^{131}I–anti-CD45 antibody plus busulfan and cyclophosphamide before allogeneic hematopoietic cell transplantation for treatment of acute myeloid leukemia in first remission

John M. Pagel, Frederick R. Appelbaum, Janet F. Eary, Joseph Rajendran, Darrell R. Fisher, Ted Gooley, Katherine Ruffner, Eneida Nemecek, Eileen Sickle, Larry Durack, Jeanette Carreras, Mary M. Horowitz, Oliver W. Press, Ajay K. Gopal, Paul J. Martin, Irwin D. Bernstein, and Dana C. Matthews

In an attempt to improve outcomes for patients with acute myeloid leukemia (AML) after allogeneic hematopoietic cell transplantation (HCT), we conducted a phase 1/2 study in which targeted irradiation delivered by ^{131}I–anti-CD45 antibody was combined with targeted busulfan (BU; area-under-curve, 600-900 ng/mL) and cyclophosphamide (CY; 120 mg/kg). Fifty-two (88%) of 59 patients receiving a trace ^{131}I-labeled dose of 0.5 mg/kg anti-CD45 murine antibody had higher estimated absorbed radiation in bone marrow and spleen than in any other organ. Forty-six patients were treated with 102 to 298 mCi (3774-11 026 MBq) ^{131}I, delivering an estimated 5.3 to 19 (mean, 11.3) Gy to marrow, 17-72 (mean, 29.7) Gy to spleen, and 3.5 Gy (n = 4) to 5.25 Gy (n = 42) to the liver. The estimated 3-year nonrelapse mortality and disease-free survival (DFS) were 21% and 61%, respectively. These results were compared with those from 509 similar International Bone Marrow Transplant Registry patients who underwent transplantation using BU/CY alone. After adjusting for differences in age and cytogenetics risk, the hazard of mortality among all antibody-treated patients was 0.65 times that of the Registry patients (95% CI 0.39-1.08; *P* = .09). The addition of targeted hematopoietic irradiation to conventional BU/CY is feasible and well tolerated, and phase 2 results are sufficiently encouraging to warrant further study. (Blood. 2006;107:2184-2191)

Introduction

Despite many advances in the field of hematopoietic cell transplantation (HCT), long-term disease-free survival for patients with acute myeloid leukemia (AML) in first remission undergoing HLA-matched related allogeneic transplantation has not exceeded 50% to 65% over the past 2 decades.[1-7] Recurrent malignancy remains a major problem, particularly for patients with high-risk disease.[3] Efforts to decrease the risk of relapse after HLA-matched related HCT have included increasing the intensity of the preparative regimen. A prospective randomized study of different radiation doses in patients with AML in first remission undergoing matched sibling HCT suggested a substantial beneficial impact of whole-body radiation dose on relapse rates. In that study, the relapse rate was 12% in patients receiving 15.75 Gray (Gy) total body irradiation (TBI), compared with 35% following 12 Gy.[8] A similar study in patients with chronic-phase chronic myeloid leukemia (CML) found that the recurrence rate was 0% after 15.75 Gy, compared with 25% after 12 Gy.[9] However, in both studies the higher TBI exposure was associated with significantly higher transplant-related mortality, such that there was no difference in long-term disease-free survival between the 2 randomized groups. The relatively steep dose-response curve of AML and CML for radiation demonstrated by these studies led to the hypothesis that if radiation could be better targeted directly to sites of leukemic involvement in bone marrow and spleen, while avoiding normal organs such as liver, lung, kidneys, and mucous membranes, relapse rates might be decreased without excessive toxicity.

Radiolabeled monoclonal antibodies have been used in both preclinical[10-19] and clinical[20-38] studies to deliver radiation to sites of leukemia or lymphoma. We selected CD45 as a target antigen because its expression is limited to myeloid and lymphoid cells, it is expressed by most AML samples at relatively high levels, approximately 200 000 copies per cell, and the antigen does not internalize after antibody binding.[16] Since CD45 is expressed on both normal and leukemic cells, it can be used to target marrow in both remission and relapse. Radioiodinated monoclonal antibodies reactive with the CD45 antigen have been demonstrated to deliver more radiation to bone marrow, spleen, and lymph nodes than to normal nontarget organs in murine and macaque studies.[39,40]

From the Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA; the Departments of Pediatrics, Medicine, and Radiology, University of Washington, Seattle, WA; the Pacific Northwest National Laboratory, Richland, WA; and the Medical College of Wisconsin, Milwaukee, WI.

Submitted June 16, 2005; accepted October 12, 2005. Prepublished online as *Blood* First Edition Paper, October 27, 2005; DOI 10.1182/blood-2005-06-2317.

Supported by National Institutes of Health grants K08CA95448, CA44991, CA18029, and CA76930, and Leukemia and Lymphoma Society SCOR grant 7040-03. J.M.P. is a recipient of a Career Development Award form the Lymphoma Research Foundation, an ASCO Career Development Award, and is a Scholar of the Damon Runyon Cancer Research Foundation. D.C.M. is a Clinical Scholar of the Leukemia Society of America. A portion of this work was conducted through the General Clinical Research Center at the University of Washington and supported by National Institutes of Health grant M01RR-00037.

