Allogeneic hematopoietic cell transplantation after conditioning with ^{131}I–anti-CD45 antibody plus fludarabine and low-dose total body irradiation for elderly patients with advanced acute myeloid leukemia or high-risk myelodysplastic syndrome

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We conducted a study to estimate the maximum tolerated dose (MTD) of ^{131}I–anti-CD45 antibody (Ab; BC8) that can be combined with a standard reduced-intensity conditioning regimen before allogeneic hematopoietic cell transplantation. Fifty-eight patients older than 50 years with advanced acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS) were treated with ^{131}I-BC8 Ab and fludarabine plus 2 Gy total body irradiation. Eighty-six percent of patients had AML or MDS with greater than 5% marrow blasts at the time of transplantation. Treatment produced a complete remission in all patients, and all had 100% donor-derived CD3$^+$ and CD33$^+$ cells in the blood by day 28 after the transplantation. The MTD of ^{131}I-BC8 Ab delivered to liver was estimated to be 24 Gy. Seven patients (12%) died of nonrelapse causes by day 100. The estimated probability of recurrent malignancy at 1 year is 40%, and the 1-year survival estimate is 41%. These results show that CD45-targeted radiotherapy can be safely combined with a reduced-intensity conditioning regimen to yield encouraging overall survival for older, high-risk patients with AML or MDS. This study was registered at www.clinicaltrials.gov as #NCT00008177. (Blood. 2009;114:5444-5453)

Introduction

The success of allogeneic hematopoietic cell transplantation (HCT) after high-dose preparative regimens in older patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) has been limited by high rates of nonrelapse mortality (NRM) and graft-versus-host disease (GVHD). For this reason, most centers limit the use of high-dose regimens to patients younger than 55 years. During the past decade, reduced-intensity regimens have been explored in an effort to capture the benefits of a graft-versus-tumor effect in older patients, while avoiding the unacceptably high NRM rates associated with high-dose approaches.[1-3] At our institution more than 1300 patients with a variety of hematologic malignancies who would not have been candidates for high-dose regimens because of their age or comorbidities have been treated with a reduced-intensity regimen of fludarabine (FLU; 90 mg/kg) and 2 Gy total body irradiation (TBI) followed by allogeneic mobilized blood cell transplantation.[4-10] With this regimen complete engraftment is achieved in more than 95% of patients, and NRM rates have been less than 10% during the first 100 days after the transplantation and approximately 20% overall. Five-year disease-free survival (DFS) rates in patients with AML in first remission are approximately 40%.[11] Relapse rates, however, are greater than 50% among patients who have more than 5% blasts in the marrow at the beginning of the conditioning regimen.[10,12,13] New approaches to reduce this rate are required.

Our group has used an ^{131}I-labeled anti-CD45 antibody (Ab; BC8) to deliver targeted hematopoietic irradiation to the marrow, spleen, and lymph nodes of patients in an effort to improve leukemia cell kill and to decrease the risk of relapse without excessive transplantation-related mortality .[14-16] Our results to date show that ^{131}I-BC8 Ab can deliver between 2- and 3-fold more radiation to sites of leukemia than to the total body and that significant radiation delivered in this manner can be added to high-dose preparative regimens without undue toxicity. Given the minimal regimen-related toxicity (RRT) of the reduced-intensity approach and the encouraging results that we have seen with ^{131}I-BC8 Ab, we hypothesized that the antileukemic effect of the reduced-intensity regimen could be improved by the addition of targeted hematopoietic irradiation delivered by a radiolabeled Ab for older patients with advanced AML or high-risk MDS who have a high probability of relapse and would not be candidates for transplantation with standard myeloablative conditioning regimens.[14,17-24]

We therefore performed a phase 1 dose-escalation study combining ^{131}I–anti-CD45 Ab with FLU and 2-Gy TBI as a conditioning regimen before allogeneic HCT for patients with advanced AML or high-risk MDS. The goal of this study was to estimate the maximum tolerated dose (MTD) of targeted hematopoietic irradiation combined with our reduced-intensity conditioning regimen and, at the highest tolerable dose, to begin to explore the

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effectiveness of the regimen. In this report we demonstrate that a maximum dose of 24 Gy delivered by radiolabeled Ab to the liver can be tolerated in addition to FLU and 2-Gy TBI for this high-risk patient population and that initial results are sufficiently encouraging to warrant further study of this approach in a phase 2 clinical trial.

Methods

Patient and donor selection

Sixty-nine patients older than 50 years with advanced AML or high-risk MDS with a human leukocyte antigen (HLA)–matched related or unrelated donor were considered for this study. Patients were eligible if they had AML that was refractory to treatment, beyond first remission, in relapse (> 5% blasts in the marrow by morphology), or evolved from MDS or myeloproliferative syndromes, if they had MDS with greater than 5% blasts in the marrow, or if they had chronic myelomonocytic leukemia. Patients were excluded if they had evidence of major organ dysfunction, seropositivity for human immunodeficiency virus, allergies to mouse protein, or human Ab specific for mouse immunoglobulin (HAMA). Patients were informed of the investigational nature of this study and signed a consent form approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center (FHCRC) in accordance with the Declaration of Helsinki.

Related donors were matched by intermediate resolution molecular typing for HLA-A, -B, -C, and -DQB1 according to FHCRC Standard Practice Guidelines and by high-resolution typing for HLA-DRB1. Eligible unrelated donors were allele matched for HLA-A, -B, -C, and -DRB1 by high-resolution typing and for HLA-DQB1 by intermediate-resolution typing. A single allele disparity for HLA-A, -B, or -C was allowed for both related and unrelated donors. Donors were typed prospectively by oligonucleotide hybridization or by DNA sequencing methods.[25]

Antibody production, purification, and radiolabeling

BC8 Ab is a murine IgG1 that binds to all CD45 isoforms. BC8 Ab was produced and purified in the Biologics Production Facility at the FHCRC as previously described.[14] The Ab was labeled with ^{131}I (New England Nuclear; specific activity ~ 8.0 Ci [29.6×10^{10} Bq]/mg) by the chloramine-T method and was purified and tested as previously described.[14]

Determination of antibody biodistribution and radiation-absorbed dose

Patients first received an infusion of trace-^{131}I–labeled BC8 Ab to determine the biodistribution of Ab and to estimate radiation-absorbed doses to marrow, spleen, nontarget organs, and the whole body delivered per millicurie (mCi; megabecquerel [MBq]) ^{131}I. Patient serum was tested by enzyme-linked immunoabsorbent assay to detect HAMA.[14] Organ volumes (liver, lungs, spleen, and kidney) were calculated by computed tomography of the chest and abdomen.[26] Thyroid uptake of free ^{131}I was blocked by oral Lugol solution (strong iodine/potassium iodide solution). Treatment was started 2 days before the test dose of labeled Ab and continued until 3 weeks after the therapeutic dose of ^{131}I-labeled BC8 Ab. The biodistribution study dose of 0.5 mg/kg BC8 Ab was labeled with 4 to 10 mCi (148-370 MBq) ^{131}I and was administered at 7.5 mg/h after the patient was premedicated with acetaminophen, diphenhydramine, and hydrocortisone.[16] Patients who had symptoms such as chills or nausea were treated with meperidine and lorazepam as needed. Infusion-related symptoms were graded prospectively according to the National Institutes of Health Common Toxicity Criteria (CTC) Version 2.0 toxicity scale.[27]

