High-Dose Etoposide, Cyclophosphamide, and Total Body Irradiation With Allogeneic Bone Marrow Transplantation for Patients With Acute Myeloid Leukemia in Untreated First Relapse: A Study by the North American Marrow Transplant Group


Relapse is a major cause of treatment failure following allogeneic bone marrow transplantation (BMT) for acute myeloid leukemia (AML). To reduce the risk of relapse following BMT for patients with hematologic malignancy, our group developed a novel preparative regimen which combines high-dose etoposide with cyclophosphamide and total body irradiation (VPCyTBI). We now report the outcome of therapy with VPCyTBI followed by allogeneic BMT for 40 patients with AML in untreated first relapse. With the exception of increased stomatitis, the toxicity of this regimen was similar to that reported by others for CyTBI. Forty-four months after transplant the actuarial probabilities of disease-free survival (DFS), persistent or recurrent leukemia, and transplant-related mortality were .29, .44, and .47, respectively. DFS was improved ($P < .01$) and risk of persistent or recurrent leukemia reduced ($P = .005$) among patients with significant (grade $\geq 2$) acute GVHD. Patients with 30% or more blasts on pre-BMT bone marrow examination were not at increased risk for persistent or recurrent leukemia. We conclude that VPCyTBI with allogeneic BMT is effective therapy for AML in untreated first relapse and that a randomized trial comparing this regimen with CyTBI is warranted.

CCONSOLIDATION with high-dose cytosine arabinoside produces durable complete remission (CR) in 25% to 50% of patients with acute myeloid leukemia (AML) in first CR.1-3 Based on this, a number of centers have adopted a policy of delaying allogeneic bone marrow transplantation (BMT) until first relapse for patients with newly diagnosed AML. Actuarial disease-free survival (DFS) 3 to 5 years after transplant is 20% to 30% for such patients.4-6 Transplantation in second CR does not improve outcome, so the optimal time for allogeneic BMT in patients with relapsed AML is during untreated first relapse.7

Recurrent leukemia accounts for up to one half of all treatment failures after allogeneic BMT for relapsed AML.4,8 One approach to reducing relapse is intensification of the preparative regimen. Based on the activity of high-dose etoposide and cyclophosphamide in resistant hematologic malignancy,9 our group performed a trial in which a standard preparative regimen, cyclophosphamide with total body irradiation (CyTBI), was modified by addition of etoposide and by escalation of cyclophosphamide dose. Pulmonary and hepatic toxicity prevented escalation above the maximum tolerated dose, which included etoposide (1.8 g/m²) with cyclophosphamide 180 mg/kg and 1,000 cGy TB1 (VP1.8/Cy180/ 1,000). Forty patients with AML in untreated first relapse received allogeneic BMT from histocompatible siblings during phase II/II trials with this regimen (VPCyTBI). We now report the outcome of transplantation for these patients.

PATIENTS AND METHODS

Eligibility. From September 1984 to November 1992, 40 patients with AML in untreated first relapse received VPCyTBI followed by allogeneic BMT (Table 1). Inclusion criteria were relapse based on standard criteria10; age $= 10$ and $\leq 55$ years; sibling donor serologically matched for 5/6 (1 patient) or 6/6 HLA A,B and DR antigens; Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2; no severe organ dysfunction unless related to malignancy. Informed consent was obtained from all patients and protocols were approved by institutional review boards.

Preparative regimen. One patient received etoposide 900 mg/m² over 19 hours (Table 1). Others received etoposide as previously described.8 Cyclophosphamide 50 to 60 mg/kg (true or ideal weight,10 whichever was less) was given over 2 hours on 2 or 3 consecutive days starting within 24 hours of completing etoposide. TB1 started on the day after the last cyclophosphamide dose and was given in 200 cGy fractions twice daily with at least 6 hours between fractions (total, 1,000 to 1,200 cGy). Bone marrow was infused on the day after completing TB1 (day 0). Hydration at 150 mL/m²/h was begun when etoposide was complete and continued until 24 hours after cyclophosphamide.

