Our current procedure involves initial laser alignment of the patient in a Vac-lok bag and thermoplastic mask. A megavoltage CT scan is obtained with fusion to the planning kilovoltage CT. The necessary couch shifts are then made, followed by initiation of treatment. A slice thickness of 2.5 to 5.0 cm, pitch of 0.3 to 0.45, and modulation factor of 2.5 to 3.0 were used for treatment, resulting in a beam-on time of approximately 25 to 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 fields given the lack of sensitive organs in this area in the adult population. At the time of treatment planning, a radio-opaque marker was placed in the thigh region to define the lower border (50% isodose line) of the HT plane. The anteroposterior-posteroanterior fields were gapped to this border at mid-plane.

Peripheral blood stem cell procurement

All patients received granulocyte colony-stimulating factor-mobilized peripheral blood hematopoietic progenitor cells. Cells were procured using standard mobilization protocols and leukopheresis techniques. All donors provided written informed consent. Peripheral blood hematopoietic progenitor cells procured from unrelated donors were obtained through the National Marrow Donor Program according to standard procedures. All unrelated donors provided informed consent at the donor center, as required by the National Marrow Donor Program.

Supportive care

Infection prophylaxis during transplantation therapy consisted of the standard operating procedures at the City of Hope: ceftazidime and cefazolin for first fever, low-dose amphotericin B lipid complex or micafungin for prevention of fungal infection, and acyclovir. Cytomegalovirus was screened twice weekly by quantitative polymerase chain reaction methods and cultures with preemptive use of ganciclovir or foscarnet in the event of a positive assay. Blood product transfusions were irradiated and filtered to remove leukocytes. After recovery of the neutrophil count to more than 1.0×10^9/L blood, patients received prophylaxis against *Pneumocystis jirovecii* infection using trimethoprim-sulfamethoxazole given orally twice weekly, dapsone, or atovaquone.

Engraftment and chimerism

Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count more than 0.5×10^9/L. Platelet engraftment was defined as the first of 7 consecutive days that the platelet count exceeded 20×10^9/L without transfusion support. Chimerism analysis was performed on day 30 after transplantation. Chimerism was monitored using short tandem repeat polymorphism and G-banding, or fluorescence in situ hybridization studies in sex-mismatched cases for Y chromosome.

Statistical methods

The primary endpoint was the treatment feasibility in terms of toxicity of TMLI using HT in combination with FLU/MEL followed by allogeneic HCT. The goal was to evaluate the treatment for its anticancer effects and short-term toxicities. The secondary endpoints were the incidences of neutrophil and platelet engraftment, relapse, and acute and chronic transplantation-related complications, including acute GVHD (aGVHD) and chronic GVHD (cGVHD) and secondary malignancies, as well as the 100-day, 1-year, and 2-year overall survival (OS) and event-free survival (EFS). Descriptive statistics were used to summarize most data outcomes, including demographic and clinical characteristics, observed toxicities, transplantation engraftment parameters, and clinical and survival outcomes. The type and grade of toxicities during therapy were tabulated using the Bearman and National Cancer Institute Common Toxicity Criteria (NCI CTC) scales. OS and other survival endpoints without competing risk were estimated using Kaplan-Meier curves and described as proportions and 95% confidence intervals (95% CIs) based on Greenwood variance. Event-free survival, nonrelapse mortality (NRM) time to relapse, and other survival outcomes with competing risks are estimated using the cumulative incidence estimator and tested with the Gray k-sample test.[26] Binary outcomes, such as engraftment and relapse events, are quantified using proportions with 95% CIs. Numerical outcomes, such as timing of neutrophil engraftment, patient and donor characteristics, and laboratory parameters, are quantified using mean, SD, or median and range when appropriate, and tested with Student *t* tests or Wilcoxon rank-sum tests.

Table 1. Patient characteristics

Characteristic	No. (%)
Age at transplantation, y	
Median (range)	55.2 (12.2-68.4)
< 50	11 (33)
≥ 50	22 (67)
Sex	
Male	14 (42)
Female	19 (58)
Diagnosis/disease status	
NHL	
1RL	2 (6)
2RL	1 (3)
IF	1 (3)
MM	
PR	2 (6)
PD	1 (3)
CMML	1 (3)
ALL	
1CR	2 (6)
2CR	1 (3)
AML	
1CR	7 (21)
2CR	2 (6)
1RL	3 (0)
3RL	1 (3)
IF	6 (18)
CML	
2CP	1 (3)
CMLt	1 (3)
MDS	
RARS	1 (3)
Prior BMT	
Auto	1 (3)
MUD	2 (6)
Race	
White	29 (88)
Black	3 (9)
Asian	1 (3)
Donor type	
Matched related	13 (39)
Mismatched related	3 (9)
Matched unrelated	15 (46)
Mismatched unrelated	2 (6)

