Improved Outcome for High-Risk Acute Myeloid Leukemia Patients Using Autologous Bone Marrow Transplantation and Monoclonal Antibody-Purged Bone Marrow


We have conducted a 9-year multicenter trial of autologous bone marrow transplantation (ABMT) for acute myeloid leukemia (AML). Remission BM was purged in vitro using monoclonal antibodies (MoAbs: PM-81, AML-2-23) and complement targeting myeloid differentiation antigens (CD15, CD14). In 1988, the preparative regimen changed from 60 mg/kg/d cyclophosphamide × 2 and fractionated total body irradiation (TBI) total dose, 1,200 cGy (Cy/TBI), to 4 mg/kg/d busulfan × 4 and 80 mg/kg/d Cy × 2 (Bu/Cy/TBI). Recent analysis (October 1, 1993) shows that the Bu/Cy2 regimen along with the same MoAb purging method yields an improved outcome. Seven first complete-remission (CR) (CR1), 45 second- or third-CR (CR2/3), and 11 first-relapse (R1) patients were treated with chemotherapy and TBI or chemotherapy alone followed by ABMT with MoAb-purged BM. Median age at ABMT for these patients in CR 2/3 and R1 patients was 36 years. Twenty-nine CR 2/3 and R1 patients were conditioned with Cy/TBI, and 27 CR2/3 and R1 patients were conditioned with Bu/CY. Using the Kaplan-Meier method, the Cy/TBI, CR2/3, and R1 patients have a 3-year disease-free survival (DFS) of 21%. On the other hand, the Bu/Cy2, CR2/3, and R1 patients have a 3-year DFS of 48%. Nineteen CR2/3 and R1 patients relapsed post-ABMT. On analysis by conditioning regimen, those treated with Cy/TBI have a 3-year relapse rate (RR) of 58%, whereas the patients conditioned with Bu/Cy2 have a 39% 3-year RR. Long-term DFS can be achieved in about 50% of patients with advanced remissions and relapsed AML using Bu/Cy2 with MoAb-purged BM.

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ABMT FOR AML WITH MoAb-PURGED MARROW

Table 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>CR</th>
<th>N</th>
<th>Age (median)</th>
<th>Male/Female</th>
<th>M1/M2</th>
<th>M3</th>
<th>M4/M5</th>
<th>M6/M7</th>
<th>Biphenotypic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>7</td>
<td>35-52 (42)</td>
<td>5:2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2nd/3rd*</td>
<td>45</td>
<td>11-57 (36)</td>
<td>24:21</td>
<td>120</td>
<td>6</td>
<td>16</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1st Relapse</td>
<td>11</td>
<td>16-53 (27)</td>
<td>4:7</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>63</td>
<td>11-57 (36)</td>
<td>33:30</td>
<td>29</td>
<td>8</td>
<td>23</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* For one patient in CR3, FAB subclass was unknown.

Ongize antigens on multilineage progenitor cells, and thus, probably do not recognize antigens on the pluripotent stem cells necessary for successful engraftment of BM.19,20

From August 1984 until April 1, 1992, we harvested, MoAb-purged, and performed 63 ABMT on patients who were in CR or first relapse at the time of transplant. Thirty of these patients were described in a previous report.11 Analysis as of October 1, 1993, suggests that long-term DFS can be achieved in about 50% of patients with advanced remissions and relapsed AML.

PATIENTS AND METHODS

Patients. Patients less than 60 years old with a Karnofsky performance status of 80% to 100% and an expected survival time of greater than 2 months were eligible for this protocol.

Patients had the diagnosis of AML in second or third CR (CR2/3), AML in first relapse (R1) or AML in first CR (CR1). All patients had a left ventricular ejection fraction ≥ 50%, a diffusion capacity of carbon monoxide of ≥ 60%, or a forced expiratory volume ≧ 75% predicted, as well as adequate renal and liver function as determined by a serum creatinine ≤ 2 times normal, and a bilirubin, serum glutamic oxaloacetic transaminase, and alkaline phosphatase ≤ 3 times normal, respectively. Leukemia blast cells obtained at diagnosis or at relapse, when available, were required to express the antigens reactive with PM-81 and/or AML-2-23 on greater than 20% of cells. The study was approved by the Institutional Review Board of the respective institutions and a signed informed consent was obtained from each patient before study entry.