Gamma images were obtained at the end of infusion (hour 0) and then daily for 3 days with the use of a dedicated GE MAXXUS, dual-headed, large-field-of-view camera with high-energy collimators. Regions of interest, including 2 marrow sites (right acetabulum and sacrum), spleen, liver, lungs, and kidneys, were imaged with a 180-degree opposing-view quantitative planar technique.[26] Results were compared with an ^{131}I imaging standard for quantitation and were corrected for whole-body thickness attenuation and radioactive decay. A bone marrow biopsy was obtained the day after infusion (14-24 hours after the end of infusion) and was weighed and counted against a weighed reference aliquot of the injected dosage to calculate the percentage of injected dose per gram in marrow. The red marrow clearance curve was scaled by correcting the biopsy-determined percentage of injected dose per gram of ^{131}I-BC8 by a multiplication factor of 2, because Ab cannot bind to the trabecular bone and fat, which makes up approximately half of the total biopsy weight.[28,29] Time-activity curves were generated for each major source organ, marrow, and the whole body from the gamma camera region-of-interest images. The fractional time-activity curves for each source organ were integrated to obtain source-organ residence times. Radiation-absorbed doses were then estimated using methods consistent with those recommended by the Society of Nuclear Medicine's special committee on Medical Internal Radiation Dose as previously described.[30] Patient marrow volumes were normalized to the Medical Internal Radiation Dose model values of 1120 g for the standard 73-kg adult and 1050 g for the 58-kg smaller adult woman for dosimetry purposes. Appropriate red marrow-to-marrow S values for the absorbed dose per unit-cumulated activity were used consistently for marrow dose calculations throughout the multiyear period of the study.[31]

Therapy

All patients were eligible to receive a therapy dose of ^{131}I-BC8, regardless of the results of the biodistribution study because the estimated radiation doses delivered to marrow and spleen in previous studies were greater than doses to lung, kidney, and total body even in those few patients whose marrow dose was slightly lower than liver dose.[14,16] The therapy infusion of Ab was labeled with the amount of ^{131}I calculated to deliver the desired dose to the normal organ estimated to receive the highest radiation dose. The therapy dose was administered on day −12 of the preparative regimen, which was 8 to 14 days after the biodistribution dose. Serum was retested for HAMA 1 day before the scheduled therapy dose, and, if the test result was positive, the patient was treated with an alternative conditioning regimen. The radiolabeled Ab was infused through an automatic pump from a lead-shielded reservoir as described previously.[14,16] Vital signs, blood counts, and blood chemistry analyses were performed daily while patients were in radiation isolation. Proximity of the nursing staff to the patient was limited except as needed for delivery of intravenous medications. Patients remained in radiation isolation in lead-lined rooms after the therapy dose until radiation exposure was less than or equal to 7 mR/h at 1 milliRem (median, 6 days; range, 2-11 days). FLU 30 mg/kg was given daily intravenously ×3 days on days −4, −3, and −2. Patients then received TBI (200 cGy; 6-7 cGy/min from a linear accelerator) followed by infusion of unmanipulated mobilized blood cells on day 0. For GVHD prophylaxis, mycophenolate mofetil was given at 15 mg/kg orally (or same dose intravenously if oral administration could not be tolerated) every 8 hours, starting on day 0 to day 27 for patients with a related donor, or to day 40 followed by tapering doses ending on day 96 for patients with an unrelated donor. Cyclosporine (CSP) was given at 3.75 mg/kg orally (or 1.5 mg/kg intravenously if oral administration could not be tolerated) every 12 hours, beginning on day −3 to day 56 followed by tapering doses ending on day 80 for patients with a related donor. For patients with an unrelated donor, CSP prophylaxis was continued to day 100 followed by tapering doses ending on day 177. Patients received ursodiol for prophylaxis against veno-occlusive disease (VOD) according to FHCRC standard practice guidelines.

Dose-finding algorithm

The MTD for this study was defined as the dose associated with a true dose-limiting toxicity (DLT) rate of 25%, where a DLT was defined as Bearman grade 3 or grade 4 RRT through day 100 after HCT, as defined by the Bearman criteria, a scale developed specifically for patients who have received a HC transplant.[32] Dose modifications were conducted after the 2-stage approach introduced by Storer.[33] In the first stage, single patients were enrolled and treated at doses escalating in 2-Gy increments until the

first DLT was observed. The second stage then began at the next lower dose level, when patients were treated in cohorts of 4. This cohort size was dictated by the target DLT rate of 25%. Doses were escalated in increments of 2 Gy, and escalation to the next higher dose level was permitted if no DLT was observed among the 4 patients. An additional cohort of 4 was treated at the same level if 1 of the 4 patients experienced a DLT, and the next cohort of 4 was treated at the next lower dose level if 2 or more DLTs were seen among the current cohort of 4. After 20 patients were treated in the second stage, a 2-parameter logistic model was fit to the observed dose-toxicity data from both stages, and the MTD was estimated as the dose associated with the target toxicity rate of 25% from this fitted model. We recognized the possibility that a patient could be enrolled in the study before all patients in a cohort could be evaluated for DLT. Given the high-risk features of the treated patient population, however, it was not feasible to delay treatment until all previously treated patients in a cohort could be evaluated for DLT. Such patients were therefore treated at the current dose level, although their outcome did not contribute to the decision to modify the current dose unless required in the interests of patient safety, based on the clinical judgment of the principal investigator. These patients also did not contribute to the required number of patients for completion of the second stage. The outcomes for these patients were used, however, when fitting the dose-toxicity curve used to estimate the MTD. Accrual in some instances was fairly rapid, and the above provisions contributed to the fact that some dose levels had more than 4 patients enrolled.

Statistical analysis

The primary objective of this study was to estimate the MTD, and the dose-finding algorithm used for this purpose is detailed in "Dose-finding algorithm." On completion of the second stage, a decision was made to enroll additional patients at the 24-Gy dose level, primarily to gain a more precise estimate of the MTD but also to gather preliminary data on potential efficacy within the confines of a phase 1 study. Escalation above 24 Gy was not to be allowed among these additional patients, although de-escalation was permitted. Secondary objectives included an examination of potential efficacy, as stated in "Dose-finding algorithm," in terms of overall survival (OS) and DFS, each estimated according to the method of Kaplan and Meier.[34] The number of additional patients treated at 24 Gy was loosely based on the fact that 21 patients allow 79% power to observe a statistically significant (at the one-sided level of .10) improvement from the fixed DFS rate of 20% if the assumed-true rate is 40%. Twenty-one patients also allow 80% confidence that the estimate of a particular parameter will be within .14 of the true value of the parameter. Other secondary efficacy measures included NRM and relapse, and probabilities of each were computed as cumulative incidence estimates.[35] Relapse was considered a competing risk for NRM, and death without relapse was considered as a competing risk for relapse.

