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Phase I Trial of Total Marrow and Lymphoid Irradiation Transplantation Conditioning in Patients with Relapsed/Refractory Acute Leukemia

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Current conditioning regimens provide insufficient disease control in relapsed/refractory acute leukemia patients undergoing hematopoietic stem cell transplantation (HSCT) with active disease. Intensification of chemotherapy and/or total body irradiation (TBI) is not feasible because of excessive toxicity. Total marrow and lymphoid irradiation (TMLI) allows for precise delivery and increased intensity treatment via sculpting radiation to sites with high disease burden or high risk for disease involvement, while sparing normal tissue. We conducted a phase I trial in 51 patients (age range, 16 to 57 years) with relapsed/refractory acute leukemia undergoing HSCT (matched related, matched unrelated, or 1-allele mismatched unrelated) with active disease, combining escalating doses of TMLI (range, 1200 to 2000 cGy) with cyclophosphamide (CY) and etoposide (VP16). The maximum tolerated dose was declared at 2000 cGy, as TMLI simulation studies indicated that >2000 cGy might deliver doses toxic for normal organs at or exceeding those delivered by standard TBI. The post-transplantation nonrelapse mortality (NRM) rate was only 3.9% (95% confidence interval [CI], .7 to 12.0) at day +100 and 8.1% (95% CI, 2.5 to 18.0) at 1 year. The cumulative incidence of grades II to IV acute graft-versus-host disease (GVHD) was 43.1% (95% CI, 29.2 to 56.3) and for grade III and IV, it was 13.7% (95% CI, 6.9 to 27.3). The day +30 complete remission rate for all patients was 88% and was 100% for those treated at 2000 cGy. The overall 1-year survival was 55.5% (95% CI, 40.7 to 68.1). The TMLI/CY/VP16 conditioning regimen is well tolerated at TMLI doses up to 2000 cGy with a low 100-day and 1-year NRM rate and no increased risk of GVHD with higher doses of radiation.

INTRODUCTION

Acute leukemia patients who fail induction therapy or relapse after achievement of first complete remission (CR) require allogeneic (allo) hematopoietic stem cell transplantation (HSCT) as the primary curative option. Standard myeloablative alloHSCT regimens use high-dose chemotherapy, frequently in combination with total body irradiation (TBI), but provide insufficient disease control for patients who undergo alloHSCT with active disease, with a 3-year overall survival (OS) of only 19% for acute myeloid leukemia (AML) and 16% for acute lymphoblastic leukemia (ALL) [1].

Increasing the TBI dose has the potential to decrease the post-transplantation relapse rate, as demonstrated in a randomized trial comparing 1200 cGy versus 1575 cGy in AML

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Table 1
Dose Levels for Dose Escalation of TMLI in TMLI/CY/VP16 alloHSCT Conditioning Regimen

Level	No. of Patients	Fraction and Schedule	Total Dose
1	3	150 cGy bid x days 1-4	1200 cGy
2	3	150 cGy bid day 1-4,150 cGy qd 5	1350 cGy
3	9	150 cGy bid days 1-5	1500 cGy (ribs, sternum, liver, brain limited to 1200cGy)
4	6	150 cGy bid days 1-5	1500 cGy (liver, porta hepatis, brain limited to 1200cGy)
5	6	160 cGy bid days 1-5	1600 cGy (liver, porta hepatis, brain limited to 1200cGy)
6	6	170 cGy bid days 1-5	1700 cGy (liver, porta hepatis, brain limited to 1200cGy)
7	6	180 cGy bid days 1-5	1800 cGy (liver, porta hepatis, brain limited to 1200cGy)
8	6	190 cGy bid days 1-5	1900 cGy (liver, porta hepatis, brain limited to 1200cGy)
9	6	200 cGy bid days 1-5	2000 cGy (liver, porta hepatis, brain limited to 1200cGy)

Bid indicates twice daily.

patients in first CR with a 3-year relapse rate of 35% versus 12% [2]; however, disease-free survival (DFS) was similar in the 2 arms because of the increased mortality from toxicity and/or graft-versus-host disease (GVHD) in patients treated on the higher dose arm. Furthermore, in a retrospective study [3], the relapse rate was improved for patients with AML and chronic myelogenous leukemia treated with TBI doses >990 cGy. In a Center for International Blood and Marrow Transplant Research study, Marks et al. reported that patients with ALL beyond first CR receiving TBI/cyclophosphamide (CY) conditioning regimens had a lower relapse rate and increased DFS if treated with a TBI dose >1300 cGy [4]. Kal et al. compared results of different TBI regimens [5] and showed that TBI regimens with higher biologically effective doses were associated with lower relapse rates and improved DFS and OS. Biologically effective doses was used as an endpoint to normalize regimens for differences in dose per fraction, number of fractions, and dose rates.