Sixty-one AML patients with two patients undergoing retransplantation, ranging in age from 11 to 57 and who were in CR or first relapse, were transplanted between August 1984, and April 1, 1992 (Table 1). All but three patients had de novo AML at the time of initial diagnosis. Two patients had a myelodysplastic syndrome before the diagnosis of AML, and one had been previously cured of Burkitt's lymphoma. Twenty patients were treated on Cancer and Leukemia Group B protocols 8822 or 8781. Three patients were transplanted at the Scripps Clinic, one patient at Children's Hospital (San Diego, CA), 48 patients at the Dartmouth-Hitchcock Medical Center (DHMC), 4 patients at Bowman-Gray School of Medicine, 2 patients at the Medical Center of Delaware, 3 patients at the University of Iowa Hospitals, and 2 patients at the University of Pittsburgh. The French-American British (FAB) subcategories of the cases were as follows: M1/M2, 29; M3, 8; M4/M5, 23; M6/M7, 1; biphenotypic, 1; unknown, 1. The median time between the current remission or relapse and ABMT was 45 days with a range of 3 days to 14 months. Twenty-eight patients were harvested in CR1, 30 patients in CR2, and 5 patients in CR3.

On all available cases, data on cell-surface antigen expression was greater than 20% positive for PM-81. On average, 75% of leukemia cells were positive for binding to MoAb PM-81 (anti-CD15). The median was 82%. On average, 25% of leukemia cells were positive for binding to MoAb AML-2-23 (anti-CD14) with a median of 14%.

Marrow harvesting and purging. BM was harvested from the posterior and anterior iliac crests under general anesthesia and passed through a series of filters according to the method of Thomas and Storb.21 An effort was made to harvest 6 x 10⁶ cells/kg from each patient. A mean of 6.56 x 10⁶/kg were actually harvested. BM mononuclear cells were prepared first by buffy-coat concentration by apheresis of the marrow. Postpheresis, there was a mean recovery of 15.3% of the cells. The buffy-coat preparation was further treated on a Ficoll-Hypaque gradient centrifugation (Organon Teknika Corp, Durham, NC) on the Haemonetics (Brainmire, MA) automated cell processor to obtain a mononuclear cell preparation to be treated with MoAb + C. A mean of 8.06 x 10⁶ cells/kg were treated, and from that, there was a mean recovery of 55.6%. An average of 4.77 x 10⁷ cells/kg was used for the transplant.

Saturating amounts of purified MoAb were preincubated with these cells as previously described.22 To ensure saturation of all antigenic sites, the amount of each MoAb used was 10 μg per 10⁶ cells. Treatment on the Haemonetics cell processor was performed for 1 hour with continuous exposure to fresh C and simultaneous removal of spent C, while centrifuging at room temperature.22 The MoAb treatment was performed in the presence of the enzyme deoxyribonuclease (10 U/mL) to decrease cell clumping. This treatment was performed on the Haemonetics cell processor for patients treated after May 1987 at the DHMC, Bowman Gray Medical Center, and at the University of Pittsburgh. Before that date at the DHMC, Scripps Clinic, Children's Hospitals, and the Medical Center of Delaware, the marrow cells were treated in plastic or Teflon vessels (Savillex, Minnetonka, MN) with gentle shaking. For these treatments, two separate incubations with MoAb and C were performed as previously described.23

Cells were then washed and resuspended in a mixture of medium 199 containing 10% dimethyl sulfoxide (Tera Pharmaceuticals, Buena Park, CA) and 5% irradiated autologous plasma and then frozen at 1°C/min in a controlled-rate freezer and stored in the vapor phase of liquid nitrogen. Samples of untreated and MoAb-treated marrow cells from each patient were analyzed for colony-forming unit-granulocyte, monocyte (CFU-GM); erythroid burst-forming unit (BFU-E); CFU-granulocyte, erythroid, monocyte, megakaryocyte (CFU-MIX) in methylcellulose cultures and were cultured in trypticase-soy broth to determine sterility.