Results

Patient characteristics

Sixty-nine patients with advanced AML or high-risk MDS enrolled in this study. Eight patients who had favorable biodistribution after the test dose of ^{131}I-BC8 Ab were not treated with a therapeutic dose of radiolabeled Ab. Three patients developed HAMA consistent with the small number of patients treated with the BC8 Ab on our prior studies,[14] 1 had infection, 3 had allergic-type reactions after the Ab infusion, and 1 had disseminated intravascular coagulation. Three additional patients decided to withdrew from the study after the test dose but before the therapeutic dose of ^{131}I-BC8. Fifty-eight patients (median age, 63 years; range, 50-74 years) with advanced AML (n = 28 de novo AML; n = 19 secondary AML) and high-risk MDS (n = 11) received a therapeutic infusion of ^{131}I-BC8 Ab followed by FLU, 2-Gy TBI, and allogeneic HCT between December 2000 and March 2008. Twenty-two patients had HLA-matched related donors, and 36 had unrelated donors. The characteristics of these patients are summarized in Table 1. Patients were distributed across FAB classifications at diagnosis, with the exception that patients with acute promyelocytic leukemia were specifically not enrolled in the study. Eight patients (14%) had de novo AML in morphologic remission (CR2 or CR3). Four of the 8 had remission after a single cycle of reinduction chemotherapy, and the other 4 required a second cycle of reinduction chemotherapy. Twenty patients (35%) with de novo AML had either refractory disease that showed no response to prior induction therapy (n = 8) or had AML in relapse (n = 12) at the beginning of the conditioning regimen. All 19 patients with secondary AML or MDS had more than 5% blasts in the marrow at the beginning of the conditioning regimen. Fifty-six of the 58 patients treated with ^{131}I-BC8 Ab had marrow cytogenetics tested at initial diagnosis. According to criteria of the Southwest Oncology Group, 24 had intermediate-risk cytogenetic abnormalities, and 32 had unfavorable cytogenetic abnormalities.[36]

^{131}I-BC8 biodistribution

The average (± SD) estimated radiation dose delivered per unit administered activity to bone marrow of the 58 patients treated with ^{131}I-BC8 Ab was 6.0 (± 3.2) cGy/mCi [MBq], 17.9 (± 9.7) cGy/mCi [MBq] to spleen, 3.7 (± 1.2) cGy/mCi [MBq] to liver, 0.3 (± 0.1) cGy/mCi [MBq] to lung, 0.5 (± 0.2) cGy/mCi [MBq] to kidney, and 0.5 (± 0.2) cGy/mCi [MBq] to the total body (Figure 1A). Ab uptake in marrow and spleen was similar in patients with refractory/relapsed AML or active secondary AML compared with those with AML in remission (Figure 1B). Likewise, antibody biodistribution was similar in patients with MDS compared with those with AML (Figure 1B).

Estimated MTD, therapy, estimated radiation-absorbed doses, toxicities, and engraftment

Approximately 10 days after the biodistribution study, patients received BC8 Ab labeled with the amount of ^{131}I activity calculated to deliver an estimated 12 to 26 Gy to the normal organ receiving the highest dose (ie, the liver). The ^{131}I activity administered at each dose level and estimated radiation-absorbed doses delivered to marrow and spleen are summarized in Table 2, together with the number of patients and DLT that occurred at each dose. Thirteen patients had DLTs as defined per protocol. Three patients developed reversible Bearman grade 3 renal insufficiency, respectively, on days 2, 8, and 84 related to high concentrations of CSP in the blood. Five patients had reversible cardiac grade 3 supraventricular tachycardia associated with infection between days 7 and 48, and 1 of these patients also had a grade 3 non-Q wave myocardial infarction. Five patients had grade 3/4 pulmonary RRT. One patient had aspiration pneumonia on day 97, 1 patient developed bronchiolitis obliterans organizing pneumonia (BOOP) associated with chronic GVHD on day 70, and 3 patients had pulmonary toxicities suggestive of radiation-induced lung injury. Two of the 3 patients had acute respiratory distress syndrome, respectively, on days 7 and 13, and 1 had BOOP on day 25. Shown in Figure 2 are the observed DLT rates at each of the doses used in this study, together with the fitted dose-toxicity curve. Based on these results, the estimated MTD was 24 Gy.

Patients generally experienced the same Ab-related side effects during the therapy infusion as they had with the biodistribution infusion of Ab. No patients had CTC grade 4 Ab-infusion–related side effects. Despite the use of premedication, 33% of patients had moderate (CTC grade 2) infusional toxicities, and all of these

Table 1. Patient characteristics

Characteristic	De novo AML (n = 28)		Secondary AML (n = 19)	High-risk MDS (n = 11)*	All patients (n = 58)
	REM	REF/REL			
Sex, M/F, no.	5/3	8/12	15/4	8/3	36/22
Median age, y (range)	59 (50-73)	57 (54-68)	65 (51-74)	65 (57-72)	63 (50-74)
Median WBC/mm^3 at diagnosis (range)	12.7 (0.8-98)	3.5 (2.1-97)	2.7 (1-126)	3.4 (1.5-105)	3.6 (0.8-126)
FAB, no. of patients					
M0	2	2	0		4
M1	2	4	0		6
M2	1	1	3		5
M3	0	0	0		0
M4	2	3	1		6
M5	0	5	0		5
M6	0	0	2		2
M7	0	1	0		1
ND	1	4	13		18
IPSS, No. of patients					
Low				0	0
Intermediate 1				0	0
Intermediate 2				6	6
High				4	4
ND				1	1
Cytogenetics, no. of patients					
Favorable	0	0	0	0	0
Intermediate	3	8	7	6	24
High	4	11	12	5	32
Unknown	1	1	0	0	2
Donor status, no. of patients					
Related	4	7	7	4	22
Unrelated	4	13	12	7	36
Induction therapy cycles, no. of patients					
0	0	0	1	0	1
1	4	10	5	1	20
2	4	2	2	1	9
More than 3	0	2	2	0	4
Unknown	0	6	9	9	24†
Consolidation cycles, no. of patients					
0	3	4	14	9	30
1	2	4	0	0	6
2	0	2	0	0	2
3	1	3	0	0	4
4	1	2	1	0	4
5	0	1	0	0	1
Unknown	1	4	4	2	11†
CNS involvement, no. of patients					
Yes	1	2	3	0	6
No	7	18	16	11	52

REM indicates remission; REF/REL, refractory/relapsed; WBC, white blood cell; FAB, French-American-British; IPSS, International Prognostic Scoring System; ND, not determined; and CNS, central nervous system.

*High-risk MDS includes refractory anemia with excess of blasts and chronic myelomonocytic leukemia.

†The exact numbers of cycles of induction and/or consolidation therapies delivered were not described in the records obtained from referring physicians and thus are listed as unknown.

toxicities resolved by the end of each infusion. Seventeen percent of patients had chills, and 20% required treatment with meperidine. Twelve percent of patients had nausea and vomiting, and 26% of patients developed respiratory symptoms such as throat or chest tightness. Two percent of patients developed CTC grade 2 hypotension requiring treatment with parenteral fluids.

Eight patients (14%) developed less than or equal to grade 2 mucositis (Bearman scale) that required narcotic therapy. No patient developed Bearman grade 3/4 VOD of the liver. Neutrophil counts surpassed 500/μL at a median of 14 days (range, 10-23 days), and transfusion-independent platelet counts surpassed 20 000/μL at a median of 11 days (range, 7-81 days) after HCT. Chimerism studies showed 100% donor-derived cells in the marrow and in isolated $CD33^+$ and $CD3^+$ fractions of the blood by day 28 after the transplantation. Forty-four (76%) of the 58 patients developed grades II to IV acute GVHD (Table 3).[37,38] Thirty (52%) of 58 patients developed chronic GVHD. Eleven (19%) of 58 evaluable patients had elevated concentrations of thyroid stimulating hormone in the blood by day 100 after HCT and were treated with thyroxine.

