Therapy for Chronic Myelogenous Leukemia With Unrelated Donor Bone Marrow Transplantation: Results in 102 Cases

By Philip B. McGlave, Patrick Beatty, Robert Ash, and Jill M. Hows

From April, 1985, to February, 1989, 102 consecutive patients received unrelated donor bone marrow transplantation therapy for chronic myelogenous leukemia (CML) at four centers. Median age of the group was 31 years (range, 4.5 to 51 years). Fifty-four patients were in first chronic phase (CP) at time of transplantation, and 48 had evidence of more advanced disease (AD) (accelerated phase, 32; blast crisis, 9; second CP, 7). In 44 cases, the donor and recipient were identical at the HLA A, B, and DR loci and were nonreactive in bidirectional mixed leukocyte culture (MLC) ("matched"). In 58 cases, nonidentity between donor and recipient could be determined at least at one HLA locus or in bidirectional MLC ("mismatched"). Fifty-eight patients were prepared for transplantation with a combination of cyclophosphamide and fractionated total body irradiation (FTBI) and received acute graft-versus-host disease (GVHD) prophylaxis consisting of methotrexate alone or in combination with cycloporine, prednisone, or antithymocyte globulin (ATG). In 44 cases, patients received preparative agents in addition to cyclophosphamide and FTBI, and marrow depleted of mature T lymphocytes by ex vivo incubation with either anti-CD3 antibody plus complement (n = 24) or Campath-1 (n = 20). Engraftment defined by a peripheral blood neutrophil count greater than 0.5 × 10^9/L was demonstrated in 92 cases and occurred at a median of 22 days (range, 11 to 46 days). In 10 cases, peripheral blood evidence of engraftment did not occur, and in one case, engraftment was followed by aplasia. Hematologic relapse was seen in four cases.

At present, the only proven curative therapy for chronic myelogenous leukemia (CML) is allogeneic bone marrow transplantation (BMT) using marrow obtained from HLA-matched related donors.1-3 Fewer than 40% of otherwise eligible patients have an HLA-identical sibling,4 and only an additional 10% have a suitable partially HLA-matched related donor.5 Unrelated donors matched or partially mismatched for HLA by serologic methods have been used successfully in bone marrow transplantation therapy for severe combined immunodeficiency, aplastic anemia, acute leukemia, and CML.5-12 We recently reported preliminary results of unrelated donor marrow transplantation therapy for CML in 35 patients.13 This expanded report of 102 patients receiving unrelated donor BMT as therapy for CML demonstrates that prolonged disease-free survival can be achieved, but identifies failure to engraft and acute graft-versus-host disease (GVHD) as important problems to be anticipated in the unrelated donor setting.

METHODS

Patient population. The study group consisted of 102 recipients receiving consecutive unrelated donor BMT as therapy for CML at four separate centers, located in Seattle, WA; Milwaukee, WI; London, UK; and Minneapolis, MN. Patient characteristics are shown in Table 1. The median age of the recipients was 31 years (range, 4.5 to 51 years). Fifty-four patients were in first chronic phase, 32 patients were in accelerated phase, nine patients were in blast crisis, and seven patients were in second or greater chronic phase. In 44 cases defined as "matched," donors and recipients were serologically identical for HLA A, B, and DR antigens using standard serotyping trays and were nonreactive (less than 15% relative response index) in bidirectional mixed leukocyte culture (MLC). Fifty-eight cases were "mismatched," i.e., defined as serologically nonidentical for one HLA A or B locus (n = 30), for the HLA DR locus (n = 2), reactive in one or both arms of a bidirectional MLC (n = 21), or manifested by evidence of nonidentity by both serologic testing and MLC (n = 5).

Transplant preparation and acute GVHD prophylaxis. All patients were prepared for BMT with a combination of high-dose cyclophosphamide and fractionated total body irradiation (FTBI), although dose schedules varied (Table 2). In 44 patients receiving T
lymphocyte-depleted marrow, additional preparation was given. In vivo acute GVHD prophylaxis alone was given in 58 cases and consisted of long-course methotrexate alone (n = 5), short-course methotrexate and cyclosporine (n = 33), long-course methotrexate, antithymocyte globulin (ATG), and prednisone (n = 8) and short-course methotrexate, cyclosporine, and prednisone (n = 12). Twenty-four patients received marrow depleted of T lymphocytes with an anti-CD3 monoclonal antibody plus complement and additional prophylaxis with cyclosporine. Twenty patients received donor marrow depleted of T lymphocytes with Campath-1,2,8 plus complement and, in some cases, additional prophylaxis with cyclosporine.