Colony-forming assays. BM mononuclear cells (2 x 10⁵ cells) from pre- and posttreatment samples were cultured in quadruplicate.19 Erythropoietin (1 U/mL) (Connaught Laboratories, Swiftwater, PA) and giant cell tumor conditioned medium or recombinant granulocyte-monocyte colony-stimulating factor (50 ng/mL) and interleukin-3 (50 ng/mL) (provided by Dr Steven Gillis, Immunex Corp, Seattle, WA) were added as sources of growth factors. BFU-E, CFU-GM, and CFU-MIX of greater than 40 cells/aggregate were scored using an inverted microscope after 14 days in 37°C, 5% CO₂ atmosphere. Representative colonies were plated from methylcellulose using a Pasteur pipet (Fisher Scientific, Pittsburgh, PA) and Wright's-Giemsa-stained cytopenetrifuge preparations were made to confirm cell lineage.
Preparative regimens. Thirty-six patients were treated with the following preparative regimen: Cy (60 mg/kg intravenously [IV] for 2 days) (days -5 to -3) and fractionated TBI (TFTBI; 200 cGy twice daily for 3 days, total dose of 1,200 cGy) (days -2 to 0). In 1988, the preparative regimen changed from Cy/TFTBI to Bu/Cy2. Twenty-six patients were treated with Bu (4 mg/kg/d orally for 4 days [days -8 to -5]) and Cy2 (60 mg/kg/d IV for 2 days) (days -4 and -3). One patient in CR2 was treated with Bu (4 mg/kg/d orally for 4 days [days -9 to -6]), and Cy (50 mg/kg/d IV for 4 days [days -5 to -2]).

Bu was administered orally. All patients were given phenytoin 300 mg every 8 hours beginning 48 hours before the first dose of busulfan. The patients were maintained on 300 mg daily until 48 hours after the last dose of Bu. TFTBI was administered with a cobalt source at a dose rate of 5 to 10 cGy/min as described previously.12 No growth factors were used after either preparative regimen.

Statistical methods. We estimated rates of relapse, overall survival, and DFS following ABMT using the product-limit or Kaplan-Meier method24 in patients transplanted before April 1, 1992 with follow-up to October 1, 1993.

We used the Cox proportional hazards model to evaluate factors associated with overall and DFS post-ABMT in high-risk patients (those in CR2/3 and R1).24 Categorical factors evaluated were remission/relapse status at ABMT (CR2/3/R1), status at cell harvest (CR2 v CR3), FAB subclass at diagnosis (subclasses M1 or M2 v other subcategories), gender, preparative regimen (Cy/TFTBI v Bu/Cy2), and cellular processing method (Haemotronics v other methods). Factors evaluated as continuous variables were height, body mass index, total number of cells, CFU-GM, CFU-MIX, and BFU-E transplanted, age, number of days from last CR or relapse event to transplant, time in CR1, and percent reactivity with MoAb PM-81 and AML-2-23.

RESULTS

Colony-forming assays. The effect of the MoAb and C' treatment on CFU was determined by culture of cells in methylcellulose. The median recovery of CFU-GM progenitor cells was 38% (range 22 to 150) for the CR1 group, 48% (range 1 to 190) for the CR2/3 group and 87% (range 58 to 248) for the R1 group. Median recovery of BFU-E was 49% (range 29 to 136) for the CR1 group, 69% (range 1 to 2,500) for the CR2/3 group, and 100% (range 0 to 392) for the R1 group. Median recovery of CFU-MIX was 50% (range 17 to 60) for the CR1 group, 37% (range 0 to 381) for the CR2/3 group, and 13% (range 0 to 249) for the R1 group.

Engraftment. A median number of 4.0 \times 10^7 cells/kg body weight (range 2.30 to 8.23 \times 10^7) were infused into each CR1 patient. The median number of cells transfused into the CR2/3 group was 2.80 \times 10^7 (range 0.075 to 1.16 \times 10^8). A median number of 4.10 \times 10^7 cells/kg body weight (range 2.38 to 59.6 \times 10^7) were infused into each R1 patient. Times to engraftment of granulocyte, monocyte, and erythrocyte precursors are shown in Table 2. Median observed recovery times for neutrophils to 500 cells/μL were 33, 37, and 41 days for the CR1, CR2/3, and R1 patients, respectively. Median times to reach platelet counts of greater than 20,000 and greater than 50,000/μL independent of platelet transfusions were 50 and 90 days (CR1), 42 and 69 days (CR2/3), and 49 and 79 days (R1). Median times, in days, to reach a hemoglobin (Hb) concentration of greater than 10 g% independent of red blood cell transfusions were 71, 46, and 67 for CR1, CR2/3, and R1 patients, respectively.

Analysis of engraftment of granulocytes, platelets, and erythrocyte precursors by preparative regimen is shown in Table 3. For those patients conditioned with Bu/Cy2 the median days to achieve an absolute neutrophil count greater than 500/μL, Hb greater than 10 g%, platelet count greater than 20,000/μL, and platelet count greater than 50,000/μL were 36, 40, 39, and 77, respectively. These values in patients receiving Cy/TFTBI were 41, 61, 54, and 83, respectively.