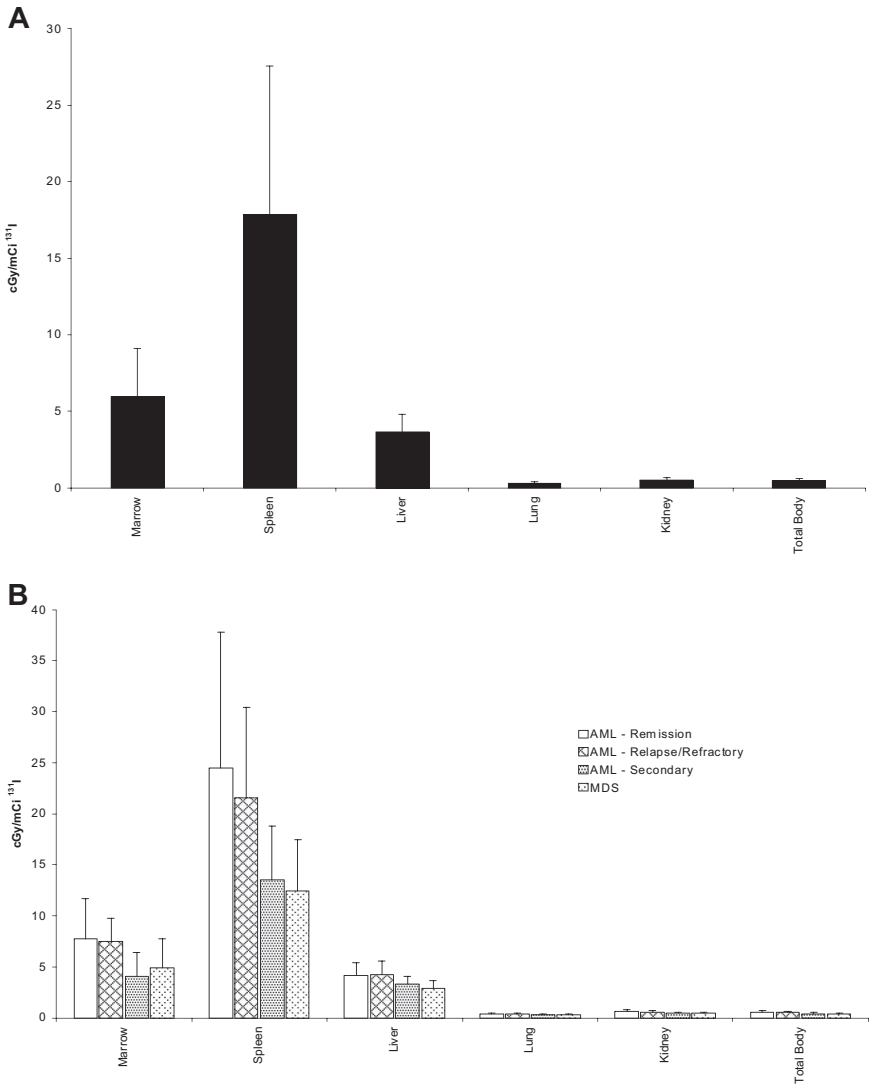

Figure 1. Estimated radiation absorbed doses per millicurie of ^{131}I. Estimated radiation absorbed doses per millicurie of ^{131}I administered for (A) all patients, (B) patients with AML in remission, in relapse, with refractory AML, and patients with high-risk MDS. Results are shown as mean ± SEM.

OS and DFS, NRM, and relapse

Of the 58 patients who received a therapeutic dose of ^{131}I-BC8 Ab, 40 have died, and 2 additional patients had recurrent malignancy but were alive at last contact. Median follow-up among the 18 surviving patients by last contact was 2.6 years (range, 0.7-4.3 years). Of the 21 patients treated at the estimated MTD, 12 have died, 7 with recurrent malignancy and 5 without recurrent malignancy. Figure 3 summarizes the probabilities of OS, DFS, relapse, and NRM among all 58 patients, and Figure 4 summarizes the outcomes among the 21 patients who received the MTD of 24 Gy. Median OS and DFS among all 58 patients is 199 days and 159 days, respectively, and among the 21 patients treated at the MTD, 206 and 189 days, respectively. The 1-year survival estimate is 41% (95% confidence interval [CI], 28%-54%; Figure 3) among

Table 2. ^{131}I activity administered, total radiation absorbed doses, and grade 3 or 4 regimen–related toxicities

Dose to liver (Gy), dose level	mCi ^{131}I [MBq]	Dose to marrow, Gy	Dose to spleen, Gy	DLT/no. of patients treated
12	438 ± 209 (300-678)* [16 206 ± 7733 (11 100-25 086)]	24.8 ± 8.5 (17.2-33.9)	54.1 ± 3.2 (50.4-56.4)	0/3
14	325 ± 112 (246-404) [12 025 ± 4144 (9102-14 948)]	28.7 ± 13.6 (19.0-38.3)	109.6 ± 64.9 (63.7-155.5)	0/2
16	496 ± 114 (368-587) [18 352 ± 4218 (13 616-21 719)]	18.3 ± 3.8 (14.0-20.5)	59.7 ± 12.3 (45.6-68.2)	1/3
18	427 ± 23 (410-443) [15 799 ± 851 (15 710-16 391)]	24.1 ± 7.7 (18.7-29.5)	39.6†	0/2
20	605 ± 159 (334-841) [22 385 ± 5883 (12 358-31 117)]	25.1 ± 11.3 (6.3-41.3)	91.9 ± 27.4 (47.7-145.5)	3/12
22	513 ± 196 (296-932) [18 981 ± 7252 (10 952-34 484)]	33.0 ± 13.6 (5.2-45.9)	91.3 ± 30.0 (42.2-136.2)	3/9
24	629 ± 206 (319-1147) [23 273 ± 7622 (1183-42 439)]	36.1 ± 11.5 (14.6-48.0)	101.5 ± 34.4 (55.0-187.6)	4/21
26	735 ± 222 (510-1084) [27 195 ± 8214 (18 870-40 108)]	32.1 ± 10.7 (17.9-46.9)	108.4 ± 39.9 (45.2-145.3)	2/6

*Mean ± SD (range).

†Estimated absorbed dose to spleen for 1 patient treated at the 18-Gy level; a second patient treated at this dose level had prior splenectomy.

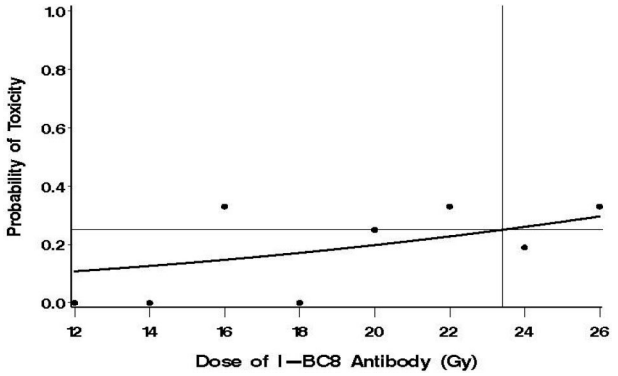

Figure 2. The fitted dose-toxicity curve from the observed data. The solid circles indicate the observed DLT rate at the appropriate dose, and the vertical line represents the dose associated with a DLT rate of 25% from the fitted curve.