Reprints: John M. Pagel, Fred Hutchinson Cancer Research Center D5-380, 1100 Fairview Ave N, PO Box 19024, Seattle, WA 98109; e-mail: jpagel@fhcrc.org.

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In a previous phase 1 study combining escalating doses of radiation delivered by ^{131}I-labeled anti-CD45 antibody with cyclophosphamide (CY) and 12 Gy TBI in patients with advanced acute leukemia and myelodysplastic syndrome, 84% of patients had favorable biodistribution of antibody (a higher estimated radiation-absorbed dose to marrow and spleen compared with liver, lung, and kidney).[29] The estimated radiation doses delivered to marrow and spleen were 2.3- and 4.8-fold greater than to liver, the normal organ estimated to receive the highest dose in all but one patient. The maximum tolerated dose of radiation delivered by ^{131}I–anti-CD45 antibody was estimated to be 10.5 Gy to the liver when combined with CY/TBI.

Based on our demonstration that, in the majority of patients, greater estimated radiation doses could be delivered to marrow and spleen compared with liver, lung, and kidney, and that significant supplemental doses of hematopoietic radiation could be safely combined with a conventional transplant preparative regimen, a trial for patients with AML in first remission receiving HLA-matched related marrow was then initiated. The initial results of this phase 1/2 study combining radiolabeled anti-CD45 antibody with busulfan (BU) and CY are reported in this article. Radiolabeled antibody was combined with BU/CY because a prospective randomized study in chronic-phase CML had demonstrated lower toxicity with BU/CY,[41] while retrospective comparisons of BU/CY and CY/TBI for transplantation of AML in first remission have shown similar incidences of long-term disease-free survival.[1] In this article, we also compare the results using ^{131}I–anti-CD45 antibody/BU/CY to those observed in historical cohorts of patients with AML in CR1 treated with BU/CY alone.

Patients, materials, and methods

Patient selection

Between February 1994 and November 2003, patients with AML in first remission with an HLA-identical family donor were considered for this study. Patients were excluded if they had evidence of major organ dysfunction, seropositivity for HIV, allergies to mouse protein or to iodine, or antibody specific for mouse immunoglobulin. Patients were informed of the investigational nature of this phase 1/2 study and signed a consent form approved by the Human Subjects Committee of the University of Washington and the institutional review board of the Fred Hutchinson Cancer Research Center (FHCRC), per the Declaration of Helsinki. The primary objective of the study was to determine the efficacy (as measured by survival) and toxicity of the experimental regimen in patients with AML in first remission receiving HLA-identical related peripheral blood stem cell (PBSC) transplants. The designed primary end point of the study was an estimated observed OS at 2 years of 60% or greater.

Antibody production, purification, and radiolabeling

BC8 antibody is a murine IgG1 reactive with all CD45 isoforms, secreted by a hybridoma developed and kindly provided by Dr Claudio Anasetti of the FHCRC. The first 4 patients received BC8 antibody produced by Brunswick (San Diego, CA), while subsequent patients received BC8 antibody produced and purified in the Biologics Production Facility at the FHCRC as previously described.[29] BC8 antibody was labeled with ^{131}I (specific activity 8.0 Ci [296 GBq]/mg; New England Nuclear, Boston, MA) by the chloramine-T method and purified and tested as previously described.[42]

Determination of antibody biodistribution and radiation absorbed dose

Patients first received an infusion of trace-^{131}I–labeled BC8 antibody to determine the biodistribution of antibody and estimate radiation absorbed doses to marrow, spleen, nontarget organs, and the whole body delivered per millicurie (mCi) ^{131}I. Patient serum was tested for the presence of human antimouse antibody (HAMA) using an enzyme-linked immunosorbent assay (ELISA) assay.[42] Organ volumes (liver, lungs, spleen, and kidney) were calculated from chest and abdominal computed tomography.[43] Thyroid uptake of free ^{131}I was blocked by oral Lugol solution (strong iodine/potassium iodide solution). Lugol solution was started 2 days before the administration of the test dose of labeled antibody and continued until 3 weeks after the administration of the therapeutic dose of ^{131}I-labeled BC8 antibody. The biodistribution study dose of 0.5 mg/kg BC8 antibody was labeled with 4 to 10 mCi (148-370 MBq) ^{131}I and was administered at 7.5 mg/hour after premedication with acetaminophen, diphenhydramine, and hydrocortisone. Patients experiencing symptoms such as chills or nausea received additional medications as needed, including meperidine and lorazepam. Infusion-related symptoms were graded prospectively using the National Institutes of Health (NIH) Common Toxicity Criteria (CTC) v2.0 toxicity scale (Cancer Therapy Evaluation Program [National Cancer Institute] Common Toxicity Criteria, version 2.0, http://ctep.info.nih.gov.).