Statistical methods. Clinical data were retrieved from the four bone marrow transplant centers and then collated and analyzed at the University of Minnesota using the facilities of the University of Minnesota Bone Marrow Transplant Program Database. Univariate analyses were performed using the Kaplan-Meier product limit method, and the Mantel-Cox test was used to determine the significance of differences between various subgroups.

RESULTS

Engraftment and graft failure. The median time to engraftment, defined by an absolute peripheral blood neutrophil count greater than 0.5 x 10^9/L, was 22 days (range, 11 to 46 days). Time to engraftment is depicted in Fig 1. Ten of the recipients failed to develop peripheral evidence of engraftment. In two cases, recipients died at day +20 and day +26, respectively, with pancytopenia. In eight cases, recipients survived a minimum of 6 weeks after transplantation without peripheral blood evidence of engraftment. One additional patient engrafted at day +21, but developed pancytopenia in association with severe chronic GVHD at day +160 and died subsequently of complications associated with GVHD. Univariate analysis failed to demonstrate an association between failure to engraft and recipient age (P = .32), T lymphocyte-depleted donor marrow (P = .32), BMT center (P = .64), disease phase at transplantation (P = 1.0), or donor matching (P = 1.0). Eight patients experiencing failure to engraft died of related complications.

GVHD. The Kaplan-Meier prediction of the incidence of grade II to IV acute GVHD was 65% (95% confidence interval [CI], ±10%). The 91% incidence (95% CI, ±12%) of grade II to IV acute GVHD in recipients of mismatched, non-T lymphocyte-depleted donor marrow was significantly higher than the 49% incidence (95% CI, ±19%) seen in recipients of mismatched, but T lymphocyte-depleted donor marrow (P = .004) (Fig 2). Similarly, the 79% incidence (95% CI, ±16%) of grade II to IV acute GVHD seen in recipients of matched, non-T lymphocyte-depleted donor marrow was significantly higher than the 20% incidence (95% CI, ±20%) seen in recipients of matched and T lymphocyte-depleted unrelated donor bone marrow (P = .0004) (Fig 2).

Relapse. Hematologic relapse has occurred in four cases (Table 3). In three cases, hematologic evidence of relapse occurred within 1 month of marrow infusion in patients who were transplanted with advanced disease. In the fourth case, a 16-year-old transplanted in chronic phase developed hematologic evidence of relapse 38 months after marrow transplantation. The Kaplan-Meier incidence of hematologic relapse

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Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Total</td>
<td>102</td>
</tr>
<tr>
<td>Median age (y) (range)</td>
<td>31  (4.5-51)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>Chronic phase</td>
<td>54</td>
</tr>
<tr>
<td>Advanced disease phase</td>
<td>48</td>
</tr>
<tr>
<td>Accelerated</td>
<td>32</td>
</tr>
<tr>
<td>Blast crisis</td>
<td>9</td>
</tr>
<tr>
<td>≥ 2nd chronic</td>
<td>7</td>
</tr>
<tr>
<td>Donor/recipient histocompatibility</td>
<td></td>
</tr>
<tr>
<td>Matched</td>
<td>44</td>
</tr>
<tr>
<td>Mismatched</td>
<td>58</td>
</tr>
<tr>
<td>1 HLA A or B</td>
<td>30</td>
</tr>
<tr>
<td>1 HLA DR</td>
<td>2</td>
</tr>
<tr>
<td>MLC</td>
<td>21</td>
</tr>
<tr>
<td>HLA + MLC</td>
<td>5</td>
</tr>
<tr>
<td>Median follow-up (mo) (range)</td>
<td>12  (3-46)</td>
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</table>

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Table 2. Preparation and Acute GVHD Prophylaxis

<table>
<thead>
<tr>
<th>Center</th>
<th>Preparation</th>
<th>GVHD Prophylaxis</th>
<th>N</th>
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<tbody>
<tr>
<td>Hutchinson, Seattle, WA</td>
<td>Cyclophosphamide, FTBI</td>
<td>Methotrexate or methotrexate, cyclosporine</td>
<td>38</td>
</tr>
<tr>
<td>University of Minnesota, Minneapolis, MN</td>
<td>Cyclophosphamide, FTBI</td>
<td>Methotrexate, cyclosporine, prednisone or methotrexate, ATG, prednisone</td>
<td>20</td>
</tr>
<tr>
<td>Medical College of Wisconsin, Milwaukee, WI</td>
<td>Cyclophosphamide, cytosine arabinoside, FTBI</td>
<td>Anti-CD3 T depletion, cyclosporine</td>
<td>24</td>
</tr>
<tr>
<td>Hammersmith Hospital, London, England</td>
<td>Cyclophosphamide, FTBI, other</td>
<td>Campath-1 T depletion, ± cyclosporine</td>
<td>20</td>
</tr>
</tbody>
</table>