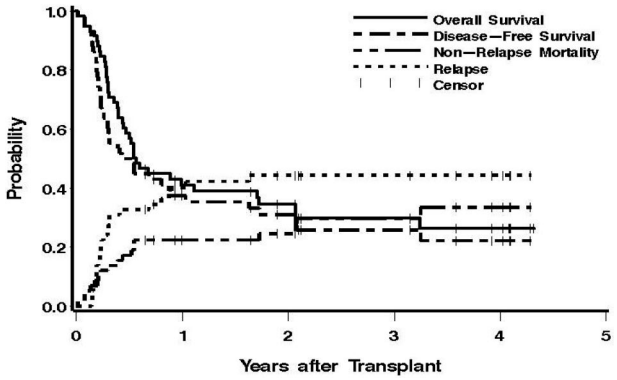

Figure 3. Estimates of the probability of OS, DFS, NRM, and relapse among all patients who received a therapeutic dose of ^{131}I-BC8 Ab, followed by TBI/FLU.

all 58 patients and 48% (95% CI, 26%-67%) among the 21 who received 24 Gy. The 1-year survival estimate is 46% (95% CI, 20%-71%) among patients with AML in remission and 46% (95% CI, 20%-71%), 38% (95% CI, 12%-65%), and 33% (95% CI, 9%-57%), respectively, among patients with AML in relapse, refractory disease, and high-risk MDS. Of the 18 surviving patients, 4 had high-risk MDS, 4 had AML in either second or third complete remission, 7 had AML in florid relapse, and 3 had refractory AML at the time of transplantation.

Twenty-five patients have had recurrent malignancy, all with involvement of the marrow, and 17 have died of nonrelapse causes (Table 4). The absorbed-radiation doses to the bone marrow and spleen were 31 (± 12) Gy and 86 (± 31) Gy for the patients with recurrent malignancy after HCT, respectively, compared with 31 (± 12) Gy and 99 (± 36) Gy, respectively, for those without recurrent malignancy. The estimated probabilities of relapse and NRM at 1 year were 40% (95% CI, 27%-53%) and 22% (95% CI, 12%-33%), respectively (Figure 3).

Table 3. Acute GVHD in patients receiving ^{131}I-BC8/FLU/TBI and HLA-matched related and unrelated allogeneic transplants for advanced AML and high-risk MDS

	AML (n = 28)		Secondary AML	MDS*	All patients
	REM	REF/REL	(n = 19)	(n = 11)	(n = 58)
Acute GVHD overall grade					
Grade II	4 (14)	12 (43)	12 (63)	5 (45)	33 (57)
Grade III	5 (18)	0 (0)	4 (21)	1 (9)	10 (17)
Grade IV	0 (0)	0 (0)	0 (0)	1 (9)	1 (2)
Acute GVHD, gut					
Grade II	1 (4)	1 (7)	3 (16)	1 (9)	6 (10)
Grade III	5 (18)	6 (40)	5 (26)	5 (45)	21 (36)
Grade IV	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Acute GVHD, skin					
Grade II	1 (4)	0 (0)	1 (5)	0 (0)	2 (4)
Grade III	1 (4)	0 (0)	1 (5)	1 (9)	3 (5)
Grade IV	0 (0)	0 (0)	0 (0)	1 (9)	1 (2)
Acute GVHD, liver					
Grade II	0 (0)	0 (0)	2 (11)	1 (9)	3 (5)
Grade III	1 (4)	0 (0)	1 (5)	1 (9)	3 (5)
Grade IV	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Values are n (%).

REM indicates remission; REF/REL, refractory/relapsed.

*MDS includes refractory anemia with excess of blasts and chronic myelomonocytic leukemia.

Discussion

Although allogeneic HCT is an important and widely used tool for the treatment of advanced AML and high-risk MDS, many patients have recurrent malignancy.[39,40] Efforts to decrease relapse rates have focused largely on intensification of cytoreductive therapy, either by increasing the TBI dose or by intensifying chemotherapy. Controlled randomized studies have shown that relapse rates can be reduced by increasing the TBI dose. In a randomized study of patients with AML in first CR, the relapse rate was 12% after 15.75-Gy TBI, compared with 35% after 12-Gy TBI.[41] In a similar study of patients with chronic-phase chronic myeloid leukemia, the recurrence rate was 0% after 15.75-Gy TBI, compared with 25% after 12-Gy TBI.[42] Although these studies have shown improved tumor control with escalated doses of therapy, the increased doses of TBI were associated with increased NRM, confirming the clinical impression that conventional transplantation preparative regimens are currently at the limit of normal organ tolerance. To overcome this limitation we have used an ^{131}I–anti-CD45 Ab to deliver targeted radiation to malignant cells in the marrow and spleen, with relative sparing of normal organs, which are the sites of DLT. In both preclinical and clinical studies we found that ^{131}I–anti-CD45 Ab can deliver relatively specific radiation to hematopoietic tissues, with 2 to 3 times more radiation delivered to bone marrow, up to 12 times more to spleen, and 2 to 8 times more to lymph nodes compared with liver, lung, or kidney.[14-16,43-45]

The encouraging results achieved with ^{131}I-BC8 Ab and myeloablative conditioning regimens in younger patients has led us to ask

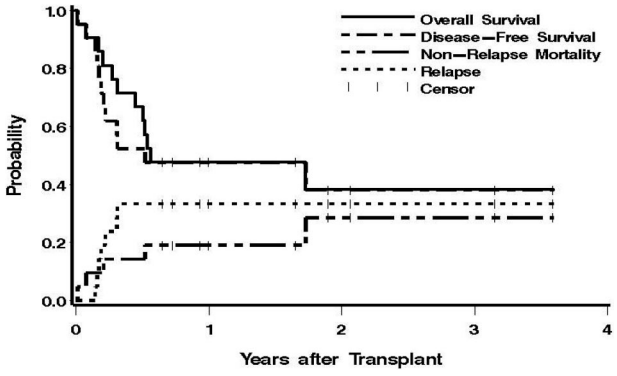

Figure 4. Estimates of the probability of OS, DFS, NRM, and relapse among patients treated at the MTD of 24 Gy of radiation delivered to the liver by the ^{131}I-BC8 Ab, followed by TBI/FLU.

Table 4. Nonrelapse related causes of death for patients treated with ^{131}I-BC8/FLU/TBI

Fatal toxicity	AML (n = 28)		Secondary AML (n = 19)	MDS* (n = 11)	All patients (n = 58)
	REM	REF/REL			
Infection, n	1	3	4	3	11
Pulmonary, n†	0	2	2	1	4
GVHD, n	0	0	0	1	1
CNS, n	0	0	1	0	1

Total 100-day TRM (12 %).

REM indicates remission; REF/REL, refractory/relapsed; CNS, central nervous system.

*MDS includes refractory anemia with excess of blasts and chronic myelomonocytic leukemia.