Patients underwent quantitative gamma imaging at the end of infusion (hour 0) and then daily for 3 days using a dedicated GE MAXXUS (General Electric Medical Systems, Milwaukee, WI), dual-headed, large-field-of-view camera with high-energy collimators (Figure 1). Regions of interest including 2 marrow sites (right acetabulum and sacrum), spleen, liver, lungs, and kidneys were imaged using a 180° opposing view quantitative planar technique.[43] 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 to 24 hours after the end of infusion), and weighed and counted against a weighed reference aliquot of the injected dosage to calculate the

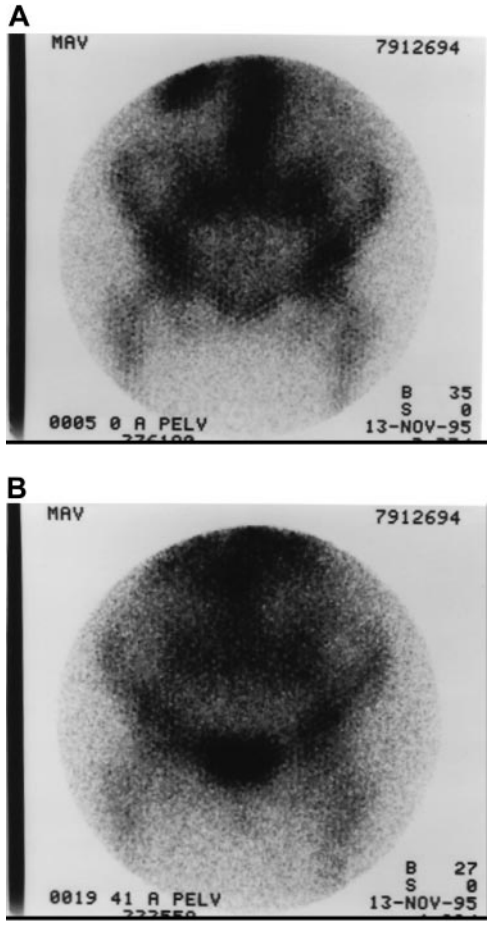

Figure 1. ^{131}I–anti-CD45 antibody localization. Anterior images of pelvis demonstrating localization of ^{131}I-BC8 antibody in a patient with AML in remission 0 hours (A) and 41 hours (B) after infusion of trace-labeled antibody.

percent injected dose per gram (% ID/g) in marrow. The red marrow clearance curve was scaled by correcting the biopsy-determined % ID/g of ^{131}I-BC8 by a multiplication factor of 2, since antibody cannot bind to the trabecular bone and fat, which makes up approximately half of the total biopsy weight.[44,45] 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.[46] Patient marrow volumes were normalized to the MIRD model values of 1120 g for the standard 73-kg adult and 1050 g for the 58-kg smaller adult woman, or 15-year-old, 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.[45]

Therapy

Those patients for whom the biodistribution study estimated that a greater radiation-absorbed dose would be delivered to the marrow and spleen than to any normal organ were considered to have favorable biodistribution and were eligible to receive a therapy dose of ^{131}I-BC8. The therapy infusion of antibody 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 initial 4 patients were treated at dose level 1, with an estimated 3.5 Gy delivered to the normal organs by ^{131}I-BC8 antibody. The dose was then escalated to level 2, 5.25 Gy, after these first 4 patients did not experience excessive (grade III, life-threatening, or grade IV, fatal) regimen-related toxicity, as defined by Bearman criteria, a scale developed specifically for marrow transplant patients.[47] Patients were prospectively evaluated for regimen-related toxicities daily for 30 days prior to dose escalation for subsequent patients. Escalation of the dose was to be allowed only if none of 10 patients treated at dose level 2 developed grade III/IV regimen-related toxicity.

The therapy dose was administered on day −13 of the preparative regimen, which was 8 to 14 days after the biodistribution dose except for one patient with a 52-day interval. Patient serum was retested for HAMA the day prior to the therapy dose and if positive, the patient was off study and received an alternative HCT regimen. Patients remained in radiation isolation in lead-lined rooms after the therapy dose until radiation exposure was less than or equal to 2 mR/hour at 1 meter. The radiolabeled antibody was infused through an automatic pump from a lead-shielded reservoir. Vital signs were determined and 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. Phenytoin was administered beginning at day −8 and BU was started at day −7. The first 3 patients received a total BU dose of 16 mg/kg adjusted ideal body weight administered as 1 mg/kg every 6 hours by mouth for 16 doses. To avoid excess toxicity, subsequent patients underwent pharmacokinetic monitoring of plasma BU levels with adjustment of BU dosing to maintain an average BU concentration of 600 to 900 ng/mL.[48] Patients then received CY 60 mg/kg intravenously on days −3 and −2, followed by infusion of unmanipulated bone marrow or PBSCs on day 0. Pharmacokinetic monitoring of CY was not performed in this study. Patients received cyclosporine (CSP) and methotrexate (MTX) for graft-versus-host disease (GVHD) prophylaxis. MTX was delivered at 15 mg/m^2 intravenously on day 1 and 10 mg/m^2 on days 3, 6, and 11. CSP was delivered beginning on day −1 at 3 mg/kg per day intravenously in 2 divided doses or oral dosing as tolerated to achieve equivalent serum levels until day 50 followed by 5% taper per week through day 180.[49]

Statistical analysis

Overall and disease-free survival were estimated using the method of Kaplan and Meier. Nonrelapse mortality (NRM) and relapse probabilities were computed using cumulative incidence estimates.[50] Relapse was considered a competing risk for NRM, and death without relapse a competing risk for relapse. Cox regression was used to compare the hazard of mortality among patients entered on this antibody study to that among historical controls.