Despite the evidence of a dose-dependent antileukemia activity of TBI, more intense dosing is difficult to deliver to high-risk patients because of significant increases in toxicities and long-term morbidities, which eventually offset any potential clinical advantage [2,6-12]. As a result and despite the potential for disease control from higher doses of radiation, patients with comorbid conditions, older than 50 years, or with disease refractory to salvage chemotherapy are often ineligible for TBI-containing regimens.

Targeted forms of TBI delivery such as total marrow and lymphoid irradiation (TMLI) that selectively target diseased tissue while sparing healthy tissue are being pursued with the goal to reduce radiation-associated side effects and maximize the radiation therapeutic index [13-17]. TMLI as part of alloHSCT conditioning regimens may make radiotherapy-containing regimens available to a broader spectrum of patients and allow safe dose intensification with curative intent for patients undergoing treatment with active disease [14-16]. We report here a novel high-intensity alloHSCT conditioning regimen combining TMLI with CY and etoposide (VP16) for patients with acute leukemia who are treatment refractory or beyond second remission and, therefore, undergoing transplantation with active disease. In a phase I dose-escalation trial, we demonstrated that the TMLI/CY/VP16 conditioning regimen for alloHSCT is feasible, well tolerated at TMLI-targeted doses of up to 2000 cGy, and provides encouraging antileukemic activity.

METHODS

This phase I clinical trial was registered with clinicaltrials.gov (NCT00576979, NCT02094794) and approved by the City of Hope institutional review board. An assurance was filed with and approved by the Department of Health and Human Services. Informed consent was obtained for all study participants in compliance with the Declaration of Helsinki.

Eligibility Criteria

Between February 2008 and October 2014, 51 eligible adult patients ages <60 years with relapsed/refractory AML or ALL and resistant to salvage conventional chemotherapy regimens were accrued on this trial. All patients had active disease at start of transplantation preparative treatment. Stem cell donors were either HLA-identical (siblings or unrelated) or 9/10 allele–matched unrelated donors. The number of patients accrued to each dose level (DL) is indicated in Table 1; patient and disease characteristics are shown in Table 2.

TMLI

Details of the technique have been previously published [13]. Briefly, all patients receiving TMLI underwent computed tomography simulation and were treated on a TomoTherapy system (Accuray, Sunnyvale, CA). For treat-

Table 2
Patient and Disease Characteristics

Variable	Value
Age at HSCT, median (range), yr	34 (16-57)
Disease diagnosis	
AML	33
ALL Ph-	14
ALL Ph+	2
Biphenotypic	1
Undifferentiated	1
Disease status at time of alloHSCT	
1 RL	14
2 RL	3
IF	34
Cytogenetic risk (SWOG criteria), AML	
Favorable	0
Intermediate	19
Unfavorable	14
Cytogenetic risk (SWOG criteria), ALL	
Favorable	1
Intermediate	7
Unfavorable	5
Unknown significance	3
Risk score, median (range)*	3 (0-6)
KPS at HSCT, median (range)	80 (60-100)
Donor source	
Sibling	25
HLA matched unrelated	5
Mismatched (1 allele) unrelated	21
WBC at HSCT, median (range)	1.4 (.1-14.9)
Blasts in blood at HSCT†, median (range), %	5 (0-85)
Blasts in marrow at HSCT†, median (range), %	52 (5-98)
Extramedullary disease at time of HSCT	9

Data presented are n (%) unless otherwise indicated.
Ph indicates Philadelphia chromosome; RL, relapse; IF, induction failure; SWOG, Southwest Oncology Group; KPS, Karnofsky performance status.
* Scoring based on criteria by Duval et al [1].
† Excludes patients with solely extramedullary disease (blasts in BM < 5%), n = 4.