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Fig 1. The time to engraftment defined as an absolute peripheral blood neutrophil count greater than 500/μL. The median time to engraftment was 22 days, with a range of 11 to 46 days. Ten recipients failed to develop peripheral evidence of engraftment.
was 27% (95% CI, ±42%). In four additional cases recurrence of the Ph1 chromosome without hematologic relapse has been observed. In one of these cases, recurrence of the Ph1 was transient. All four of these patients received donor marrow that had been depleted of lymphocytes by Campath-1 treatment.

**Disease-free survival.** Of 102 recipients, 46 are alive, with a median post-BMT follow-up of 12 months (range, 3 to 46 months). The Kaplan-Meier estimate of disease-free survival for all patients in the study is 29% (95% CI, ±19%) at 2½ years. A nonsignificant trend towards better disease-free survival (39%; 95% CI, ±26%) is seen in the group receiving matched marrow, which consisted of 23 chronic phase patients and 21 advanced phase patients (median age, 31 years), when compared with disease-free survival seen in the group receiving mismatched donor marrow (27%; 95% CI, ±15%), which consisted of 31 chronic phase patients and 27 advanced phase patients (median age, 26 years) (P = .14) (Fig 3). This trend towards better survival in the matched group could not be attributed to significant differences in the incidence of grade II to IV acute GVHD, failure to engraft or relapse, or to differences in principal causes of death (Table 4) between the matched and mismatched groups. Although T lymphocyte-depletion of donor marrow significantly decreased the incidence of grade II to IV acute GVHD in this series, it did not significantly affect survival (P = .34), disease-free survival (P = .51), or relapse rate (P = .39) after adjustment for disease stage.

**Table 3. Hematologic Relapse**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Stage</th>
<th>Time to Relapse (mo)</th>
<th>Match</th>
<th>T Depletion</th>
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<tr>
<td>17</td>
<td>AD</td>
<td>&lt;1</td>
<td>Mismatch</td>
<td>N</td>
</tr>
<tr>
<td>29</td>
<td>AD</td>
<td>&lt;1</td>
<td>Match</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>AD</td>
<td>1</td>
<td>Match</td>
<td>Y</td>
</tr>
<tr>
<td>16</td>
<td>CP</td>
<td>38</td>
<td>Match</td>
<td>Y</td>
</tr>
</tbody>
</table>

Abbreviations: AD, advanced phase; CP, chronic phase.

**Table 4. Principal Causes of Death**

<table>
<thead>
<tr>
<th>Cause</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial pneumonitis</td>
<td>16</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
</tr>
<tr>
<td>GVHD</td>
<td>9</td>
</tr>
<tr>
<td>Graft failure</td>
<td>8</td>
</tr>
<tr>
<td>Liver failure</td>
<td>8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>7</td>
</tr>
<tr>
<td>Relapse</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In this series we demonstrated failure to achieve engraftment in 10 of 102 cases. In one additional case, peripheral blood evidence of engraftment was followed by pancytopenia associated with severe chronic GVHD. The proportion of patients failing to achieve durable engraftment in this series is similar to that reported in related, non-sibling donor-recipient pairs phenotypically matched for HLA antigens or mismatched for one HLA A, B, or D antigen.16 T lymphocyte-depletion of donor marrow has been implicated in failure to achieve durable engraftment.17 No association between T depletion of donor marrow and failure to engraft could be identified in this series. Similarly, failure to engraft could not be associated with matched or mismatched donor/recipient status, recipient age, preparative regimen, or a “center effect.” Failure to engraft was the primary cause of death in eight patients and must be considered a serious potential complication of unrelated donor bone marrow transplantation. Our findings suggest than an effort to preserve “backup” autologous stem cells or to develop contingency plans for second marrow transplants may be justified in selected cases.