Survival. The DFS from transplant of all patients as of October 1, 1993 is shown in Fig 1 by status at transplant. The median relapse-free survival of the CR1 group is 73 months after ABMT. Four of the seven patients remain in CR at 36 months, 72 months, 74 months, and 84 months post-ABMT, respectively. Actuarial 2- and 3-year DFS and overall survival is 71% and 71% (95% confidence interval [CI], 38% to 100%), respectively.

Fourteen CR2/3 patients survive disease-free from 32 to 105 months with a median of 53 months. They have an actuarial 2- and 3-year DFS of 33% (95% CI, 26 to 47%) and 31% (95% CI, 18% to 45%), respectively. For 11 of these patients, the duration of their post-ABMT remission exceeds their duration of the CR1 and CR2. Follow-up on the other three patients is ongoing.

The inversion rates for patients who have not relapsed post-ABMT and who were transplanted in CR2, CR3, or R1 are 24/24, 4/4, and 7/7 respectively. The inversion rates for patients who have relapsed post-ABMT and who were transplanted in CR2, CR3, or R1 are 3/14, 0/3, and 0/2 respectively.

Five of the 11 patients transplanted in R1 remain disease free with a median relapse-free survival post-ABMT of 24 months (range 21 to 53 months). Their 2- and 3-year actuarial DFS is 45% (95% CI, 16% to 75%).

Analysis of all patients by preparative regimen (Bu/Cy2 v Cy/TFTBI) is shown in Fig 2. The two- and three-year DFS of
patients who received Cy/FTBI as the conditioning regimen are 33% (95% CI, 18% to 49%) and 31% (95% CI, 16% to 46%), respectively, whereas those patients who received Bu/Cy2 have a 2- and 3-year DFS of 48% (95% CI, 29% to 67%) (P = .30). The median age in the Cy/FTBI group is 41 years and is 30 years in the Bu/Cy2 group.

When examining the CR2/3 and R1 groups of patients according to the preparative regimen used, we observed an encouraging trend (Fig 3). Twenty-seven patients in CR 2/3 and R1 conditioned with Bu/Cy2 have an actuarial 2- and 3-year DFS of 48% (95% CI, 29% to 67%) whereas 29 CR2/3 and R1 patients conditioned with Cy/FTBI have 24% (95% CI, 9% to 40%) and 21% (95% CI, 6% to 35%) 2- and 3-year DFS (P = .07).

Evaluation of CR2/3 and R1 patients by conditioning regimen and age is shown in Fig 4. Patients under age 30 treated with either regimen tended to have better DFS (P = .048).

The effect of PM-81 reactivity on time to death or relapse was significant but apparently different for younger and older patients (P = .024). In patients under 30, the relative risk of death or relapse for low PM-81 (less than 80%) was about 0.76 (although it seems unlikely that low reactivity would confer a benefit). In patients over 30, the relative risk was 2.22, indicating an advantage associated with higher PM-81 reactivity.

The effect of time in CR1 was also significant (P = .032). However, the magnitude of the effect depended on which preparative regimen was used. Among Cy/FTBI patients, the relative risk associated with short CR1 (less than 18 months) was about 1.46. However, among Bu/Cy2 patients, the same relative risk was 2.69, indicating that the Bu/Cy2 patients who were in CR1 longer had an increased advantage over Cy/FTBI patients. This result may be caused by some difference in the preparative regimens or to other improvements in patient care.

Relapse. Three of seven CR1 patients relapsed at 11, 17, and 43 months post-ABMT. At the time of their ABMT the median CR1 duration of these patients was 12.3 months. The actuarial 2- and 3-year relapse rate for these seven patients is 29% (95% CI, 0% to 62%).

Seventeen CR2/3 patients relapsed at times ranging from 1.5 to 30 months post-ABMT (median 4.0 months). Their median time in first CR was 8.6 months. The actuarial 2- and 3-year RR for all CR2/CR3 patients is 45% (95% CI, 28% to 62%) and 52% (95% CI, 34% to 69%) respectively. Analysis by conditioning regimen shows an actuarial 3-year RR of 56% (95% CI, 31% to 81%) for CR2/3 patients conditioned with Cy/FTBI and 49% (95% CI, 24% to 73%) for those conditioned with Bu/Cy2 (P = .51).

Two patients transplanted in first relapse relapsed at 6 and
12 months post-ABMT. The actuarial 2- and 3-year RR for this group is 43% (95% CI, 0% to 92%).

Toxicity and preparative regimen. The preparative regimens were generally well tolerated. Most patients experienced mild to moderate nausea and vomiting during the administration of chemotherapy and TBI. Mucositis was moderate to severe. Diarrhea was experienced by the majority of patients in the first 2 weeks after TBI. Almost all patients became febrile during the period of marrow hypoplasia and leukopenia and required multiple parenteral antibiotics including amphotericin B.