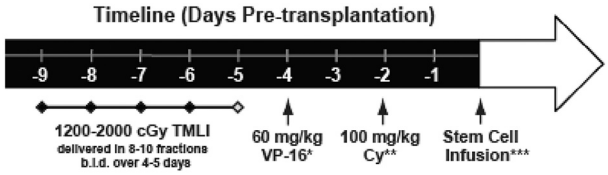

Figure 1. Treatment schema. TMLI was delivered in 8 to 10 fractions b.i.d. over 4 to 5 days with total targeted dose ranging from 1200 to 2000 cGy. VP16 indicates etoposide; CY, cyclophosphamide. *Adjusted body weight, **Ideal body weight, ***A window of 1 to 2 days is allowed for stem cell availability. Interval between CY and stem cell infusion must be >48 hours.

ment planning purposes, the target regions identified included the bone and bone marrow (BM), major lymph node chains, spleen, testes, liver, and brain. Mesenteric and Waldeyer Ring lymph nodes, as well as the mandible, were excluded as target regions to minimize dose to the oral cavity and gastrointestinal tract. All other organs (such as lungs, heart, small and large intestine, kidneys, eyes, lenses, oral cavity, bladder, parotid glands, stomach, and esophagus) were identified as organs at risk (OARs), and efforts were made to minimize dose to these organs.

Preparative Regimen and GVHD Prophylaxis

All patients underwent BM or peripheral blood stem cell alloHSCT with a conditioning regimen that combined escalating doses of TMLI with VP16 (60 mg/kg) and CY (100 mg/kg) (see Figure 1 for treatment schema). Eight to 10 planned doses of TMLI, ranging from 1200 to 2000 cGy, were administered in twice-daily fractions over 4 or 5 days (Table 1). BM, major lymph node chains (excluding mesenteric lymph nodes and Waldeyer ring), and testes were escalated up to 2000 cGy with liver, porta hepatis, and brain kept at 1200 cGy (Table 1). Palifermin was administered to reduce the risk of mucositis [18]. GVHD prophylaxis consisted of tacrolimus and sirolimus [19]. No post-transplantation maintenance therapy was part of the planned therapy.

Study Design and Statistical Analysis

This single-institution phase I trial tested escalating doses of TMLI in a TMLI/CY/VP16 alloHSCT conditioning regimen. The primary objectives were to establish the maximum tolerated dose (MTD) of TMLI in this regimen and to describe the toxicities at each DL. Secondary objectives included estimation of nonrelapse mortality (NRM), CR rate, OS, and an assessment of radiation dose to target and off-target organs.

Dose-limiting toxicity (DLT) was defined as any grade 3 or 4 nonhematological toxicity per the modified Bearman scale. *Hematologic DLT* was defined as grade 4 neutropenia associated with fever or infection lasting beyond 3 weeks or grade 4 neutropenia lasting for more than 28 days per Common Terminology Criteria for Adverse Events (CTCAE) 3.0 toxicity criteria. In addition, *septic DLT* was defined per CTCAE 3.0 as any grade 5 sepsis-related toxicity attributable to the protocol treatment/conditioning regimen.

DL escalation/deescalation/expansion proceeded using a standard 3 + 3 design for DL 1 to 4. Patients were treated in cohorts of 3 on each DL. If 0 of 3 patients experienced a DLT, 3 patients were treated at the next DL. If a DLT attributable (definite, possible, probable) to the study treatment was experienced in exactly 1 of 3 patients, 3 more patients (for a total of 6) were treated at that DL. If no additional DLTs were observed at the expanded DL (ie, 1 of 6 with DLT), the dose was escalated.

On the basis of our myeloma trial, which declared an MTD of 1600 cGy [16], DL 5 to 9 (at ≥1600 cGy) employed a modified rolling 3 + 2 design (a more conservative version of the 3-at-risk design [20]) to allow for up to 6 patients on a given DL for further evaluation of toxicity. Six patients were accrued to DL 5 and higher. At most, 3 patients were observed for DLT on the current DL at any time. Once each patient was evaluable for toxicity and passed without a DLT, an additional patient *could be* accrued on the tested DL. Once 3 patients were evaluable at a DL and none experienced dose-limiting toxicities, 3 additional patients were enrolled at that or an escalated DL. If a DLT was documented with fewer than 6 evaluable patients for a given DL, accrual continued at that DL until 6 patients were evaluable. MTD was declared at the highest DL at which 6 patients were treated and at most 1 of 6 patients experienced a DLT.

