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)
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.15

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 131I (New England Nuclear; specific activity ~ 8.0 Ci [29.6 × 1010 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-131I–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]) of 131I. Patient serum was tested by marrow, spleen, nontarget organs, and the whole body delivered per the biodistribution of Ab and to estimate radiation-absorbed doses to chloramine-T method and was purified and tested as previously described.14

The therapy infusion of Ab was labeled with the amount of 131I 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.25 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. 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. 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 withdraw 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
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 CD34 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). 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.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>De novo AML (n = 28)</th>
<th>Secondary AML (n = 19)</th>
<th>High-risk MDS (n = 11)*</th>
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<td>REM/F</td>
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<td>65 (57-72)</td>
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<td>2.7 (1-126)</td>
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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.
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
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).

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 a 131I–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 131I–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 131I-BC8 Ab and myeloablative conditioning regimens in younger patients has led us to ask...
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. 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 131I-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 131I-BC8 Ab.

The results presented in this report show the feasibility of using 131I-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 131I-BC8 Ab was determined for each patient individually, because the range of estimated radiation dose to liver per millicurie (megabecquerel) 131I delivered in both this study and our previous studies was wide. These 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) 131I, indicating considerable variability in the amount of 131I required to deliver 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. 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. 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. 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.

As a phase 1 dose-finding trial, this study was not designed to examine the potential efficacy of the preparative regimen of 131I-anti-CD45 Ab combined with FLU/TBI. Whether the delivery of supplemental hematopoietic irradiation with the use of 131I-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

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>AML (n = 28)</th>
<th>Secondary AML (n = 19)</th>
<th>MDS* (n = 11)</th>
<th>All patients (n = 58)</th>
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<td>Infection, n</td>
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<td>GVHD, n</td>
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<tr>
<td>CNS, n</td>
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</table>

Total 100-day TRM (12 %). REM indicates remission; REF/REL, refractory/relapsed; CNS, central nervous system.

*Pulmonary toxicity indicates noninfectious pneumonitis.

†Pulmonary toxicity includes refractory anemia with excess of blasts and chronic myelomonocytic leukemia.

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

A 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. 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. 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.
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. Most treatment failures were approximately 40%. The median age of these patients was 59 years.

Our group has focused on the CD45 antigen targeting CD33, CD45, or CD66 antigens into treatment regimens for leukemias. Our current study was designed to evaluate the efficacy of 131I conjugated to HuM195 to target CD33+ AML cells, showing that 90Y-HuM195 has antileukemic activity and that the 90Y isotope resides for prolonged periods of time at leukemic sites and in marrow. More recent studies have used α-emitters (211Bi, 225Ac, 211At) 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 131I–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 131I–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 131I–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.

Acknowledgments

We thank Nathan Holm for his expert data management, Jennifer Davies for her expert management of regulatory affairs, and Larry Durack and Carolyn Thostensen for their 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.

This work was supported by the National Institute of Health (grants K08CA95448, PO1CA44991, CA109663, CA78902, CA15704, HL366444, CA18029), a SCOR grant from the Leukemia & Lymphoma Society of America, the Edison Foundation, and the Frederick Kullman Memorial Fund.

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
Conflict-of-interest disclosure: The authors declare no competing financial interests.

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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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