NHL indicates non-Hodgkin lymphoma; MM, multiple myeloma; CMML, chronic myelomonocytic leukemia; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; CMLt, CML in transformation; MDS, myelodysplastic syndrome; Auto, autologous; MUD, matched unrelated donor; CR, complete remission; CP, chronic phase; IF, induction failure; PD, progressive disease; PR, partial response; and RARS, refractory anemia with ring sideroblasts.

Results

Patient characteristics

Thirty-three patients with a median age at HCT of 55.2 years (range, 12.2-68.4 years) met eligibility criteria and were enrolled in the study for allogeneic HCT after a conditioning regimen of FLU/MEL with TMLI, using HT. The diagnoses were: AML (n = 19), acute lymphoblastic leukemia (n = 3), non-Hodgkin lymphoma (n = 4), multiple myeloma (n = 3), chronic myeloid leukemia (n = 2), chronic myelomonocytic leukemia (n = 1), and myelodysplastic leukemia (n = 1). Three patients had prior transplantations (auto/auto tandem, n = 1; matched unrelated donor, n = 1; matched related donor, n = 1). Twenty-two patients (67%) were considered at very high risk for relapse (induction failure, n = 7; first relapse, n = 5; second CR, who entered remission after multiple attempts of reinduction, n = 4; second or third relapse, n = 2; progressive disease, n = 1; chronic myelomonocytic leukemia and chronic myelogenous leukemia in second chronic phase or in transformation, n = 2; refractory anemia with ringed sideroblasts, n = 1). Mobilized peripheral blood stem cells were collected from HLA-identical siblings (n = 13), mismatched related donors (n = 3), matched unrelated donors (n = 15), or partially matched unrelated donors (n = 2). Median follow-up was 13.1 months (range, 0.8-35.4 months) in all 33 patients, 10.9 months (range, 0.8-31.9 months) in the 14 deceased, and 14.7 months (range, 6.1-35.4 months) in the 19 surviving patients. Patient demographics, diagnosis, disease status, and treatment characteristics are detailed in Table 1.

TMLI radiation therapy

Isodose distributions are shown in Figure 1 for a typical patient. Table 2 shows the mean and range of D50 (median dose) for each of the major organs for the 33 patients reported in this study. The D50 dose is the dose that no more than 50% of the organ receives. D50 doses compare favorably with those seen with standard TBI. For example, D50 dose to lung in a patient treated with standard TBI using 50% transmission lung blocks is typically 8 to 9 Gy, which is higher than the 5.8 Gy seen in this study.[23,24]

Toxicity

Toxicities were recorded using both the Bearman Regimen-Related Toxicities Scale (for nonhematologic events)[27] and the NCI CTC scale. Results of toxicities according to the Bearman scale are summarized in Table 3. Twenty-eight instances of grade II Bearman toxicities occurred in 22 patients, and 17 of 28 of these events were mucositis. Eighteen instances of grade III toxicities occurred in 9 patients and there were no grade IV, lethal, regimen-related toxicities. In an effort to focus on potential toxicities related to the addition of TMLI, we also reviewed the risk of mucositis using the NCI CTC scale. The combination of TMLI with FLU/MEL was associated with severe, grade 3 or 4 mucositis (NCI CTC scale) in 30 of 33 patients (91%). No intubation was required for any patient,

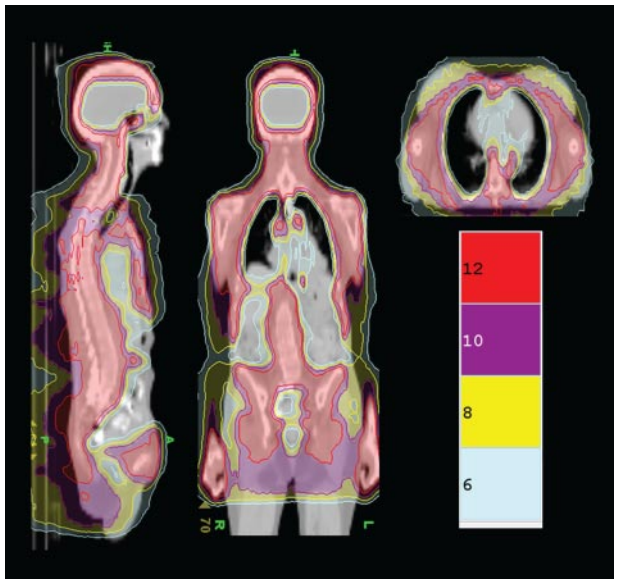

Figure 1. TMLI isodose distribution shows the colorwash isodose distribution of a patient receiving 12 Gy TMLI. Representative sagittal, coronal, and axial planes. Isodose distributions for 12, 10, 8, and 6 Gy are shown.