The incidence of grade II to IV acute GVHD was 65% in this series, and 29% of evaluable patients had either grade III or grade IV acute GVHD. The 79% incidence (95% CI, ±16%) of grade II to IV acute GVHD in recipients of matched non-T lymphocyte-depleted unrelated donor marrow is probably higher than that observed when non-T lymphocyte-depleted marrow taken from phenotypically iden-
tical related donors is used. Use of non-T lymphocyte-depleted unrelated donor marrow mismatched at one or more HLA loci results in an extremely high incidence (91%; 95% CI, ±12%) of grade II to IV acute GVHD. T lymphocyte-depletion of the unrelated donor marrow results in a significant decrease in grade II to IV GVHD in recipients of either matched or mismatched marrow. The use of T lymphocyte-depleted marrow in our study is not associated with a significant advantage in survival, despite its obvious impact on the development of acute GVHD. This study provides information suggesting that the incidence of acute GVHD in the unrelated donor transplant setting will be high. Trials testing the efficacy of innovative approaches to acute GVHD prophylaxis may, therefore, be warranted. Moreover, use of newly developed methods to detect donorrecipient sensitization, such as analysis of cytotoxic T cell precursor frequencies, as well as methods to determine HLA class I and class II identity, such as restriction fragment length polymorphisms, allospecific oligonucleotide probing techniques, and isoelectric focusing techniques may help to predict GVHD and graft failure.

At present, hematologic relapse has occurred in four patients. In three advanced phase patients, hematologic evidence of recurrent disease occurred within 1 month of transplant. In a fourth case, hematologic relapse occurred at 38 months in a chronic phase recipient of T lymphocyte-depleted bone marrow. Both transplant with T lymphocyte-depleted donor bone marrow and transplant in patients with advanced disease have been associated with a significantly higher incidence of relapse after matched sibling donor BMT for CML. Further follow-up of this series and analysis of larger series, taking into account patient characteristics and transplant conditions known to be associated with relapse, will be required to determine if the relapse rate in the unrelated donor setting will be inordinately high, as might be expected if the donor graft is at a relative disadvantage to host cells, or inordinately low, as might be expected if use of unrelated donor marrow imposes a graft-versus-leukemia effect that supersedes that seen in the related donor setting.

Forty-six patients survive in this series with a median follow-up of 12 months. A nonsignificant trend \( (P = .14) \) towards better disease-free survival in recipients of matched donor marrow compared with mismatched donor marrow is apparent. This trend towards a higher incidence of disease-free survival in matched donor/recipient pairs was not identified in earlier analysis of this group and cannot be ascribed to significant differences in recipient age, disease stage, incidence of acute GVHD, incidence of relapse, or incidence of failure to engraft in the matched and mismatched groups. Considerably longer follow-up will be needed to determine the relative effects of these clinical features on disease-free survival.

Current estimates suggest that HLA A, B, and DR-matched, MLC nonreactive, unrelated donors can be found for 25% to 45% of potential recipients using existing donor registry resources. Development of large, unrelated bone marrow donor registries in Canada, Europe, the United States, and other countries, as well as efforts underway to link these registries, will improve efficiency of donor searches. Should further studies demonstrate that use of unrelated donors mismatched at one HLA antigen is acceptable, it will be possible to extend marrow transplantation therapy to the majority of otherwise acceptable CML patients for whom a suitably matched, related donor is not available.

The availability of unrelated donors may not only provide the possibility of bone marrow transplantation for patients without a suitably matched related donor, but may actually have advantage over the use of related donors in certain circumstances. Further studies may demonstrate that the choice of a cytomegalovirus-seronegative unrelated donor, a younger unrelated donor, or an unrelated donor of appropriate sex or pregnancy history will be beneficial. Furthermore, use of an unrelated donor not subjected to the element of coercion implicit in the matched sibling donor setting may be beneficial to either recipient or donor in some situations.

This study suggests that therapy for CML with BMT using unrelated donors can provide stable engraftment in a majority of recipients and prolonged disease-free survival in some cases. The efficient identification of matched unrelated donors through a rapidly expanding network of donor registries will make unrelated donor BMT available to more patients with CML. Problems associated with failure to achieve sustained engraftment and with a high incidence of acute GVHD can be anticipated. Further clinical studies are needed to determine the importance of donor/recipient matching, GVHD prophylaxis, disease stage at transplant, and other variables affecting the outcome of unrelated donor bone marrow transplantation.

ACKNOWLEDGMENT

The authors acknowledge Drs Mortimer Bortin, John Goldman, John Hansen, and John Kersey for their support in this project. The authors particularly wish to acknowledge Dr Robert Haake for the compilation and analysis of data from the four centers.

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Therapy for chronic myelogenous leukemia with unrelated donor bone marrow transplantation: results in 102 cases [published erratum appears in Blood 1990 Aug 1;76(3):654]

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