†Pulmonary toxicity indicates noninfectious pneumonitis.

how this approach might be applied to older patients with AML or MDS who would not be considered candidates for high-dose conventional therapies. Reduced-intensity HCT approaches have been developed for an older patient population, providing the ability to achieve donor engraftment that is dependent on both pretransplantation and posttransplantation immunosuppression. In particular, administration of reduced-intensity HCT regimens have been shown to be feasible in older patients and that stable complete donor chimerism can be achieved with a low, nonablative dose of TBI combined with FLU, and by administering standard posttransplantation immunosuppressive therapy.[3,4] These observations provide a compelling argument for combining targeted therapy with reduced-intensity transplantations. To this end we now have combined delivery of myeloablative doses of ^{131}I-BC8 Ab with a reduced-intensity HCT strategy in an effort to gain the benefit of a graft-versus-malignancy effect, hopefully without increasing the occurrence of toxicities associated with a standard HCT regimen and providing additional antileukemic-targeted radiation therapy delivered by the ^{131}I-BC8 Ab.

The results presented in this report show the feasibility of using ^{131}I-BC8 Ab to enhance the efficacy of reduced-intensity allogeneic HCT for elderly patients with AML or MDS who are not candidates for high-dose regimens. The biodistribution of ^{131}I-BC8 Ab was determined for each patient individually, because the range of estimated radiation dose to liver per millicurie (megabecquerel) ^{131}I delivered in both this study and our previous studies was wide.[14,16] The biodistribution results showed that all patients had a higher estimated radiation dose delivered to red marrow and spleen than to the liver, the normal organ receiving the highest dose. Hepatic doses ranged from 1.7 to 7.7 cGy/mCi (MBq) ^{131}I, indicating considerable variability in the amount of ^{131}I required to deliver 12 to 26 Gy to liver. The MTD suggested by this study was 24 Gy delivered by ^{131}I-BC8 Ab to the normal organ receiving the highest dose, which was considerably higher than the estimated MTD (10.5 Gy) of radiation delivered by the anti-CD45 Ab seen in our prior myeloablative studies in which the Ab was combined with cyclophosphamide and TBI.[14] On the basis of the average estimates of radiation absorbed dose, the 24-Gy dose level delivered an overage of 36 Gy to marrow and 102 Gy to spleen, combined with FLU and 2-Gy TBI. On average, the estimated radiation doses delivered by ^{131}I-BC8 Ab in the marrow were 1.5-fold greater than in the liver, and doses in the spleen were 4.3-fold greater than in the liver. The ratios of radiation delivered to marrow and spleen compared with lung, kidney, and total body were even greater.

Intensified conditioning with ^{131}I-BC8 Ab resulted in few toxicities beyond those expected with FLU or TBI alone. Engraftment was not delayed after delivery of ^{131}I-BC8 Ab, and infusion-related toxicities were mild and manageable. Although the direct contribution of the radiolabeled Ab to cardiac and renal DLTs is difficult to ascertain, the pulmonary toxicities of acute respiratory distress syndrome and BOOP were suggestive of acute radiation-induced lung injury that could have been caused by the Ab. Although there was no difference in the estimated average absorbed radiation dose delivered to the lungs for the patients with cardiopulmonary DLT (2.2 Gy; range, 0.7-3.9 Gy) compared those without cardiopulmonary toxicities (1.7 Gy; range, 0.9-3.1 Gy), these results are consistent with the results found in similar high-dose radiolabeled Ab studies for treatment of lymphoma[21,23] Conversely, all 3 episodes of renal insufficiency were reversible and appeared to be related to high serum levels of calcineurin inhibitor therapy and thus not suggestive of radiation nephritis. Likewise, each cardiac-associated DLT was an event that may have been triggered by the physiologic stress of infection in this older patient population.

The most frequent causes of death in these high-risk patients were infections seen in 11 patients. Only 1 infectious-related death occurred within the first 30 days after transplantation during the period of neutropenia. The other 10 fatal infections occurred between days 49 and 1186, when patients were well engrafted and not neutropenic. We attribute these infections to effects of GVHD and steroid treatment. Despite the planned delivery of 12 to 26 Gy to the liver, severe VOD was not seen; thus, the incidence of severe hepatic toxicity did not appear to be worse than what has been reported with FLU or TBI alone.[46] Some additional toxicities, however, were clearly attributable to treatment with the radiolabeled Ab. Despite administration of Lugol solution to all patients during both the biodistribution and therapy phases of radiolabeled Ab treatment, 20% of patients had increased concentrations of thyroid-stimulating hormone by day 100. The hypothyroidism is due to the high doses of radioactive iodine and the inability to block all radioiodine uptake in the thyroid gland by administration of nonradioactive iodine. All patients who developed hypothyroidism received exogenous thyroid supplementation. Further studies will be needed to determine whether these nonlethal toxicities caused by the radioactive iodine will be offset by the benefit of a decreased risk of recurrent leukemia.

The overall incidence of grades II to IV acute GVHD in this study was 76%. This incidence is similar to that seen with FLU or TBI alone in similarly aged patients at our center.[47] The apparent high rate of GVHD reported from our center has been attributed to an increased use of endoscopy in patients with posttransplantation anorexia, leading to an increased incidence of grade II acute GVHD.[38] The estimated 52% probability of chronic GVHD in the current study is comparable to that among older patients who received reduced-intensity conditioning without targeted radiotherapy, suggesting that the radiolabeled Ab has no demonstrative effect on the risk of chronic GVHD.[10,48,49]

As a phase 1 dose-finding trial, this study was not designed to examine the potential efficacy of the preparative regimen of ^{131}I–anti-CD45 Ab combined with FLU/TBI. Whether the delivery of supplemental hematopoietic irradiation with the use of ^{131}I–anti-CD45 Ab will benefit patients with advanced leukemia or high-risk MDS requires more careful evaluation in future clinical trials that are designed to test this hypothesis. However, the experience reported in this dose-escalation study suggests that the ability to deliver such supplemental doses of radiation to sites of leukemic involvement in marrow and spleen has the potential to improve the cure rate by decreasing the risk of relapse compared with patients who received a with the use of the FLU/TBI conditioning regimen alone. The patients treated in this study were considered at such

high risk that they were not candidates for a reduced-intensity transplantation at our center and thus had no alternative strategy with curative intent. Although the estimated probability of relapse at 1 year remains high (40%), these results appear to be encouraging, considering that 86% of the patients in our study had active AML or MDS with more than 5% blasts at the beginning of the conditioning regimen, in contrast to results from studies that used FLU/TBI reduced-intensity conditioning alone whereby a graft-versus-malignancy effect appeared to be most effective in patients with a low burden of malignant cells.[10,12,13,50] In a recent study of 258 patients who had allogeneic HCT after nonmyeloablative conditioning for treatment of AML, the 1-year estimated cumulative incidence of relapse was approximately 40%. The median age of these patients was 59 years (range, 5-74 years). Notably, more than 95% of the patients had AML in morphologic remission, and approximately 60% had AML in first CR at the beginning of the conditioning regimen. Most treatment failures were caused by recurrent malignancy.[11] Despite the more favorable characteristics of these patients compared with those enrolled in our current study, the relapse rates were similar in the 2 studies. Taken together, the results suggest that a graft-versus-leukemia effect alone may be inadequate for patients with AML in relapse or with refractory disease, whereas additional targeted antileukemic therapy may be beneficial.