Table 2. Median (D50) organ doses (Gy)

Organ	Mean (range)
Lens	2.4 (1.3-3.1)
Oral cavity	3.0 (2.3-4.2)
Stomach	4.5 (3.6-6.4)
Esophagus	4.8 (3.2-6.1)
Small intestine	5.0 (3.7-6.3)
Rectum	5.2 (3.8-7.7)
Parotids	5.7 (4.0-9.0)
Eyes	5.8 (3.4-7.2)
Lungs	5.8 (4.9-6.8)
Thyroid	6.2 (3.8-10.0)
Heart	6.6 (5.4-8.1)
Optic nerve	6.7 (5.0-9.2)
Brain	6.8 (4.1-12.1)
Kidneys	6.8 (5.0-8.1)
Liver	7.4 (6.8-8.2)
Ovary	7.4 (5.1-9.7)
Testis	7.5 (5.0-13.0)
Bladder	9.1 (7.1-11.8)
Breasts	9.8 (8.3-11.0)

and no lethalities resulted. By the Bearman scale, there were only 17 instances of grade II mucositis, and no mucositis events of grade III or higher.

Five patients died before day 100: one of disease progression, 2 of invasive pulmonary fungal infection, one of cytomegalovirus with diffuse alveolar hemorrhage, and one of respiratory failure secondary to viral infection. Transplantation-related toxicities are shown in Table 4. Late toxicities were those not related to the primary disease or to GVHD, documented after day 100 after transplantation. Two such events were reported in 2 patients: hypokalemia (day 370 after bone marrow transplantation) and tremor (day 361 after bone marrow transplantation). Other late severe adverse effects were related to either disease progression or development of severe chronic GVHD.

Engraftment and chimerism

All 33 patients achieved a neutrophil recovery of more than 0.5×10^9/L in a median of 14 days (range, 9-20 days). Thirty patients achieved platelet transfusion independence at a median of 14 days (range, 10-83 days); 3 patients had relapses or died before achieving this endpoint. Thirty-two patients had chimerism studies using short-tandem repeat techniques, and the median percentage of donor cells at the time of first posttransplantation bone marrow examination ($\sim$ 30 days after stem cell transplantation) was 100% (range, 94%-100%). One patient with adequate recovery of his counts experienced acute respiratory failure before he could be evaluated for chimerism. The time to myeloid and platelet engraftment is shown in Table 4.

Table 4. Summary of transplantation outcomes (n = 33)

Outcome	Value
Engraftment (range)	
Time to ANC > 500/μL, d	14 (9-20)
Time to platelet > 20 000, d	14 (10-83)
Acute GVHD	
Grade 0	7 (21%)
Grade I	8 (24%)
Grade II	9 (27%)
Grade III	6 (18%)
Grade IV	3 (9%)
GVHD time to onset, d (range)	
Acute > grade II	14.5 (9-69)
Chronic	190 (101-341)
Relapse cummulative incidence (1-y), % (95% CI)	16% (7%-33%)
Survival (1-y), % (95% CI)	
Overall	75% (56%-87%)
Event-free	65% (46%-79%)
Causes of death, n (%)	
Respiratory failure	1 (7%)
Chronic GVHD	1 (7%)
Infection	3 (21%)
Multiorgan failure	2 (14%)
Relapse/disease progression	7 (50%)
Day 100 nonrelapse cause, n (%)	
Infection	2 (50%)
ARDS/diffuse alveolar hemorrhage	1 (25%)
Multiorgan failure	1 (25%)

ANC indicates absolute neutrophil count; and ARDS, acute respiratory distress syndrome.