Results

Patient characteristics

Fifty-nine patients with AML in first remission received a biodistribution infusion of ^{131}I-BC8 antibody. Fifty-two (88%) patients (median age, 41 years; range, 16-55 years) receiving a biodistribution dose had favorable antibody biodistribution. All patients with unfavorable biodistribution of the radiolabeled antibody subsequently received HLA-matched related allogeneic transplants using standard BU/CY conditioning. Forty-six patients with a favorable biodistribution received a therapeutic dose of BC8 Ab labeled with an amount of ^{131}I estimated to deliver 3.5 Gy (first 4 patients) to 5.25 Gy (all subsequent patients) to the normal organ receiving the highest dose (Table 1). Six patients with favorable biodistribution were not treated with a therapeutic dose of radiolabeled antibody because of donor problems in 2 patients, active fungal infection in 2 patients, relapse in 1 patient, and an elevated AST after biodistribution in 1 patient.

Patients were distributed across FAB classifications at diagnosis, with the exception that patients with acute promyelocytic leukemia were specifically not enrolled in the study (Table 1). Of the 46 patients receiving a therapy dose of antibody on study, marrow cytogenetics at diagnosis were available for 42 patients. Using current SWOG criteria for classification of cytogenetic risk,[51] 1 patient had favorable cytogenetics, 26 had intermediate-risk cytogenetics, and 15 had unfavorable cytogenetics. For patients treated in the study, the median time from achievement of remission to HCT was 4.0 months, with a range of 1.3 to 7.5 months. Treated patients received a median of 2 cycles of chemotherapy. Twenty-six of the patients were reported to be in remission after the first cycle of induction chemotherapy, with 20 other patients requiring a second cycle of induction chemotherapy. The first induction therapy consisted of 7 days of conventional-dose cytosine arabinoside combined with 3 doses of an anthracycline in 72% of cases. Thirty patients received consolidation chemotherapy (19 of whom received high-dose cytosine arabinoside), with a median of one cycle of consolidation therapy delivered. Table 1 shows the characteristics of patients receiving ^{131}I-BC8/BU/CY conditioning prior to allogeneic HCT for AML in first complete remission.

^{131}I-BC8 antibody infusion, biodistribution, and radiation-absorbed dose

No patients experienced grade 4 antibody infusion–related side effects. Moderate (grade 2) infusional toxicities were experienced by 47% of patients despite premedications, and all of these toxicities resolved by the end of each infusion. Forty-one percent of patients experienced chills, and 46% of these patients required administration of meperidine. Thirty-seven percent of patients developed nausea and vomiting, and 29% of patients developed respiratory symptoms such as throat or chest tightness. Eight percent of patients developed grade 2 hypotension requiring intravenous fluid administration, and 7% experienced grade 3 hypotension that resolved without further physiologic consequences in less than 24 hours. The average calculated concentration of ^{131}I-BC8 antibody in marrow at the end of infusion (hour 0) was

Table 1. Patient characteristics for all ^{131}I-BC8 studied and treated patients receiving BU/CY alone

Characteristic	All ^{131}I-BC8 studied patients	All ^{131}I-BC8 treated patients
Number of patients	52	46
Median age, y (range)	41 (16-55)	42.5 (16-55)
Median WBCs × 10^9/L at diagnosis (range)	9.8 (0.6-180)	12.9 (0.6-180)
FAB classification*, no. (%)		
M0	2 (3.8)	1 (2.2)
M1	9 (17)	9 (20)
M2	11 (21)	8 (17)
M3	0 (0)	0 (0)
M4	14 (27)	13 (28)
M5	7 (13)	6 (13)
M6	1 (1.9)	1 (2.2)
M7	1 (1.9)	1 (2.2)
ND	7 (13)	7 (15)
Cytogenetic risk group†, no. (%)		
Favorable	1 (1.9)	1 (2.2)
Intermediate	30 (58)	26 (57)
Unfavorable (high)	16 (31)	15 (33)
ND	5 (9.6)	4 (8.7)
More than 1 cycle of chemotherapy to achieve CR1, no. (%)	24 (46)	20 (44)
3 or fewer mo from CR1 to HCT, no. (%)	NA	10 (22)
No. of consolidation courses, no. of patients (%)		
0	15 (29)	15 (33)
Fewer than 2 cycles	23 (44)	21 (46)
2 or more cycles	9 (17)	9 (20)
Unknown	5 (9.6)	1 (2.2)
Secondary AML/MDS, no. (%)	6 (12)	5 (11)
Source of stem cells, no. (%)		
Bone marrow	NA	40 (87)
Peripheral blood	NA	6 (13)

WBC indicates white blood cell count; ND, not determined; MDS, myelodysplastic syndrome; NA, not applicable.
*French-American-British classification of blast morphology.
†Southwest Oncology Group criteria.

0.024% ± 0.01% ID/g, with an average antibody retention half-time in the marrow of 42.1 ± 13.7 hours. The average concentration of ^{131}I-BC8 antibody in marrow at the time of biopsy 14 to 24 hours after infusion was 0.020% ± 0.007% ID/g.

