Allogeneic Bone Marrow Transplantation as Treatment for Accelerating Chronic Myelogenous Leukemia

By Philip B. McGlave, Diane C. Arthur, Daniel Weisdorf, Tae Kim, Anne Goldman, David D. Hurd, Norma K. C. Ramsay, and John H. Kersey

Sixteen patients with chronic myelogenous leukemia (CML) underwent allogeneic bone marrow transplantation (BMT) when they presented with or developed objective signs suggesting acceleration of disease. Patients have been followed for a median of 515 days (range 216–806 days). Seven patients are alive from 319 to 732 days (median 538 days). Four patients are in complete remission 501–732 days after BMT. Three patients have developed cytogenetic evidence of relapse after BMT; however, these patients are alive and not dependent on therapy and have normal activity levels at 319, 515, and 550 days following BMT. Three additional patients have developed cytogenetic and hematologic evidence of relapse after BMT, progressed to blast crisis, and died. Six patients have died of other causes. Allogeneic BMT can eradicate the abnormal clone and provide normal hematopoiesis when performed during the accelerated phase of CML; however, this approach is associated with relapse and with relatively high mortality. The long-term efficacy of this approach and the relative efficacy of transplant during acceleration rather than during the chronic phase of CML have yet to be established.

CHRONIC MYELOGENOUS LEUKEMIA has an unusual natural history characterized by a stable chronic phase of unpredictable length, but averaging 36 mo. Most patients then experience a transition period, termed the accelerated phase, in which one or more laboratory or clinical signs of progressive disease appear. Eventually, patients undergo blast crisis and die within 1–5 mo of marrow failure.

Fefer and colleagues have shown that cytoreductive therapy followed by syngeneic BMT during chronic phase can eradicate all evidence of CML and can provide long-term disease-free survival in some patients. Allogeneic BMT performed during blast crisis can ablate cytogenetic and hematologic evidence of the malignant hematopoietic clone, but is associated with a high relapse rate and short survival, which is attributed to advanced disease, compromised patients, and the toxicity of previous therapy.

Allogeneic BMT carried out during the chronic phase of CML has been attempted, and several reports documenting early success in small numbers of patients have been published.

As part of a stepwise study of the application of allogeneic BMT to the treatment of CML, we have tested the hypothesis that BMT performed when patients present with or develop objective signs of acceleration could ablate the malignant clone and could establish normal hematopoiesis. Such an approach, if feasible, would avoid the premature morbidity and mortality that might be associated with BMT performed during the stable, unpredictably long, chronic phase.

MATERIALS AND METHODS

Patients Studied

Sixteen patients with CML received allogeneic BMT when they presented with or developed one or more signs suggesting acceleration of disease. Objective evidence of acceleration included: (1) leukocytosis (WBC greater than 50 x 10^9/liter), thrombocytosis (platelet count greater than 500 x 10^9/liter), or anemia, uncontrolled by single-agent chemotherapy; (2) peripheral blood blast percentage greater than 5%, uncontrolled by single-agent chemotherapy; (3) splenomegaly uncontrolled by single-agent chemotherapy; (4) cytogenetic abnormalities in addition to a single Philadelphia chromosome (Ph'); (5) severe, progressive myelofibrosis or osteosclerosis; (6) successful achievement of “chronic phase” after blast crisis.

Patients ranged in age from 7 to 45 yr, median 29 yr (Table 1). Disease duration at time of BMT ranged from 6 to 107 mo, median 37 mo. No patient was in stable chronic phase or in blast crisis at the time of BMT; however, four patients had developed blast crisis and had received successful therapy to induce a second (patients no. 196, 219), third (no. 203), or fourth (no. 234) “chronic phase.” Eight patients had a single Ph' chromosome; five had marrow chromosome abnormalities in addition to the Ph'; one patient (no. 148) had marrow cytogenetic abnormalities other than the Ph' chromosome; and one patient (no. 196) had all normal marrow metaphases at the time of BMT, but had experienced a Ph'-positive chronic phase and blast crisis at another institution. Two patients had a single Ph' chromosome in marrow metaphases, but had additional cytogenetic abnormalities in the spleen (no. 194) or in a jaw mass (no. 230).