Patient Evaluation

The modified Bearman Scale was used to define nonhematologic DLT events [21], and the CTCAE 3.0 scale was used to define hematologic DLT events as well as to report all adverse events [22]. To be evaluable for toxicity, a patient had to start treatment and be observed for at least 30 days after the completion of the transplantation procedure or experience a DLT. Hematological toxicities were evaluated from day 0, whereas other DLTs were evaluated from days -9 to +30. *Engraftment* was defined as the first of 3 consecutive days in which the absolute neutrophil count exceeded $.5 \times 10^9$/L. GVHD grading was scored according to published criteria [23-25]. Clinical response was assessed according to National Cancer Institute criteria [26] with blood draws at regularly scheduled visits and BM biopsies at days 30, 100, and years 1 and 2 after transplantation. Patients were also followed for longer periods on companion protocols assessing radiation-related toxicity for TMLI patients and late effects of transplantation for HSCT patients.

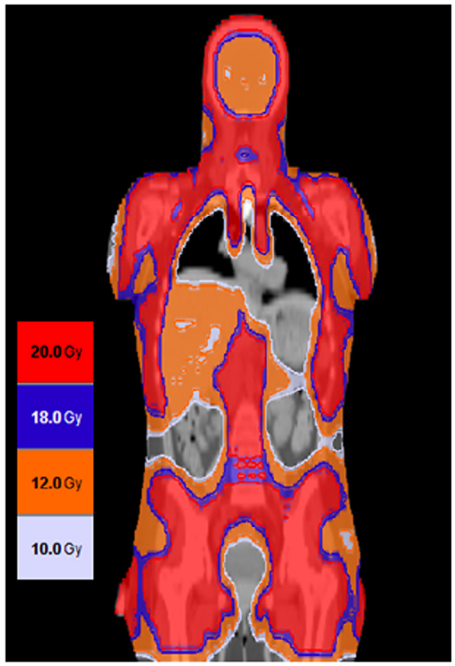

Figure 2. Dose distribution map for patient treated at MTD. TMLI was delivered at 2000 cGy to bone and lymph nodes (excluding mesenteric lymph nodes and Waldeyer ring) and 1200 cGy to liver, spleen, and brain. Doses delivered are coded according to the colors indicated in the legend. (This figure is available in color online at www.bbmt.org.)

RESULTS

Patient Characteristics

Fifty-one patients with a median age of 34 years (range, 16 to 57) and active disease refractory to salvage chemotherapy were enrolled for alloHSCT after receiving a conditioning regimen of TMLI in combination with CY and VP16 (Figure 1). Of the 51 patients, 33 patients had AML and 16 ALL (2 Philadelphia chromosome–positive). Twenty-one patients had >10% blasts in peripheral blood at time of transplantation (17 AML, 4 ALL), and 42 patients had >10% blasts in BM (28 AML, 13 ALL, 1 other). One patient had acute biphenotypic leukemia and 1 undifferentiated acute leukemia, respectively. BM (n = 3) or peripheral blood stem cells (n = 48) were given on day 0. Donors were HLA-identical siblings (n = 25), matched unrelated (n = 5), and mismatched (single allele) unrelated (n = 21). The number of patients accrued to each DL is indicated in Table 1, and patients' demographics, diagnosis, disease status, cytogenetic risk and risk per the criteria of Duval et al. [1], and treatment characteristics are summarized in Table 2.

TMLI Radiation Therapy

TMLI was delivered to sculpt radiation dose to lymph nodes and BM in each patient. Figure 2 exemplifies the dose distribution map in an AML patient who received a TMLI dose of 2000 cGy. Figure 3 depicts the median organ dose (D_{50}) at