aGVHD and cGVHD

The cumulative incidence of aGVHD $\leq$ grade II was 55% (n = 18; 95% CI, 36%-72%), with a median time to onset of 14.5 days (range, 9-69 days). Nine patients had grade III-IV aGVHD for a probability of 27% (95% CI, 13%-46%). The risk for developing aGVHD was related, as expected, to the source of stem cells. Patients receiving unrelated donor transplantations had higher risk for aGVHD $\leq$ grade II, with odds ratio of 5.25 (95% CI, 1.15-23.9, $P = .03$) compared with transplantations from HLA-identical siblings. Results for grades III-IV were not significant (odds ratio = 2.96; 95% CI, 0.51-17.3, $P = .22$). cGVHD was documented in 13 of 28 patients surviving beyond 100 days, with a

Table 3. Nonhematologic toxicities by day 100

	Patients with an event (n = 30)		
Adverse event	Grade II, no. (%) of events	Grade III, no. (%) of events	Grade IV, no. (%) of events
CNS toxicity/confusion	4 (12)	3 (9)	0
Pulmonary	0	5 (15)	0
Gastrointestinal	1 (3)	3 (9)	0
Renal failure	0	3 (9)	0
Bladder toxicity	1 (3)	2 (6)	0
Hepatic	3 (9)	1 (3)	0
Cardiac	2 (6)	1 (3)	0
Mucositis (Bearman)	17 (52)	0	0

All reported toxicities are based on the Bearman scale.[27]
CNS indicates central nervous system.

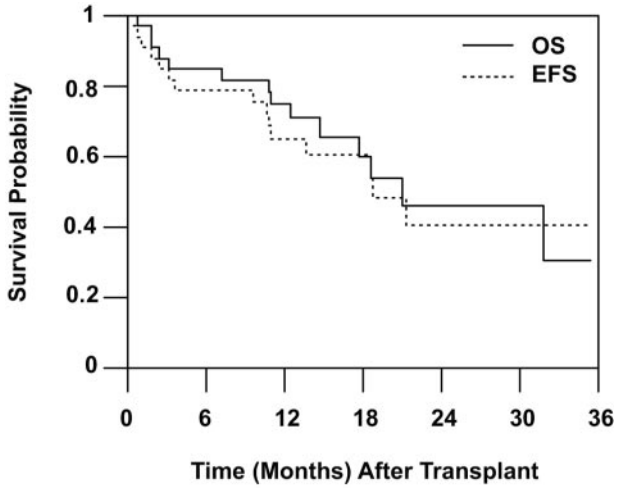

Figure 2. Survival outcome curves show OS (solid line) and EFS (hyphenated line) in months, calculated as Kaplan-Meier estimates.

cumulative incidence of 46%. Twelve patients had extensive disease. Median time to development of cGVHD was 190 days (range, 101-341 days). None of the non–relapse-related deaths was attributed to complications of aGVHD. One patient died of complications of cGVHD on day 566 after transplantation. The immediate cause of death in this patient was respiratory distress because of invasive pulmonary aspergillosis and nocardia cerebritis secondary to immunosuppressive therapy.

Response, relapse, and OS

With a median follow-up of 14.7 months (range, 6.2-35.4 months), OS and EFS are shown in Figure 2. One-year OS and EFS were 75% (95% CI, 56%-87%) and 65% (95% CI, 46%-79%), respectively, whereas at 2 years OS was estimated at 46% (95% CI, 23%-66%) and EFS at 40% (95% CI, 19%-61%). We examined early mortality as a possible surrogate of toxicity. The day 30 and day 100 mortalities were 3% (1 of 33) and 15% (5 of 33), respectively, within the expected range of allogeneic HCT. Seven patients died of non–relapse-related causes, 4 before day 100; 2 of respiratory complications of viral infections, and 2 of multiorgan failure. Three patients died with complications of GVHD: one with acute (on day 97) and 2 with chronic (on days 328 and 566, respectively). Figure 3 shows the cumulative incidence of NRM and of relapse, calculated as competing risks. NRM at 100 days was 0.12 with rates of 0.19 at 1 year and at 0.25 at 2 years. Seven patients (21%) died of progressive disease. The cumulative incidence of relapse was 0.06 at 100 days, 0.16 at 1 year, and 0.35 at 2 years.