The average estimated radiation dose delivered per unit administered activity (cGy/MBq ± SD) to bone marrow of the 52 patients with favorable biodistribution of ^{131}I-BC8 antibody was 0.16 ± 0.07, 0.44 ± 0.18 to spleen, 0.86 ± 0.027 to liver, 0.14 ± 0.0027 to kidney, and 0.4 ± 0.1 to the total body. In the 46 treated patients, the average estimated radiation doses to bone marrow (BM), spleen, liver, kidney, and to the total body per unit administered activity were 0.18 ± 0.065, 0.46 ± 0.19, 0.081 ± 0.019, 0.011 ± 0.0027, and 0.014 ± 0.0027 cGy/MBq ± SD, respectively. The 7 patients with unfavorable biodistribution had an average BM-liver ratio of 0.86 ± 0.11.

In the first 26 patients, the estimated radiation dose delivered to lung was 0.049 ± 0.016 cGy/mBq, and in each patient the estimated lung dose was less than the liver dose. However, these estimates of lung dose were obtained by gamma camera images of lung obtained "through" ribs, and thus represent overestimates of lung dose because of ^{131}I in rib marrow. Because the liver is always the normal organ estimated to receive the highest dose, and because the actual dose delivered to lung is less than these estimates suggested, lung dose was not calculated in subsequent patients. For the 52 patients with a favorable biodistribution of ^{131}I-BC8 antibody, the average ratio of radiation delivered to marrow compared with the liver was 1.9, with ratios of 12.4 and 15.5 for marrow to kidney and to total body, respectively. For the 46 patients receiving a therapeutic dose, the ratio was 2.2 ± 0.5 for marrow to liver, 16.3 ± 3.3 for marrow to kidney, and 13.0 ± 3.1 for marrow to total body.

Therapy, toxicities, and engraftment

Forty-six patients received a therapy dose of ^{131}I-BC8 antibody. The first 4 patients were treated at dose level 1, receiving 105 to 152 mCi (3885-5624 MBq) ^{131}I, estimated to deliver 7.2 to 11.2 (average, 9.2) Gy to bone marrow, 14.8 to 23.1 (average, 17.3) Gy to spleen, and 3.5 Gy to liver. As none of these patients developed grade III/IV regimen-related toxicity, the next 42 patients were treated at dose level 2. They received 102 to 298 mCi (3774-11 026 MBq) ^{131}I, estimated to deliver 5.3 to 19.0 (average, 11.3) Gy to bone marrow, 17.5 to 72.3 (average, 29.7) Gy to spleen, and 5.25 Gy to liver. Patients generally experienced the same antibody-related side effects during the therapy infusion as they had with the biodistribution infusion of antibody. Eighteen (30%) patients reported nausea and 5 (11%) emesis during the first days following the therapy dose of antibody, each complication presumably resulting from the radioiodine. All patients were discharged from radiation isolation by the fourth day after radiolabeled antibody treatment.

All patients developed at least grade II mucositis (Bearman scale) after day zero, with onset typically occurring between days 1 to 3 after HCT, and which required narcotic therapy. Three (6.5%) of the 46 patients developed grade III/IV regimen-related toxicities. Two patients treated at dose level 2 developed grade III (life-threatening) mucositis as defined by the occurrence of aspiration pneumonia. A third patient treated at level 2 was recovering from

typical grade II mucositis when he developed a severe exacerbation, documented to be associated with reactivation of herpes simplex virus and was not considered to be grade III regimen-related toxicity. No patient developed grade III veno-occlusive disease (VOD) of the liver. Eight patients treated at dose level 2 died of transplant-related causes (Table 2).

Thirty-seven (80%) of the 46 patients receiving ^{131}I-BC8 antibody developed grades I to IV acute GVHD a median of 22 days (range, 10-80 days) after transplantation, and 33 (72%) developed grades II to IV GVHD. Tables 3-4 describe the organ-specific acute GVHD stage and overall incidence of all GVHD grades.[52,53] Thirty-two (84%) of 38 evaluable ^{131}I-BC8/BU/CY patients developed chronic GVHD. Forty-three treated ^{131}I-BC8 antibody patients received all 4 planned doses of intravenous methotrexate after transplantation. Three patients did not receive the fourth, day 11, dose because of the severity of mucositis or mild VOD. Patients treated with ^{131}I-BC8 antibody followed by BU/CY conditioning took a median of 21 days (range, 13-31 days) to achieve a neutrophil count higher than 0.5×10^9/L (500/μL) and a median of 20.5 days (range, 9-47 days) until platelet counts were higher than 20×10^9/L (20 000/μL) after transplantation. Thirty (71%) of 42 evaluable patients became hypothyroid 3 to 60 months (median, 15 months) after transplantation and have been treated with thyroxine. No cases of thyroid carcinoma have been reported.

Overall and disease-free survival, nonrelapse mortality, and relapse

A total of 16 patients have died as of last contact among the 46 who received a therapeutic dose of ^{131}I-BC8 antibody. The estimated 3-year survival among all 46 patients is 63% (95% confidence interval [CI], 49%-77%). Among patients with intermediate-risk cytogenetics, the 3-year overall survival estimate is 75% (95% CI, 58%-92%) and among those with unfavorable cytogenetics, the estimate is 36% (95% CI, 11%-62%). A total of 18 patients died or relapsed (2 patients who relapsed were alive as of last contact), leading to a 3-year DFS estimate of 61% (95% CI, 46%-75%). The 3-year DFS estimates in the intermediate-risk and unfavorable cytogenetics groups are 71% (95% CI, 53%-89%) and 37% (95% CI, 11%-62%), respectively.