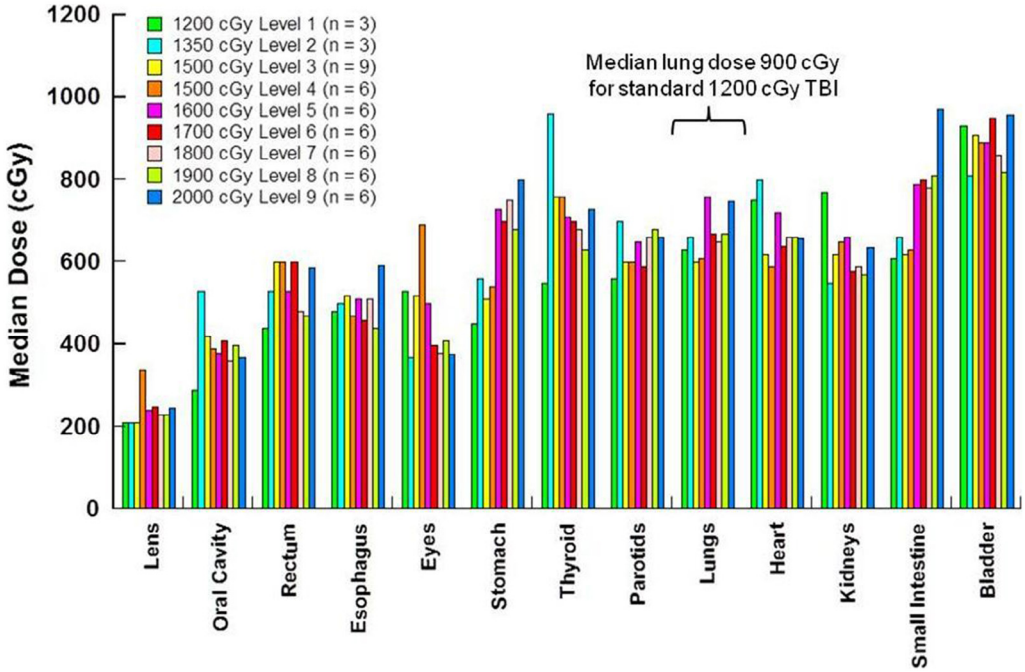

Figure 3. TMLI median organ dose (D50) by phase I dose levels. Dose levels and number of patients at each DL are indicated in the legend. The doses plotted are averaged for the patients at each DL. n = 51 total patients treated. (This figure is available in color online at www.bbmt.org.)

each DL for each OAR, for all 51 patients. The D_{50} dose for an organ was the dose received by no more than 50% of the whole organ. The D_{50} doses of TMLI compared favorably with those reported with standard TBI (see Figure 3). The D_{50} dose to a lung in a patient treated with standard TBI and shielded with 50% transmission lung blocks is usually between 850 to 900 Gy, whereas in this study the mean lung D_{50} was 680 cGy. (See Table 3 for D_{50} organ doses.) To normalize for variations with the prescribed dose, we also show, overall, that nontargeted organs received only 15% to 55% of the D_{50} received by BM (ie, lung 42%, esophagus 31%, and oral cavity 24%) (Table 3).

Treatment and Toxicities

Bearman toxicities for each DL are shown in Table 4. Nine planned TMLI DLs were tested. At DL 4 (1500 cGy), 1 patient developed grade 3 mucositis (stomatitis per Bearman toxicity scale [21] for allogeneic transplantation) attributed to radiation and chemotherapy, requiring intubation for airway protection. The same patient also had grade 3 pulmonary toxicity and grade 3 renal toxicity, which was not attributed to TMLI but was secondary to organ dysfunction related to critical illness. The only other grade 3 toxicity was a renal toxicity. Renal failure in this patient was secondary to septic shock and was not considered to be a DLT, as this infection was not directly attributed to the TMLI/conditioning regimen. An additional 3 patients were treated at 1500 cGy with no additional DLT. At the highest DL (2000 cGy), no DLTs were observed in the 6 patients treated. No patients in any DL developed veno-occlusive disease.

No early deaths (death before day +30) were observed in the entire group of patients. Between days +30 and +100, 2 deaths occurred and were not related to primary disease or GVHD: 1 patient died from a Klebsiella infection (day +56) and 1 from toxic epidermal necrolysis and disseminated human herpesvirus 6 infection (day +61). The calculated day

Table 3
D_{50} Organ Dose (Gy) (n = 51)