The standard-risk group included 9 patients in first complete remission (CR) and 2 with multiple myeloma in partial remission. The higher-risk group included patients with relapsed disease, transplantation in second CR, induction failure, or myelodysplastic syndrome with leukemic transformation (n = 22). The median patient age in the standard-risk group was 46.7 years (range, 12.2-61.0 years), and in the higher-risk group was 57.8 (range, 30.0-68.4 years). Using the Wilcoxon rank-sum test, younger age was associated with standard-risk disease ($P = .04$), reflecting poor organ function as a major reason for enrollment of younger patients to the study. The 1-year EFS was 52% (95% CI, 20%-77%) and 72% (95% CI, 48%-86%) ($P = .18$, log-rank test), respectively, for low-risk patients (7 of 11 events) and for high-risk patients (8 of 15 events) at transplantation. The cumulative relapse risk at 1 year was 0.16 (95% CI, 0.07-0.33), representing relapse rates of 0.09 (95% CI, 0.02-0.32) in the high-risk and 0.29 (95% CI, 0.09-0.63) in the standard-risk groups (Gray test, $P = .07$). No significant differences were seen between the risk groups for OS, EFS, relapse incidence, or NRM.

Discussion

Myeloablative chemotherapy followed by allogeneic HCT is one of the most important strategies to improve long-term survival in patients with hematologic malignancies. Retrospective results of allogeneic HCT, as reflected in reports by the International Bone Marrow Transplant Registry, show improved EFS compared with standard chemotherapy and/or autologous HCT.[28-31] TBI has been the cornerstone for high-dose, myeloablative preparative regimens administered together with cyclophosphamide or other chemotherapy.[32-35] The long-term complications of TBI are well documented, with pulmonary fibrosis, cardiac toxicity, renal failure, cataracts, gonadal failure, and hypothyroidism occurring in substantial numbers of patients.[8-12,36] In addition, an increased risk of secondary malignancies has been documented with the use of TBI.[13-15] RIC regimens were developed in an attempt to expand the curative potential of HCT to patients who are not eligible for a fully myeloablative regimen, such as elderly patients and those with compromised organ function. The use of relatively nontoxic, reduced-intensity preparative regimens allows engraftment and the generation of graft-versus-malignancy effects, potentially curative for susceptible malignancies while reducing the risk of treatment-related morbidity. The most commonly used strategy consists of an immunosuppressive chemotherapeutic drug, usually a purine analog, such as FLU in combination with an alkylating agent.[16-19] Multiple reports have demonstrated that long-term survival and disease control can be obtained with HCT after RIC; however, patients with advanced disease at the time of transplantation show little benefit from RIC and may require alternate approaches.[20,37] The significant reduction in intensity of the treatment by RIC may have a negative impact on long-term leukemic control.[16,37-41] In attempts to improve outcomes, reduced radiation doses of TBI have been added to RIC regimens. Petropoulos et al[21] reported the addition of 900 cGy TBI to standard FLU/MEL in 29 pediatric patients. The study showed that the regimen was well tolerated in

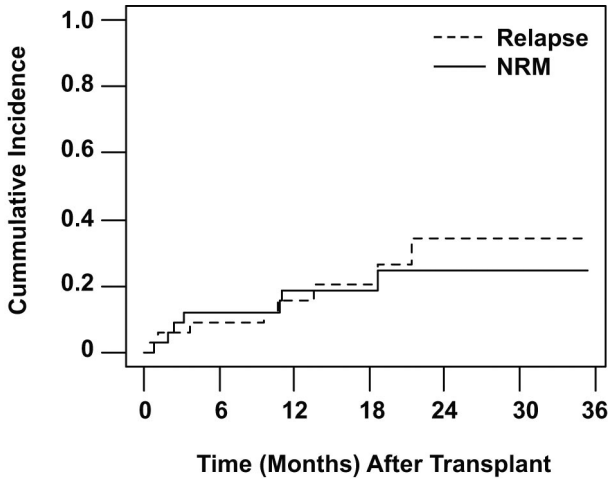

Figure 3. Cumulative incidence of NRM and relapse as competing risks shows both cumulative incidence of relapse (hyphenated line) and NRM (solid line).

Table 5. Transplantation-related toxicity and mortality comparison

Reference	No. of patients in study	Deaths, n (%)	Stomatitis, n (%)	Gut, n (%)	Hepatic, n (%)	Pulmonary, n (%)	Cardiac, n (%)	Renal, n (%)	1-year NRM, %
Giralt (2001)[16]	78	3 (4)	0	0	5 (6)	5 (6)	2 (3)	7 (9)	44.7*
Giralt (2002)[49]	22	1 (5)	0	0	1 (5)	1 (5)	1 (5)	1 (5)	40 ± 10
Ritchie (2003)[45]	39	4 (10)	2 (5)	0	2 (5)	4 (10)	1 (3)	3 (8)	30 ± 7
de Lima (2004)[44]	62	6 (10)	1 (2)	4 (6)	1 (2)	9 (14)	4 (6)	3 (5)	30
Current study	33	0	0	3 (10)	1 (3)	5 (15)	1 (3)	3 (10)	19 ± 7

All toxicities listed use the Bearman scale[27] and show grade III and IV (lethal) toxicities before day 100. Studies listed used FLU/MEL conditioning regimens. n = number of events of each toxicity; and % = n divided by the number of patients on the study multiplied by 100.