Prophylaxis and grading of graft-versus-host disease (GVHD). GVHD prophylaxis included cyclosporine A (CsA) with methylprednisolone or CsA with short-course methotrexate (Table 1).CsA was started on day $-1$ at 3 mg/kg/d and changed to oral when tolerable. Methylprednisolone was started on day $-1$ at 1 mg/kg and continued until day +28. One patient received bone marrow that was depleted with methylprednisolone. Acute GVHD was diagnosed and graded according to Glucksberg et al.11 Chronic GVHD was diagnosed and graded according to Shulman et al.12

Definitions and statistical analysis. Toxicity was graded according to National Cancer Institute Toxicity Criteria for Bone Marrow Transplantation.13 Standard criteria were used to define complete response and persistent or recurrent leukemia.9 Patients with persistent or recurrent leukemia were considered to have died of leukemia regardless of the proximal cause. Actuarial remission duration was calculated from day 0 until relapse (censored by death without leukemia or end of follow-up). Actuarial DFS was calculated from day 0 to relapse or death (censored by end of follow-up). Actuarial survival censored for relapse was calculated from day 0 until death.

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from transplant-related causes (censored by end of follow-up or relapse and on day 0 for patients with persistent leukemia). For DFS and remission duration, patients with persistent leukemia were considered complete on day 0. Events were recorded through March 1, 1994.

Remission duration, DFS, and survival censored for relapse were estimated by the Kaplan-Meier method.\(^1\) Probabilities of persistent or recurrent leukemia and transplant-related mortality were calculated as 1 − probability of remission and 1 − survival censored for relapse, respectively.

Actuarial risk of acute GVHD was calculated from day 0 until development of grade 2 or greater disease (censored by death without grade 2 GVHD). Patients dying before day +100 were excluded from analysis of chronic GVHD.

Variables examined for association with DFS, persistent or recurrent leukemia and transplant-related mortality using the log-rank statistic\(^2\) included age (continuous), time from diagnosis to allogeneic BMT (continuous), acute GVHD, and dose level (VP1.8/Cy150/1,000 ν VP1.8/Cy180/1,000). Twenty-one patients underwent bone marrow aspiration within 28 days before BMT and were divided into two groups based on the result (<30% ν ≥30% blasts). The significance of differences between these groups in risk of persistent or recurrent leukemia was analyzed by contingency table.\(^2\)

Confidence intervals were calculated using standard formulas.\(^2\) A P value less than .05 was considered statistically significant.

**RESULTS**

**Engraftment.** Median nucleated cell dose was $3.1 \times 10^7$/kg (range, 0.8 to 6.0). Thirty-three patients were evaluable for neutrophil recovery. Neutrophil count above 500/µL occurred on median day 19 (range, 12 to 27). Twenty-nine patients were evaluable for platelet recovery. Platelet count above 20,000/µL, independent of transfusion, occurred on median day 23 (range, 13 to 130).

**Toxicity and GVHD.** Thirteen patients died of transplant-related toxicity with the last death occurring 44 months after transplant (Table 2). At that time, actuarial transplant-related mortality was 47% (95% confidence interval [CI], 36% to 58%). Thirty patients (75%; 95% CI, 62% to 88%) developed grade 2 (requirement for <2 weeks of narcotics) or grade 3 (requirement for ≥2 weeks of narcotics) mucosal toxicity. Approximately 1/4 of all patients did not receive day +6 and 3/4 did not receive day +11 methotrexate because of mucosal toxicity.

Actuarial probability of grade 2 or greater acute GVHD was 48% (95% CI, 40% to 56%). Fourteen of 29 evaluable patients (48%; 95% CI, 30% to 66%) developed chronic GVHD.

**Persistent or recurrent leukemia and DFS.** Five patients had persistent leukemia and nine relapsed (Table 2 and Fig 1). The last relapse occurred 25 months after transplant at which time the actuarial probability of persistent or recurrent leukemia was 44% (95% CI, 26% to 62%). Thirteen patients survived disease-free between 18 and 112 months after transplant (median, 43 months). Performance status (ECOG) is 0 or 1 for all. Actuarial DFS 44 months after transplant was 29% (95% CI, 13% to 45%).

**Prognostic factors.** Acute GVHD was associated with improved DFS ($P = .009$) and with a reduced risk of persistent or recurrent leukemia ($P = .005$) (Fig 2). No other variable was significantly associated with these endpoints and no variable correlated with transplant-related mortality.