Organs	D_{50} Organ Dose Mean ± 1 SD	Range of the D_{50} Dose	Percent of the Prescribed Target Dose	Range of the Percent Prescribed Target Dose
Lens	2.4 ± .6	1.7-5.1	15.0 ± 4.3	10.0-34.0
Oral Cavity	3.9 ±1.1	2.5-7.7	24.3 ± 8.4	14.0-51.3
Rectum	5.4 ±1.1	3.4-9.2	33.1 ± 8.2	17.9-54.1
Esophagus	5.0 ± .8	3.1-7.1	30.8 ± 5.8	16.3-44.2
Eyes	4.5 ±1.8	2.1-11.5	28.4 ±13.0	13.1-71.9
Stomach	6.6 ±1.5	4.1-10.5	39.7 ± 7.4	27.1-58.3
Thyroid	7.2 ±1.6	2.9-12.0	44.6 ±12.7	15.3-88.9
Parotids	6.4 ±1.0	4.6-9.0	39.6 ± 7.5	26.0-60.0
Lungs	6.8 ± .7	5.1-8.6	41.5 ± 6.3	32.0-55.0
Heart	6.8 ±1.0	4.8-9.6	42.2 ±10.3	28.8-69.2
Kidneys	6.1 ± .9	3.7-8.1	37.9 ± 9.2	21.8-67.5
Small Intestine	7.5 ±1.6	4.9-11.6	45.4 ± 6.9	26.8-61.1
Bladder	8.8 ±1.7	4.8-12.2	54.5 ±12.5	25.3-89.2

Table 4
Toxicities by Dose Level

	DL1		DL2		DL3		DL4			DL5		DL6		DL7		DL8		DL9 lead-in		
	(n = 3)		(n = 3)		(n = 9)		(n = 6)			(n = 6)		(n = 6)		(n = 6)		(n = 6)		(n = 6)		
	1200 cGy		1350 cGy		1500 cGy		1500 cGy			1600 cGy		1700 cGy		1800 cGy		1900 cGy		2000 cGy		
	Grade		Grade		Grade		Grade			Grade		Grade		Grade		Grade		Grade		
Organ Assessed	1	2	1	2	1	2	1	2	3	1	2	1	2	1	2	1	2	1	2	3
Bladder toxicity	0	0	0	0	0	0	1	0	0	0	1	0	0	0	1	1	0	0	0	0
Cardiac toxicity	0	0	0	0	2	1	2	1	0	1	0	1	0	1	1	1	0	0	0	0
CNS toxicity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
GI toxicity	2	0	3	0	6	0	3	0	0	5	1	1	1	6	0	5	0	4	2	0
Hepatic toxicity	0	0	0	1	0	3	1	1	0	1	0	0	0	0	0	0	1	0	0	0
Pulmonary toxicity	0	0	0	0	2	0	0	0	1	0	0	2	0	0	0	1	1	0	0	0
Renal toxicity	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	0	0	0	0	1†
Stomatitis	2	0	1	0	1	7	2	3	1*	3	1	0	0	0	0	1	3	0	1	0

CNS indicates central nervous system; GI, gastrointestinal.
* This patient had the only dose-limiting toxicity in the trial.
† Renal failure was secondary to septic shock secondary to infection not related to the conditioning regimen and therefore not considered a DLT.

100 NRM was 3.9% (95% confidence interval [CI], .7 to 12.0). One death occurred beyond day +100 and was not due to primary disease or GVHD; this patient died from pneumonia (day +1056). At 1 year, the estimate of NRM was 8.1% (95% CI, 2.5 to 8.0). Causes of death by category are listed in Table 5.

Engraftment

All 51 patients achieved a neutrophil recovery at a median of 15 days (range, 11 to 23 days). *Platelet engraftment* was defined as the first of 7 consecutive days in which the platelet count was more than 20×10^9/L without transfusion support. Forty-five patients achieved platelet engraftment at a median of 17 days (range, 11 to 77 days). Six patients did not achieve platelet transfusion independence; contributing factors were infections and medications.

Acute GVHD and Chronic GVHD

Seven patients (14%) experienced grades III and IV acute GVHD (aGVHD). The cumulative incidence of aGVHD at day +100 was 43.1% (95% CI, 29.2 to 56.3), with a median time to onset of 30 days (range, 6 to 75). None of the nonrelapse-related deaths was attributed to complications of aGVHD. Chronic GVHD (cGVHD) occurred in 26 of the 42 patients surviving beyond 100 days. Twenty-four of these 26 patients had extensive disease. By day +365, the cumulative incidence of cGVHD was 37.9% (95% CI, 24.2 to 51.5) and the median time to onset was 138 days (range, 63 to 491). Three patients died of complications of cGVHD beyond day +100. No increase in aGVHD or cGVHD was seen with increasing dose of radiation (Table 6).