Nine patients died without disease recurrence and 9 patients have relapsed as of last contact. Eight of the 9 relapsed patients had recurrence of their disease in the bone marrow, with 1 patient developing a skin chloroma. No correlation was found between the absorbed radiation dose delivered to the bone marrow or spleen and the risk of relapse. The absorbed radiation doses to the bone marrow and spleen were 11.3 ± 3.3 Gy and 28.4 ± 4.4 Gy, respectively, for the patients who relapsed of their disease after transplantation. For patients who did not relapse, the absorbed dose to bone marrow and spleen was 11.3 ± 3.3 Gy ($P = .99$) and 30.6 ± 10.4 Gy ($P = .36$), respectively. The estimate of NRM at 3 years is 21% (95% CI, 9%-33%), and the estimated probability of relapse at this time is 19% (95% CI, 7%-30%). The 3-year NRM in the group of patients with intermediate-risk cytogenetics is 21% (95% CI, 5%-37%) and among the unfavorable group is 27% (95% CI, 4%-50%). The probability of relapse at 3 years is estimated to be 8% (95% CI, 0%-19%) in the intermediate-risk group and 36% (95% CI, 11%-61%) in the group with unfavorable cytogenetics.

Figures 2-4 summarize the probabilities of DFS, relapse, and NRM among all 46 patients who received a therapy dose of ^{131}I-BC8 antibody (Figure 2), among those with intermediate-risk cytogenetics (Figure 3), and among those with unfavorable cytogenetics (Figure 4).

Table 2. Transplant-related cause of death for patients treated with ^{131}I-BC8/BU/CY

Fatal toxicity	Treated ^{131}I-BC8/BU/CY patients
Sepsis	2
Pulmonary toxicity*	1
Viral pneumonia	2
Fungal pneumonia	2
VZV encephalitis	1
Total 100-day TRM, no. (%)	4 (8.7)

N = 46.
VZV indicates varicella-zoster virus.
*Pulmonary toxicity indicates noninfectious pneumonitis.

Table 3. Organ-specific acute GVHD stage in patients receiving ^{131}I-BC8/BU/CY and HLA-matched related allogeneic transplants for AML in first complete remission

Organ-specific GVHD severity stage[52,53]	Skin, no. (%)	Liver, no. (%)	Gut, no. (%)
No acute GVHD	27 (57)	28 (61)	11 (24)
1	4 (9)	8 (17)	27 (59)
2	7 (15)	7 (15)	3 (7)
3	7 (15)	2 (4)	5 (11)
4	1 (2)	1 (2)	0 (0)

Comparison of overall survival to historical control patients

In order to gain an idea about the potential efficacy of this treatment, we compared overall survival between an antibody group and a group of control patients taken from the International Bone Marrow Transplant Registry (IBMTR). Given the strong correlation between cytogenetic risk and outcome, this comparison was restricted to patients whose cytogenetic risks were known. Furthermore, since only one antibody patient had favorable cytogenetics, the analysis was further confined to patients who had either intermediate-risk or unfavorable cytogenetics. For this "intent-to-treat" analysis, the antibody group contained 41 of the 46 patients who received a therapy dose of ^{131}I-BC8 antibody (the remaining 5 were missing cytogenetics), and 10 of the 13 patients who did not receive a therapy dose but went on to undergo HCT without radiolabeled antibody. Three patients who did not receive a therapy dose were not included in the comparison because one had unknown cytogenetics, one did not receive a transplant, and one had the transplantation significantly delayed due to donor issues. The IBMTR patients underwent transplantation over a period of time comparable with the period that the phase 1/2 trial currently reported was conducted, and this control group consisted of 509 patients. All IBMTR patients underwent transplantation for AML in first remission and were conditioned with BU/CY alone. The IBMTR patients were, on average, younger (mean of 28 years compared with a mean of 39 years), and a higher proportion had intermediate-risk cytogenetics compared with the antibody-treated

Table 4. Acute GVHD grade in patients treated with ^{131}I-BC8/BU/CY

GVHD grade[52,53]	No. of patients (%)
No acute GVHD	9 (20)
I	4 (9)
II	20 (43)
III	12 (26)
IV	1 (2)

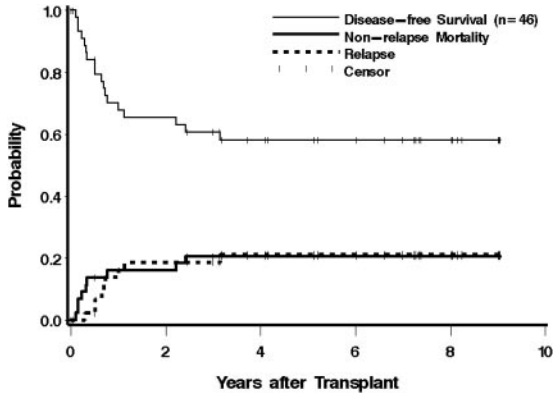

Figure 2. Estimates of the probability of DFS, NRM, and relapse among all patients who received a therapeutic dose of ^{131}I-BC8 antibody, followed by BU/CY.