*For Giralt (2001),[16] NRM not given at 1 year. At 2 years, 44.7%; at 100 days, 37.4%.

children with advanced hematologic malignancies. In the past, similar attempts to combine reduced RIC with TBI in adults failed because of increased transplantation-related mortality.[42]

The recent technologic advances in the delivery of external beam radiotherapy allow the potential for irradiating the marrow and lymphatic systems, the organ targets of TBI, while avoiding unnecessary irradiation to other organs. The HT integrates CT image-guided radiotherapy and intensity-modulated radiation therapy in a single device, in which a 6-mV linear accelerator is mounted on a CT ring gantry that rotates around the patient, who moves through the ring. The field is shaped by a binary multileaf collimator and has a maximum possible target size of approximately 60 cm wide by 160 cm long, allowing delivery of highly conforming dose distributions to large complex target shapes while simultaneously reducing dose to critical normal organs.[43] TMLI is therefore well suited for the delivery of conformal targeted radiation to the marrow and lymphatic systems[24] before HCT.

This study confirms the feasibility of augmentation of the standard FLU/MEL RIC therapy by addition of TMLI, with the goal of achieving improved antileukemic effect without substantial increases in nonrelapse morbidity and NRM. For both of these goals, the results are promising and warrant further investigation. The relapse-free outcomes for this population were comparable between patients in remission and those with advanced disease. Our results for patients with advanced disease state were improved compared with previously published reports, which show poor outcomes in patients with advanced disease.[16-18,44] Notably, the addition of TMLI to FLU/MEL does not appear to increase toxicity over that seen with FLU/MEL conditioning regimen alone, based on previous results from our institution as well as those reported by other centers.[16-18,37,39-41,44] Two patients (6%) died of multiorgan failure, a rate similar to those reported in clinical trials using MEL/FLU without radiation.[18,45-47] Although previous studies have demonstrated a maximal tolerated irradiation dose of 900 cGy in children only, the patients reported here appeared to tolerate TMLI well at 1200 cGy, with the maximal tolerated dose still to be explored. The 2-year NRM of 25% in our report is well within the range of 13% to 40% reported in the literature.[16,41,45,48,49] In a prospective study investigating the toxicity profile of FLU/MEL, Van Besien et al have shown that the most common nonhematologic toxicities were mucositis, pulmonary and renal.[47] Fatal, nonhematologic toxicities included hepatic (n = 2), pulmonary (n = 2), and cardiac, renal, and mucosal (n = 1 each).[47] The toxicity profile in patients undergoing HCT with FLU/MEL/TMLI was similar to those reported by other transplantation studies using FLU/MEL that reported toxicity using the Bearman scale, as shown in Table 5. Pulmonary toxicity in our study was on the higher end of published data: 15% as opposed to 14%, 10%, 6%, and 5% in the other groups. In our population, however, there were no lethal toxicities and the 1-year NRM was notably higher.

This report demonstrates that there no increase in toxicity resulted from the addition of TMLI to FLU/MEL in a patient population in which 72% of patients had advanced disease status. Whereas the short-term outcome of adding TMLI to FLU/MEL appears to be promising compared with previous reports,[20] a longer interval of follow-up is necessary to evaluate long-term impact with respect to toxicity, EFS, and OS. This phase 1/2 study lays the foundation for further investigations to explore the potential benefit of augmenting reduced-intensity regimens with TMLI to give patients with advanced hematologic disease access to lower-toxicity transplantations. We have already begun the next step, focusing on acute lymphoblastic leukemia and AML in a study with a targeted enrollment of 100 patients who will be compared with case-matched historical controls.

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Authorship

Contribution: J.R., J.W., A.S., and S.F. conceived and designed the study; D.H., H.N., J.R., and S.F. provided administrative, technical, or logistic support; D.H., H.N., and J.R. collected and assembly the data; A.D., D.Q., J.W., A.S., S.H.T., and J.R. analyzed and interpreted the data; and J.R., J.W., A.S., and S.H.T. drafted the article.

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