Assuming a favorable role of radioimmunoconjugates, it remains unclear which antigen should be targeted and which radionuclide should be used, because no comparative trials testing radioimmunoconjugate targeting different antigens have been reported. The accumulated clinical experience shows the feasibility of integrating radioimmunoconjugates targeting CD33, CD45, or CD66 antigens into treatment regimens for leukemias.[51] Our group has focused on the CD45 antigen as an attractive alternative target for radioimmunotherapy of AML and MDS. This antigen is expressed on more than 70% of nucleated cells in normal bone marrow, with an average copy number of approximately 200 000 molecules per cell.[52] The abundant expression of CD45 on virtually all leukocytes, including myeloid precursors in bone marrow and mature lymphocytes in lymph nodes as well as more than 90% of AML samples, provides a high number of Ab binding sites in these tissues for patients in remission or relapse.[53,54] When an anti-CD45 Ab is labeled with ^{131}I, the 0.8-mm pathlength of the isotope's beta particles results in radiation delivery to both antigen-positive and any surrounding antigen-negative cells in myeloid tissues. Therefore, the radioimmunoconjugate does not need to bind to every leukemia cell at a high density or penetrate homogeneously into bone marrow or tumor cell masses to induce lethal DNA damage.

Despite the extensive experience with the use of radioiodine in targeted radiotherapy, however, the high-energy gamma component of ^{131}I poses a radiation exposure risk for staff and family and requires that patients be treated in radiation isolation. Radiolanthanides have thus been the object of focus for radiotherapy by Ab targeting, given their ease of use in outpatient therapy settings. Although most radiolanthanides emit some γ rays, their emission energies do not typically require isolation of patients. Yttrium-90 (^{90}Y), which has high energy (2.3 MeV) and a relatively short half-life (2.7 days), does not emit characteristic γ rays and does not require radiation isolation. Limited data obtained with YAML568, a rat IgG2a monoclonal Ab that recognizes all CD45 isoforms, suggest that other anti-CD45 Abs can selectively deliver radiation to hematopoietic tissues when labeled with ^{90}Y, provided that patients are preloaded with unlabeled Ab.[55] Other investigators have explored the use of ^{90}Y conjugated to HuM195 to target CD33$^+$ AML cells, showing that ^{90}Y-HuM195 has antileukemic activity and that the ^{90}Y isotope resides for prolonged periods of time at leukemic sites and in marrow.[17,22,56,57] More recent studies have used α-emitters (^{213}Bi, ^{225}Ac, ^{211}At) where the deposition of energy over a much shorter range than β-emitters is of interest because targeted cells might be destroyed because of their high linear transfer energy while neighboring cells are spared; this may offer an advantage if avoidance of ablative marrow toxicity is a goal. The short half-lives, particularly of bismuth radionuclides, however, limit the clinical use to diseases in which cancer cells are readily accessible by Abs, and leukemias may be among the best candidates for radioimmunotherapy that uses α-emitters.

In summary, the delivery of supplemental radiation doses to bone marrow and spleen by ^{131}I–anti-CD45 Ab is well tolerated when combined with FLU/TBI in patients undergoing HCT for advanced AML and high-risk MDS who are not candidates for myeloablative HCT. We have now estimated the MTD of targeted radiotherapy that can be delivered in combination with a reduced-intensity strategy. The encouraging results from this study support an upcoming phase 2 trial that used the MTD of ^{131}I-BC8 Ab to further assess the antileukemic potential of this approach in older patients at high risk of disease recurrence. Because a carefully controlled randomized trial will ultimately be necessary to definitively assess the use of ^{131}I–anti-CD45 Ab when combined with FLU/TBI compared with the use of FLU or TBI alone, in a separate study we have also begun to explore the efficacy of this approach in patients in remission AML because these patients represent a relatively homogenous population that will allow us to most accurately assess the efficacy of our therapeutic approach. We are optimistic that this approach will improve the cure rates of allogeneic HCT for older patients with acute leukemia and MDS.

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Authorship

Contribution: J.M.P. contributed to the conception, design, analysis, and interpretation of the research and drafted the manuscript; T.A.G. performed all statistical analyses and revised the manuscript; J.R. and D.R.F. contributed to the conception and design of the study, performed research, and analyzed data; D.C.M. contributed to the conception and design of the research; W.A.W. performed research and revised the

manuscript; A.K.G., H.J.D., P.J.M., B.M.S., and R.F.S. contributed to the conception and design of the study, interpreted data, and revised the manuscript; and O.W.P. and F.R.A. contributed to the conception, design, analysis, and interpretation of the research and revised the manuscript.