Eight patients died within two months of ABMT while in the recovery phase. Six patients died of overwhelming sepsis despite aggressive antimicrobial therapy, one from hemorrhagic complications caused by refractoriness to platelet transfusions, and one from pulmonary and hepatic failure. All of these patients were in CR2 at the time of ABMT, and all but one had been treated with Cy/TBI as the preparative regimen.
ABMT for AML with MoAb-Purged Marrow

Therapy offers the potential for complete elimination of occult leukemia cells during CR, and BMT is probably the only curative treatment for patients with AML after first relapse.3 Encouraging results have been reported with allogeneic BMT, but the majority of patients with AML cannot undergo this therapy because of lack of an HLA-matched donor and/or advanced age.5,25 This report and others11,15,16 show that ABMT is a viable alternative.

Because of the theoretical possibility that reinforced marrow may be contaminated with residual malignant cells after ABMT, ex vivo purging is being studied in the hope of eliminating residual neoplastic cells from the graft. Although no randomized studies directly comparing ABMT with and without marrow purging have been reported, long-term survival for AML patients after ABMT using various methods for removing occult leukemia cells has been reported.16,26-29 A recent analysis of European data has shown a benefit of mafosfamide purging for patients transplanted in first CR within 6 months of attaining CR.29 Chao et al30 published a phase II trial that showed that patients who received purged BM (4-hydroperoxycyclophosphamide [4-HC] and/or etoposide) had an actuarial DFS of 57% compared with a DFS of 32% in patients who received unpurged BM. Yeger et al31 have reported favorable results similar to allogeneic BMT with 4-HC marrow purging in patients with AML who underwent ABMT.

Data from Brenner et al32 using the neomycin-resistant gene as a marker for AML relapse suggests that autologous marrow harvested from leukemia patients in clinical remission may harbor malignant cells capable of contributing to relapse. This evidence suggests that effective marrow purging may be essential for improving the outcome of ABMT for AML.

MoAb-based techniques using antimyeloid MoAbs have been used to purge AML marrow. The concerns of this ap-

DISCUSSION

BMT after high-dose chemotherapy and/or radiation therapy offers the potential for complete elimination of occult leukemia cells during CR, and BMT is probably the only curative treatment for patients with AML after first relapse.3 Encouraging results have been reported with allogeneic BMT, but the majority of patients with AML cannot undergo this therapy because of lack of an HLA-matched donor and/or advanced age.5,25 This report and others11,15,16 show that ABMT is a viable alternative.

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MoAb-based techniques using antimyeloid MoAbs have been used to purge AML marrow. The concerns of this ap-
proach are that it is a selective procedure, that the immunologic phenotype expression of AML varies between patients, and that there are differences between the clonogenic population and blast cell progeny.33 Despite these concerns, preliminary results have been encouraging.11,34

This report updates our multistitutional clinical data of ABMT in AML with MoAb and C-mediated purging. The trend toward long-term DFS is evident for those patients transplanted in R1 and CR2/3 who were conditioned with Bu/Cy2. Thus far, the 3-year relapse-free survival of 48% for those patients transplanted in CR2/3 with Bu/Cy2 is very promising. Despite the small number of R1 patients transplanted to date, a 3-year DFS of 45% warrants continuation of clinical trials with MoAb purging. These results with Bu/Cy2 as compared with Cy/TBI may be caused by the decreased RR with this regimen as well as the decreased number of toxic deaths. In addition, the observation that CD15 expression was a predictor of improved survival has at least two possible explanations. One that purging may have been more efficient, and the other is that CD15 expression acted as a prognostic indicator. These data compare well with alternative approaches to ABMT in AML, such as the use of 4-HC, and to allogeneic BMT for patients at similar risk for relapse. It is likely that these data will survive the test of time because most patients have been in remission for a longer time after ABMT than the length of the preceding remission. In addition, relapse after 2 years post-ABMT is uncommon.35 Because most remissions in AML induced by chemotherapy continue to be limited in duration, we think that this combined immunologic (MoAb and C') and chemotherapeutic (Bu/Cy2) approach to eradicating leukemia cells is efficacious in a substantial number of patients and represents an alternative to allogeneic BMT for patients with AML. The precise role of marrow purging will possibly require testing in a phase III study comparing the outcomes of ABMT using purged and unpurged marrow.

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Improved outcome for high-risk acute myeloid leukemia patients using autologous bone marrow transplantation and monoclonal antibody-purged bone marrow

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