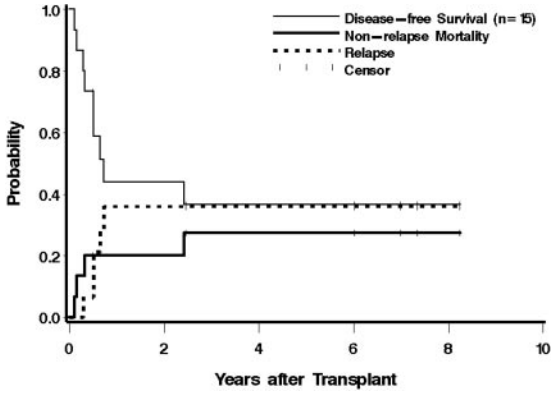

Figure 4. Estimates of the probability of DFS, NRM, and relapse among patients with unfavorable cytogenetics who received a therapeutic dose of ^{131}I-BC8 antibody, followed by BU/CY.

patients (92% compared with 65%). After adjusting for these factors in addition to the presence of secondary AML (10% of antibody-treated patients had secondary AML compared with 4% of IBMTR patients), the hazard of mortality in the antibody group was 0.65 times that of the hazard in the group that received BU/CY alone (95% CI, 0.39 to 1.08; $P = .09$).

Discussion

The use of ^{131}I–anti-CD45 antibody to deliver targeted radiation to bone marrow and spleen offers the opportunity to intensify the therapy received by leukemic cells to a greater extent than that received by the normal organs, which are the sites of dose-limiting toxicity. The results presented in this study demonstrate the feasibility of using ^{131}I–anti-CD45 antibody to deliver targeted hematopoietic radiation when combined with BU/CY in patients undergoing HCT for AML in first remission. Biodistribution administration of trace-labeled antibody showed that almost 90% of patients had a higher estimated radiation dose delivered to red marrow and spleen than to the liver, the normal organ receiving the highest dose. Determination of the biodistribution of ^{131}I-BC8 antibody for each patient was performed because of the wide range of estimated radiation dose to liver per mCi ^{131}I delivered in both this and our previous study.[29] Hepatic doses ranged from 0.051 to 0.14 cGy/MBq ^{131}I (with a single patient at 0.25), and thus there was great variability in the amount of ^{131}I required to deliver 5.25 Gy to liver. Individual determination of antibody biodistribution allowed the delivery of the highest radiation doses to hematopoietic tissues without exceeding the doses tolerated by normal organs for most patients. Based on these average estimated radiation doses, 11 Gy to marrow and 29 Gy to spleen were delivered at the higher dose level tested in patients treated with antibody labeled with therapeutic doses of ^{131}I.

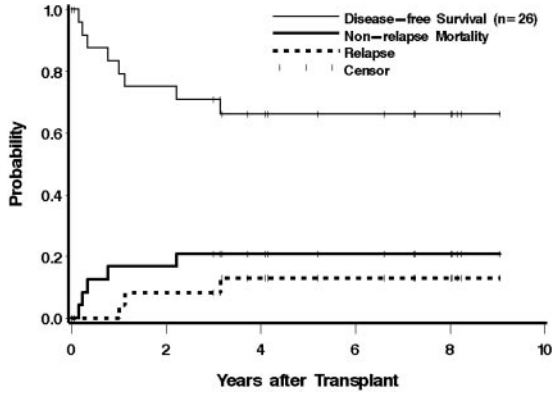

Figure 3. Estimates of the probability of DFS, NRM, and relapse among patients with intermediate-risk cytogenetics who received a therapeutic dose of ^{131}I-BC8 antibody, followed by BU/CY.

Intensified conditioning with ^{131}I-BC8 antibody resulted in few toxicities beyond those expected with BU/CY alone. Engraftment was not delayed after delivery of ^{131}I-BC8 antibody, and infusion-related toxicities were mild and manageable. The most frequent severe toxicity was grade III mucositis seen in 2 patients. Despite the planned delivery of 5.25 Gy to the liver, severe VOD was not seen and thus the incidence of severe hepatic toxicity did not appear to be substantially worse than what has been reported with BU/CY alone.[54] Some additional toxicities, however, were clearly attributable to the radiolabeled antibody. The development of grade II or greater mucositis was seen in all patients. Despite administration of Lugol solution to all patients during both the biodistribution and therapy phases of radiolabeled antibody treatment, approximately 70% of patients developed elevated thyroid-stimulating hormone levels. All patients that developed hypothyroidism received exogenous thyroid supplementation. Whether these increased nonlethal toxicities due to the delivery of supplemental, targeted radiation to hematopoietic tissues by ^{131}I–anti-CD45 antibody will be balanced by the potential of a decreased risk of recurrent leukemia is unknown.