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References

1. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood.* 1997;89(12):4531-4536.
2. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood.* 1998;91(3):756-763.
3. Storb R, Yu C, Wagner JL, et al. Stable mixed hematopoietic chimerism in DLA-identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. *Blood.* 1997;89(8):3048-3054.
4. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood.* 2001;97(11):3390-3400.
5. Sandmaier BM, Storb R. Nonmyeloablative therapy and hematopoietic cell transplantation for hematologic disorders. In: Blume KG, Forman SJ, eds. *Thomas' Hematopoietic Cell Transplantation.* 3rd ed. Malden, MA: Blackwell Publishing Ltd; 2004:1164-1176.
6. Maris MB, Niederwieser D, Sandmaier BM, et al. HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative conditioning for patients with hematologic malignancies. *Blood.* 2003;102(6):2021-2030.
7. Niederwieser D, Maris M, Shizuru JA, et al. Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood.* 2003;101(4):1620-1629.
8. Rezvani AR, Storer B, Maris M, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin's lymphoma. *J Clin Oncol.* 2008;26(2):211-217.
9. Burroughs LM, O'Donnell PV, Sandmaier BM, et al. Comparison of outcomes of HLA-matched related, unrelated, or HLA-haploidentical related hematopoietic cell transplantation following nonmyeloablative conditioning for relapsed or refractory Hodgkin lymphoma. *Biol Blood Marrow Transplant.* 2008:14(11):1279-1287.
10. Hegenbart U, Niederwieser D, Sandmaier BM, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol.* 2006; 24(3):444-453.
11. Gyurkocza B, Storb R, Storer B, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with de novo and secondary acute myeloid leukemia [abstract]. *Blood.* 2008; 112(11):Abstract 149.
12. Laport GG, Sandmaier BM, Storer BE, et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. *Biol Blood Marrow Transplant.* 2008;14(2):246-255.
13. Kahl C, Storer BE, Sandmaier BM, et al. Relapse risk in patients with malignant diseases given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *Blood.* 2007; 110(7):2744-2748.
14. Matthews DC, Appelbaum FR, Eary JF, et al. Phase I study of (131)I-anti-CD45 antibody plus cyclophosphamide and total body irradiation for advanced acute leukemia and myelodysplastic syndrome. *Blood.* 1999;94(4):1237-1247.
15. Pagel J, Gooley T, Rajendran J, et al. Targeted radiotherapy using 131I-anti-CD45 antibody followed by allogeneic hematopoietic cell transplantation (HCT): the relationships among dosimetry, bone marrow uptake, and relapse. *Eur J Nucl Med Mol Imaging.* 2006;33(supp 2):S193.
16. Pagel JM, Appelbaum FR, Eary JF, et al. 131I-anti-CD45 antibody plus busulfan and cyclophosphamide before allogeneic hematopoietic cell transplantation for treatment of acute myeloid leukemia in first remission. *Blood.* 2006;107(5): 2184-2191.
17. Scheinberg DA, Lovett D, Divgi CR, et al. A phase I trial of monoclonal antibody M195 in acute myelogenous leukemia: specific bone marrow targeting and internalization of radionuclide. *J Clin Oncol.* 1991;9(3):478-490.
18. Appelbaum F, Matthews D, Eary JF, et al. The use of radiolabeled anti-CD33 antibody to augment marrow irradiation prior to marrow transplantation for acute myelogenous leukemia. *Transplantation.* 1992;54(5):829-833.
19. Waldmann TA, Pastan IH, Gansow OA, Junghans RP. The multichain interleukin-2 receptor: a target for immunotherapy. *Ann Intern Med.* 1992;116(2): 148-160.
20. Kaminski MS, Zasadny KR, Francis IR, et al. Radioimmunotherapy of B-cell lymphoma with [131I]anti-B1 (anti-CD20) antibody. *N Engl J Med.* 1993;329(7):459-465.
21. Press OW, Eary JF, Appelbaum FR, et al. Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. *N Engl J Med.* 1993;329(17):1219-1224.
22. Schwartz MA, Lovett DR, Redner A, et al. Dose-escalation trial of M195 labeled with iodine 131 for cytoreduction and marrow ablation in relapsed or refractory myeloid leukemias. *J Clin Oncol.* 1993;11(2):294-303.
23. Press OW, Eary JF, Appelbaum FR, et al. Phase II trial of 131I-B1 (anti-CD20) antibody therapy with autologous stem cell transplantation for relapsed B cell lymphomas. *Lancet.* 1995;346 (8971):336-340.
24. Waldmann TA, White JD, Carrasquillo JA, et al. Radioimmunotherapy of interleukin-2R alpha-expressing adult T-cell leukemia with Yttrium-90-labeled anti-Tac. *Blood.* 1995;86(11):4063-4075.
25. Petersdorf EW, Anasetti C, Martin PJ, et al. Limits of HLA mismatching in unrelated hematopoietic cell transplantation. *Blood.* 2004;104(9):2976-2980.
26. Eary JF, Press OW, Badger CC, et al. Imaging and treatment of B-cell lymphoma. *J Nucl Med.* 1990;31(8):1257-1268.
27. Cancer Therapy Evaluation Program (National Cancer Institute) common toxicity criteria, version 2.0. http://ctep.info.nih.gov. Accessed March 1, 2009.
28. Sgouros G. Bone marrow dosimetry for radioimmunotherapy: theoretical considerations. *J Nucl Med.* 1993;34(4):689-694.
29. Siegel JA, Wessels BW, Watson EE, et al. Bone marrow dosimetry and toxicity for radioimmunotherapy. *Antibody Immunoconj Radiopharm.* 1990;3:213.
30. Fisher DR, Badger CC, Brietz H, et al. Internal radiation dosimetry for clinical testing of radiolabeled monoclonal antibodies. *Antibody Immunoconj Radiopharm.* 1991;4:655.
31. Siegel JA, Pawlyk DA, Lee RE, et al. Tumor, red marrow, and organ dosimetry for 131I-labeled anti-carcinoembryonic antigen monoclonal antibody. *Cancer Res.* 1990;50(3 suppl):1039s-1042s.
32. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol.* 1988; 6(10):1562-1568.
33. Storer BE. Small-sample confidence sets for the MTD in a phase I clinical trial. *Biometrics.* 1993; 49(4):1117-1125.
34. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
35. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Statist Med.* 1999;18:695-706.
36. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood.* 2000;96(13):4075-4083.
37. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant.* 1995;15(6):825-828.
38. Martin PJ, McDonald GB, Sanders JE, et al. Increasingly frequent diagnosis of acute gastrointestinal graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2004;10(5):320-327.
39. Sierra J, Storer B, Hansen JA, et al. Transplantation of marrow cells from unrelated donors for treatment of high-risk acute leukemia: the effect of leukemic burden, donor HLA-matching, and marrow cell dose. *Blood.* 1997;89(11):4226-4235.
40. Miller CB, Zehnbauer BA, Piantadosi S, Rowley SD, Jones RJ. Correlation of occult clonogenic leukemia drug sensitivity with relapse after autologous bone marrow transplantation. *Blood.* 1991;78(4):1125-1131.
41. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. *Blood.* 1990;76(9):1867-1871.
42. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: a randomized trial of two irradiation regimens. *Blood.* 1991;77(8):1660-1665.
43. Matthews DC, Badger CC, Fisher DR, et al. Selective radiation of hematolymphoid tissue delivered by anti-CD45 antibody. *Cancer Res.* 1992; 52(5):1228-1234.
44. Matthews DC, Appelbaum FR, Eary JF, et al. Radiolabeled anti-CD45 monoclonal antibodies target lymphohematopoietic tissue in the macaque. *Blood.* 1991;78(7):1864-1874.

45. Rosario E, Rajendran J, Ruffner KL, et al. Radiolabeled anti-CD45 with cyclophosphamide (CY) and total body irradiation (TBI) followed by allogeneic hematopoietic stem cell transplantation (HSCT) for patients with advanced acute myeloid leukemia (AML) or myelodysplastic syndrome [abstract]. *Blood.* 2001;98(11):857a.

46. Hogan WJ, Maris M, Storer B, et al. Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. *Blood.* 2004;103(1):78-84.

47. Mielcarek M, Burroughs L, Leisenring W, et al. Prognostic relevance of 'early-onset' graft-versus-host disease following non-myeloablative haematopoietic cell transplantation. *Br J Haematol.* 2005;129(3):381-391.

48. Wong R, Giralt SA, Martin T, et al. Reduced-intensity conditioning for unrelated donor hematopoietic stem cell transplantation as treatment for myeloid malignancies in patients older than 55 years. *Blood.* 2003;102(8):3052-3059.

49. Kroger N, Bornhauser M, Ehninger G, et al. Allogeneic stem cell transplantation after a fludarabine/busulfan-based reduced-intensity conditioning in patients with myelodysplastic syndrome or secondary acute myeloid leukemia. *Ann Hematol.* 2003;82(6):336-342.

50. Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *J Clin Oncol.* 2008;26(30):4912-4920.

51. Pagel JM. Radioimmunotherapeutic approaches for leukemia: the past, present and future. *Cytotherapy.* 2008;10(1):13-20.

52. van der Jagt RH, Badger CC, Appelbaum FR, et al. Localization of radiolabeled antimyeloid antibodies in a human acute leukemia xenograft tumor model. *Cancer Res.* 1992;52(1):89-94.

53. Omary MB, Trowbridge IS, Battifora HA. Human homologue of murine T200 glycoprotein. *J Exp Med.* 1980;152(4):842-852.

54. Taetle R, Ostergaard H, Smedsrud M, Trowbridge I. Regulation of CD45 expression in human leukemia cells. *Leukemia.* 1991;5(4):309-314.

55. Glatting G, Muller M, Koop B, et al. Anti-CD45 monoclonal antibody YAML568: a promising radioimmunoconjugate for targeted therapy of acute leukemia. *J Nucl Med.* 2006;47(8):1335-1341.

56. Jurcic JG. Antibody therapy of acute myelogenous leukemia. *Cancer Biother Radiopharm.* 2000;15(4):319-326.

57. Jurcic J. Potential for myeloablation with yttrium-90-HuM195 (anti-CD33) in myeloid leukemia [abstract]. *J Clin Oncol.* 2000;19:8a.