Clinical Activity

Patients were evaluated at day +30 for response. At this landmark time point, 45 of 51 patients (88%) achieved CR. Of the 33 patients who were treated at a DL ≤1700 cGy, 28 (85%) achieved CR, as did 17 of 18 patients (94%) who were treated at a DL >1700 cGy. All 6 patients (100%) treated at the declared MTD (2000 cGy) also achieved CR. Persistent disease was observed in 6 patients at day +30. With a median follow-up of 24.6 months, 33 patients experienced disease relapse (BM only, 26; extramedullary disease only, 6; concurrent BM/extramedullary, 1). See Table S1 for the sites of extramedullary disease before and after alloHSCT. The 1-year and 2-year OS rates were 55.5% (95% CI, 40.7 to 68.1) and 41.5% (95% CI, 27.3 to 55.1), respectively. As of the data lock date (October 26, 2015), 12 patients were alive and continuously in remission. Characteristics of these 12 patients, including age, disease type and status, and GVHD grade are listed in Table 7.

Table 5
Causes of Death by Category

Cause	n
Disease progression/persistent disease	29
Infection	3
Chronic GVHD	3

DISCUSSION

We report here a phase I dose escalation trial of TMLI in combination with VP16/CY as a preparative regimen for alloHSCT in patients with refractory/relapsed acute leukemia. We demonstrated that TMLI can be safely escalated to 2000 cGy, sparing nonhematopoietic and uninvolved organs, which received 15% to 55% of the BM dose, and is associated with a relatively low 30- and 100-day and 1-year NRM.

The declared MTD of 2000 cGy was clinically tolerable, with median doses delivered to the nontargeted healthy organs remaining below the corresponding doses delivered by TBI. However, the increase in doses to critical OARs approaching that of TBI (Figure 3 and Table 3), led us to the decision of not escalating the TMLI beyond 2000 cGy. Notably, the comparable incidence of GVHD with regard to published data [27] and the relatively low rate of sepsis-related

Table 6
Acute and Chronic GVHD

	aGVHD Max Grade					cGVHD Max Grade		
Dose Level	None	I	II	III	IV	None	Lmtd	Ext
1: 1200 cGy	3	0	0	0	0	1	0	2
2: 1350 cGy	1	0	2	0	0	1	0	2
3: 1500 cGy	6	0	0	3	0	2	0	5
4: 1500 cGy	0	1	3	1	1	1	1	3
5: 1600 cGy	5	0	1	0	0	1	1	3
6: 1700 cGy	2	1	2	1	0	2	0	4
7: 1800 cGy	2	2	2	0	0	2	0	3
8: 1900 cGy	3	0	2	1	0	4	0	1
9: 2000 cGy	1	1	4	0	0	2	0	1
All	23	5	16	6	1	16	2	24

Lmtd indicates limited; Ext, extensive.

Table 7
Characteristics of Patients Alive and in Remission

Patient No.	Age at allo-HSCT	Primary Disease at alloHSCT	Disease Status at alloHSCT	Blasts in PB*	Blasts in BM*	Duval Score	aGVHD Max Grade	cGVHD Max Grade	Days from allo-HSCT to Last Contact
01	34.4	Biphenotypic leukemia	IF	0%	1%	N/A	None	None	2190
02	22.4	AML	IF	0%	2%	1	None	None	850
03	31.3	ALL, Ph+	IF	0%	50%	3	III	Extensive	1803
04	49.2	AML	IF	0%	42%	1	None	Extensive	1457
05	47.6	ALL	IF	N/A	25%	4	II	Extensive	735
06	50.2	AML	First relapse	0%	5%	1	II	None	362
07	56.5	AML	IF	16%	70%	3	II	Extensive	762
08	53.8	AML	IF	N/A	10%	1	None	Extensive	715
09	34.3	AML	IF	30%	80%	3	II	Extensive	761
10	16.5	ALL	IF	49%	95%	3	II	Extensive	392
11	40.5	AML	IF	5%	20%	4	I	None	104
12	21.2	Undifferentiated leukemia	IF	2%	30%	N/A	II	None	100

PB indicates peripheral blood; N/A, not available.
* At time of transplantation.

complications observed in the present trial may be related to the relatively low radiation dose to the gastrointestinal tract (see Table 3). Despite sparing of nontargeted organs, the extramedullary relapse rates in our study appeared to be no higher (only 7 of 51 patients) than those reported in patients undergoing TBI, which is consistent with our earlier experience [28,29].