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>33 yrs (18-53)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>36</td>
</tr>
<tr>
<td>De novo AML</td>
<td>4</td>
</tr>
<tr>
<td>Proceding hematologic disorder</td>
<td>4</td>
</tr>
<tr>
<td>FAB classification</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>4</td>
</tr>
<tr>
<td>M2</td>
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<td>M3</td>
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<td>M4</td>
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</tr>
<tr>
<td>M5</td>
<td>1</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
</tr>
<tr>
<td>Median diagnosis to transplant (range)</td>
<td>10 mos (4-7)</td>
</tr>
<tr>
<td>Prior high-dose cytosine arabinoside</td>
<td>30</td>
</tr>
<tr>
<td>Bone marrow aspiration before BMT*</td>
<td></td>
</tr>
<tr>
<td>Blasts ≥ 30%</td>
<td>14</td>
</tr>
<tr>
<td>Blasts &lt; 30%</td>
<td>7</td>
</tr>
<tr>
<td>Preparative regimens</td>
<td></td>
</tr>
<tr>
<td>VP1.8/CY150/1000t</td>
<td>17</td>
</tr>
<tr>
<td>VP1.8/CY180/1000</td>
<td>16</td>
</tr>
<tr>
<td>VP1.8/CY150/1200</td>
<td>3</td>
</tr>
<tr>
<td>Other†</td>
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</tr>
<tr>
<td>GVHD prophylaxis</td>
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<tr>
<td>CSA/methotrexate</td>
<td>31</td>
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</tr>
<tr>
<td>CSA only</td>
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</table>

* Twenty-one patients underwent bone marrow examination within 28 days before BMT.
† VP1.8/CY150/1000 = etoposide 1.8 g/m² + cyclophosphamide 150 mg/kg + 1,000 cGy TBI.
‡ Other = three VP1.35/CY150/1000, one VP0.9/CY120/1200.

**Table 2. Transplant Outcome**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. transplanted</td>
<td>40</td>
</tr>
<tr>
<td>Alive in continuing remission</td>
<td>13</td>
</tr>
<tr>
<td>Alive in relapse</td>
<td>2</td>
</tr>
<tr>
<td>Dead</td>
<td>25</td>
</tr>
<tr>
<td>Causes of death</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>12</td>
</tr>
<tr>
<td>Toxicity</td>
<td>13</td>
</tr>
<tr>
<td>Infection</td>
<td>8</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>2</td>
</tr>
<tr>
<td>GVHD*</td>
<td>2</td>
</tr>
<tr>
<td>CNS†</td>
<td>1</td>
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<tr>
<td>Grade 3 toxicity</td>
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</tr>
<tr>
<td>Total episodes</td>
<td>17</td>
</tr>
<tr>
<td>Mucositis</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary†</td>
<td>6</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
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</tr>
<tr>
<td>Renal</td>
<td>1</td>
</tr>
<tr>
<td>GVHD</td>
<td></td>
</tr>
<tr>
<td>Acute, grade ≥ 2</td>
<td>17</td>
</tr>
<tr>
<td>Chronic§</td>
<td>14</td>
</tr>
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</table>

* GVHD, one with pulmonary fibrosis and one with hepatic failure.
† CNS, multiple cerebral infaracts.
‡ Pulmonary, two infectious and four idiopathic.
§ Twenty-nine patients survived > 100 days and were evaluable for chronic GVHD.
ETOPOSIDE, CYCLOPHOSPHAMIDE, AND TBI FOR AML

The percentage of blasts (<30% v ≥30%) present on bone marrow examination within 4 weeks before BMT did not correlate with risk of persistent or recurrent leukemia.

DISCUSSION

High-dose CyTBI has been extensively evaluated in AML and is the standard with which new preparative regimens should be compared. The largest single-institution experience with allogeneic BMT in AML was reported by Clift et al. Of 126 patients, 112 received CyTBI (cyclophosphamide 120 mg/kg with 10 to 15.75 Gy TBI). All were transplanted in untreated first relapse. The 5-year actuarial probability of DFS was 23%; relapse, 57%; and transplant-related mortality, 44%. Confidence intervals were not reported. As of August 1994, 35 patients with AML in untreated first relapse who received histocompatible sibling BMT after CyTBI have been reported to the International Bone Marrow Transplant Registry. The 5-year probability of DFS for these patients was 22% (95% CI, 7% to 37%). M. Horowitz, personal communication, September 1994. All IBMTR data presented here were obtained from the Statistical Center of the IBMTR. The analysis has not been reviewed or approved by the Advisory Committee of the IBMTR.