The overall incidence of grades II to IV acute GVHD in this study was 71%. The apparent high rate of GVHD reported may be attributed to several factors. Most significantly, the reported incidence of grades II to IV acute GVHD after hematopoietic cell transplantation with HLA-identical sibling donors has increased considerably since the early 1990s at our Center.[53] The most striking change was an increased incidence of stage 1 gut GVHD involvement from 10% to 20% before 1992 to 50% to 60% since 1992, an increase almost certainly due to the aggressive use of endoscopy in patients with posttransplantation anorexia. This increased incidence of grade II acute GVHD resulted in an overall incidence of grade II to IV acute GVHD of 60% to 70% for patients who underwent transplantation with standard conditioning regimens using sibling donors, which is consistent with the 71% incidence of grades II to IV acute GVHD in the current study. While it remains possible that the radiolabeled antibody may contribute to the high incidence of acute GVHD, in the current study 59% of patients who received ^{131}I-BC8 antibody were graded

to have stage 1 gut GVHD, suggesting that this high level of diagnostic scrutiny and increased surveillance at our Center may have led to the apparent high overall incidence of GVHD.

We have used ^{131}I as the radiolabel in our studies because there is extensive experience with its medical use, the technology for radiolabeling antibodies with iodine is well established, and its gamma component allows direct determination of labeled antibody biodistribution. Iodine-131 is a beta/gamma-emitting radionuclide with a physical half-life of 8.1 days, a principal gamma ray energy of 364 keV, and a principal beta-particle spectrum with a maximum energy of 610 keV, an average energy of 190 keV, and a 90th percentile range in tissue of 0.8 mm, which allows for kill of $CD45^-$ cells that are close to $CD45^+$ cells coated with labeled antibody.[14] However, the high-energy gamma component of ^{131}I requires that patients be treated in radiation isolation, and poses a radiation exposure risk for staff and family. We recently investigated if ^{90}Y, which does not emit characteristic gamma lines and does not require radiation isolation, might result in improved therapeutic ratios because of its higher energy and shorter half-life (2.7 days). We examined the relative organ localization and retention of ^{90}Y–anti-CD45 antibody in a nonhuman primate model, which has previously been useful for accurately predicting the biodistribution of radiolabeled anti-CD45 antibody in humans. These preliminary studies suggest that the use of ^{90}Y as a radiolabel for CD45 antibody results in an approximately similar ratio of radiation to target compared with nontarget tissues as seen with ^{131}I.[55] However, the ability to treat patients with ^{90}Y without requiring radiation isolation, and the potential for improved homogeneity of radiation delivery within tissues given its longer path length, may provide therapeutic advantages.

CD33 and CD66 are additional hematopoietic differentiation antigens that have been explored as targets for radioimmunotherapy (RIT). Scheinberg and colleagues have studied an anti-CD33 Ab, M195, labeled with ^{131}I, as well as a humanized version of M195 (HuM195) conjugated to the radiometal isotope ^{90}Y.[27,34,56-59] These studies suggest that ^{90}Y-HuM195 has antileukemic activity and that the ^{90}Y isotope resides for prolonged periods of time at leukemic sites and in BM after localization. In an attempt to avoid the relative nonspecific cytotoxicity of beta-emitting constructs due to the crossfire effect, the alpha emitters ^{213}Bi and ^{225}Ac are currently being explored as radiolabels to treat leukemia.[60,61] Bunjes et al have also investigated a ^{188}Re-labeled anti-CD66 Ab as part of conditioning regimens prior to HCT in patients with high-risk AML.[62] By targeting CD66, which is present on maturing myeloid cells, radiation is delivered to neighboring leukemia blasts, which are usually $CD66^-$.

In an effort to gain preliminary evidence of the potential efficacy of the use of ^{131}I–anti-CD45 antibody, we performed a retrospective analysis comparing our data to registry data from the IBMTR on first-remission AML patients conditioned with BU/CY alone prior to HCT. After adjusting for age and cytogenetics risk, the hazard of mortality for the patients treated in our ^{131}I-BC8 antibody study is encouraging when compared with that among AML patients who underwent transplantation using a regimen of BU/CY alone. Of course, such retrospective nonrandomized comparisons have many weaknesses and cannot be used to definitively compare efficacy. The BU/CY regimens in the IBMTR control group were not limited to BU 16 mg/kg and CY 120 mg/kg; different forms of GVHD prophylaxis were used, as were different methods of supportive care. A carefully controlled randomized trial is necessary to definitively assess the use of ^{131}I–anti-CD45 antibody when combined with BU/CY compared with the use of BU/CY alone. However, the improved survival currently observed when compared with historical controls argues that such a study is, at least, reasonable.

In summary, the delivery of supplemental radiation doses to bone marrow and spleen by ^{131}I–anti-CD45 antibody is well tolerated when combined with BU/CY in patients undergoing HCT for AML in first remission. Although the use of radiolabeled antibody is labor intensive, the encouraging results to date in patients treated with this preparative regimen support continued study of this approach. A future phase 3 randomized trial comparing ^{131}I–anti-CD45 antibody/BU/CY to BU/CY alone in this patient group will provide a definitive test of our hypothesis that the addition of ^{131}I-BC8 antibody to BU/CY will improve survival.

Acknowledgments

The authors are indebted to Michael Reed for his expert data management, Jennifer Davies for her expert management of regulatory affairs, and to Carolyn Thostensen for her expert technical assistance. We also acknowledge the excellent care provided to these patients by the physicians and nurses of the HCT teams, as well as the work of the staff in the Long Term Follow-up office.

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