TMLI is a targeted form of total body irradiation that utilizes intensity-modulated radiation therapy delivered either through a helical tomographic or volumetric arc therapy approach. The initial patient was treated using an helical tomographic approach on a TomoTherapy device [13,17], approximately 10 years ago. More recently, our group and others have demonstrated the feasibility of delivering TMLI using volumetric arc therapy approaches on non-TomoTherapy devices [30-32]. Therefore, the delivery of TMLI is now device agnostic and it is exportable and feasible in most centers with these technologies. Clinical trials have been completed or are ongoing using these different technology platforms.

Our first trial in multiple myeloma patients tested an initial autologous HSCT with melphalan (MEL) (200 mg/m^2) conditioning, followed 6 to 10 weeks later by a second autologous HSCT using only total marrow irradiation (TMI) for conditioning. The regimen was generally safe, and DLTs (based on CTCAE criteria, not Bearman) were not observed until a TMI dose of 1800 cGy [16]. The established MTD of 1600 cGy in that trial prompted us to be cautious in dosing patients above 1500 cGy and to gain more experience by switching to a rolling-6 design with dose increments of 100 cGy instead of 150 cGy. Subsequently, we evaluated TMLI in combination with a reduced-intensity chemotherapy regimen for patients with advanced hematologic malignancies (primarily AML) who were over age 50 or had comorbidities. Because fludarabine is a radiosensitizer, TMLI at only 1200 cGy was combined with a reduced-intensity regimen of fludarabine and MEL. The 1-year NRM was 19%, comparing favorably with results observed with fludarabine/MEL alone in published reports [14]. When TMI was combined with the radiosensitizer busulfan and with VP16, DLTs occurred at 1350 cGy, precluding dose escalation above 1200 cGy [15]. The dose of TMLI delivered and feasibility of dose escalation in combination with chemotherapy are dependent upon the chemotherapeutic agents delivered together with radiation.

Patients with relapsed/refractory acute leukemia (ALL/AML) have a dismal outcome, even after HSCT, with a long-term survival of 16% to 19% [1]. Unfortunately, most patients with acute leukemia who relapse after first remission are never able to achieve a second remission, even with salvage chemotherapy, and they have very few therapeutic options outside of clinical trials [33]. Since CR status at transplantation is a primary predictor of more favorable outcomes, the vast majority of patients who fail salvage treatment with active disease remaining are not usually considered for alloHSCT; only a few sparse studies have reported the outcomes of patients undergoing alloHSCT with active disease. A Southwest Oncology Group study comparing alloHSCT preparative regimens (TBI/VP16 versus busulfan/CY) in patients with poor-risk leukemia who were not in first CR at the time of transplantation reported a 2-year DFS of ~20% for both regimens [34]. A Center for International Blood and Marrow Transplant Research study found that patients with refractory acute leukemia undergoing alloHSCT between 1994 and 2005 had equally poor outcomes (3-year OS of 19% for AML and 16% for ALL); this study has led to many transplantation centers excluding these patients from consideration for alloHSCT [1]. Although our phase I trial was designed to assess toxicity and feasibility, we are encouraged by the observed preliminary clinical response for patients with advanced forms of acute leukemia.

A phase II trial is under way (NCT number 02094794) to assess the clinical activity of 2000 cGy TMLI in combination with CY/VP16 in a similar patient population as reported here, with the goal of a more precise assessment of the clinical response to this regimen. Should this study be successful, we will consider moving this approach upfront in acute leukemia patients with high-risk disease and in first CR after initial chemotherapy treatment. Furthermore, it would be possible to explore incorporation of molecular (and image-guided) therapies tailored to individuals' molecular features to provide better initial disease control and to give post-transplantation targeted therapies to further reduce the chance of relapse after transplantation.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at doi:10.1016/j.bbmt.2017.01.067.

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