Busulfan and cyclophosphamide (busulfan 16 mg/kg with cyclophosphamide 200 mg/kg; BuCy) is an alternative preparative regimen developed to permit allogeneic BMT at centers lacking facilities for delivery of TBI. In the original report, 50 patients with AML in second or third CR or early relapse (<30% blasts) received BuCy followed by histocompatible, sibling BMT. Actuarial DFS 3 years after transplant was 31% (95% CI, 18% to 44%). Over 50% of those treated died of GVHD or regimen-related toxicity. To reduce toxicity, Copelan et al modified this regimen by reducing the total cyclophosphamide dose to 120 mg/kg (BuCy2). Although this modification appeared to reduce nonleukemic deaths, 3-year DFS for patients with AML in second CR or first relapse was similar to that previously reported with BuCy.

In a recent randomized trial, BuCy2 was compared with CyTBI in 101 patients with AML in first CR. Relapse risk was significantly increased among patients who received BuCy2, indicating that the antileukemic effect of this regimen may be inferior to that of CyTBI.

Based on the activity of high-dose etoposide in resistant hematologic malignancy, Blume et al performed a phase I trial in which patients received escalating doses of etoposide in combination with TBI (etoposide/TBI) followed by allogeneic BMT. Of 14 patients with AML in relapse or second CR, four remained in CR at median of 2.2 years after transplant. In a recent trial, 114 patients with poor prognosis acute leukemia or CML were randomized to receive BuCy2 or etoposide/TBI. For the entire group, DFS did not differ significantly between the treatment arms. This study included 35 patients with AML beyond first CR or resistant to induction therapy. Although these patients were not analyzed separately, relapse risk appeared to be comparable with BuCy2 and etoposide/TBI (relapse in 8/18 v 6/17 patients, respectively).

Therefore, available data does not suggest superiority of these alternative regimens over CyTBI. Results of allogeneic BMT following several other modifications of CyTBI or BuCy have been reported. This includes studies that have examined the combination of etoposide with CyTBI. However, each report includes fewer than 15 patients with AML beyond first CR so that it is difficult to determine the merit of these regimens.

In a previous study, our group showed that high-dose etoposide with cyclophosphamide was active in patients with
high-dose cytosine arabinoside resistant AML. Based on this observation, and upon the activity shown by VPCyTBI in a phase I trial which included patients with AML, we performed a phase II trial with this regimen in relapsed AML. In the current report, we focused on patients in untreated first relapse because this is the optimal time for allogeneic BMT in relapsed AML.

With the exception of increased stomatitis, the toxicity of VPCyTBI was comparable with that reported by others for CyTBI. Actuarial DFS 44 months after transplant was 29% (95% CI, 13% to 45%) which is similar to that reported for CyTBI. Based on this, it seems unlikely that VPCyTBI will dramatically improve the outcome of allogeneic BMT for relapsed AML. However, our results do not exclude a clinically significant advantage for VPCyTBI over CyTBI. Therefore, a randomized trial that compares these regimens in patients with AML in untreated first relapse is warranted.

We found that acute GVHD was associated with a highly significant reduction in risk of persistent or recurrent leukemia. This resulted in improved DFS for patients with acute GVHD. Similar results have been reported by others and indicate the importance of immunologic mechanisms (graft versus leukemia; GVL) in eliminating minimal residual leukemia after allogeneic BMT. As suggested by Clift et al, less aggressive GVHD prophylaxis could improve DFS for patients with AML who undergo allogeneic BMT in relapse. Another approach to reducing relapse risk after allogeneic BMT is augmentation of GVL by infusion of donor peripheral blood lymphocytes. Sullivan et al administered donor buffy-coat cells in the first few days after allogeneic BMT. However, DFS was reduced because of an increased risk of severe GVHD. Data from murine models suggests that delayed infusion of donor lymphocytes preserves GVL without significantly increasing GVHD. Based on this, one of our centers is evaluating the routine administration of donor peripheral blood lymphocytes several weeks after allogeneic BMT for relapsed leukemia.

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cyclophosphamide as preparatory regimens for bone marrow transplantation in patients with leukemia who were not in first remission: A Southwest Oncology Group Study. Blood 81:2187, 1993


High-dose etoposide, cyclophosphamide, and total body irradiation with allogeneic bone marrow transplantation for patients with acute myeloid leukemia in untreated first relapse: a study by the North American Marrow Transplant Group