Six patients had undergone splenectomy prior to BMT; however, one patient (no. 163), who experienced splenectomy following trauma, had a spleen demonstrable on spleen scan prior to BMT. No patient was excluded from this series because of progression of disease while awaiting transplant. All patients had received intermittent treatment with low doses of busulfan, hydroxyurea, or both.
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age</th>
<th>Duration</th>
<th>Disease</th>
<th>Features of Acceleration</th>
<th>Cytogenetics Pre-BMT</th>
<th>Spleen</th>
<th>GVHD</th>
<th>Relapse</th>
<th>Survival</th>
<th>Cause of Death</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>148</td>
<td>27 yr</td>
<td>8 mo</td>
<td>Leukocytosis</td>
<td></td>
<td>BM: 46,XY,del(13)(q13)</td>
<td>In</td>
<td>Severe</td>
<td>No</td>
<td>Dead, day 174</td>
<td>GHVD</td>
<td>—</td>
</tr>
<tr>
<td>150</td>
<td>30 yr</td>
<td>10 mo</td>
<td>Myelofibrosis</td>
<td></td>
<td>BM: 46,XX,t(9;22)(q34;q11)</td>
<td>In</td>
<td>Severe</td>
<td>No</td>
<td>Dead, day 230</td>
<td>GVHD</td>
<td>—</td>
</tr>
<tr>
<td>163</td>
<td>34 yr</td>
<td>24 mo</td>
<td>Rising blast</td>
<td></td>
<td>BM: 46,XY,t(9;22)(q34;q11)</td>
<td>Out/recr</td>
<td>Moderate</td>
<td>No</td>
<td>Alive, day 732</td>
<td>—</td>
<td>Kanhofsky 100%</td>
</tr>
<tr>
<td>172</td>
<td>22 yr</td>
<td>62 mo</td>
<td>Cytogenetics</td>
<td></td>
<td>BM: 47,XY, + del(22)(q11), t(9;22)(q34;q11)</td>
<td>Out</td>
<td>Moderate</td>
<td>No</td>
<td>Alive, day 669</td>
<td>—</td>
<td>Kanhofsky 90%</td>
</tr>
<tr>
<td>188</td>
<td>28 yr</td>
<td>38 mo</td>
<td>Rising blast</td>
<td></td>
<td>BM: 46,XX,t(9;22)(q34;q11)/46.X. + X,46 + t(9;22)(q34;q11), + mar</td>
<td>Out</td>
<td>Moderate</td>
<td>Yes</td>
<td>Dead, day 534</td>
<td>Blast crisis</td>
<td>—</td>
</tr>
<tr>
<td>194</td>
<td>20 yr</td>
<td>107 mo</td>
<td>Rising blast</td>
<td></td>
<td>BM: 46,XX,t(9;22)(q34;q11)</td>
<td>Out</td>
<td>Moderate</td>
<td>Yes</td>
<td>Alive, day 550</td>
<td>—</td>
<td>Kanhofsky 100%</td>
</tr>
<tr>
<td>196</td>
<td>7 yr</td>
<td>10 mo</td>
<td>Rising blast</td>
<td></td>
<td>BM: 46,XX</td>
<td>In</td>
<td>Moderate</td>
<td>No</td>
<td>Alive, day 538</td>
<td>—</td>
<td>Kanhofsky 100%</td>
</tr>
<tr>
<td>200</td>
<td>19 yr</td>
<td>36 mo</td>
<td>Leukocytosis</td>
<td></td>
<td>BM: 46,XX</td>
<td>In</td>
<td>Moderate</td>
<td>Yes</td>
<td>Alive, day 515</td>
<td>—</td>
<td>Kanhofsky 100%</td>
</tr>
<tr>
<td>203</td>
<td>41 yr</td>
<td>62 mo</td>
<td>Rising blast</td>
<td></td>
<td>BM: 46,XY,t(9;22)(q34;q11)</td>
<td>In</td>
<td>Mild</td>
<td>No</td>
<td>Alive, day 501</td>
<td>—</td>
<td>Kanhofsky 100%</td>
</tr>
<tr>
<td>219</td>
<td>14 yr</td>
<td>23 mo</td>
<td>Rising blast</td>
<td></td>
<td>BM: 46,XX,t(9;22)(q34;q11)/46.XX, + 13, + del(22)(q11), t(9;22)(q34;q11)</td>
<td>In</td>
<td>None</td>
<td>Yes</td>
<td>Dead, day 150</td>
<td>Blast crisis</td>
<td>—</td>
</tr>
<tr>
<td>230</td>
<td>31 yr</td>
<td>13 mo</td>
<td>Extramedullary</td>
<td></td>
<td>BM: 46,XX,t(9;22)(q34;q11)</td>
<td>In</td>
<td>Moderate</td>
<td>No</td>
<td>Dead, day 82</td>
<td>Infection</td>
<td>—</td>
</tr>
<tr>
<td>234</td>
<td>42 yr</td>
<td>43 mo</td>
<td>Rising blast</td>
<td></td>
<td>BM: 46,XY,t(9;22)(q34;q11)</td>
<td>In</td>
<td>Moderate</td>
<td>No</td>
<td>Dead, day 19</td>
<td>Infection</td>
<td>—</td>
</tr>
<tr>
<td>238</td>
<td>43 yr</td>
<td>58 mo</td>
<td>Leukocytosis</td>
<td></td>
<td>BM: 46,XX,t(9;22)(q34;q11)</td>
<td>In</td>
<td>Moderate</td>
<td>Yes</td>
<td>Alive, day 319</td>
<td>—</td>
<td>Kanhofsky 100%</td>
</tr>
<tr>
<td>244</td>
<td>45 yr</td>
<td>43 mo</td>
<td>Leukocytosis</td>
<td></td>
<td>BM: 46,XY,t(9;22)(q34;q11)</td>
<td>In</td>
<td>Severe</td>
<td>No</td>
<td>Dead, day 62</td>
<td>GVHD</td>
<td>—</td>
</tr>
<tr>
<td>245</td>
<td>32 yr</td>
<td>40 mo</td>
<td>Cytogenetics</td>
<td></td>
<td>BM: 46,XX,t(2;14)(q24;p13), t(9;22)(q34;q11)</td>
<td>In</td>
<td>None</td>
<td>No</td>
<td>Dead, day 31</td>
<td>Infection</td>
<td>—</td>
</tr>
<tr>
<td>255</td>
<td>16 yr</td>
<td>28 mo</td>
<td>Cytogenetics</td>
<td></td>
<td>BM: 45,XX, - 17, - 18, + t(17q18q), t(9;22)(q34;q11)</td>
<td>Out</td>
<td>Moderate</td>
<td>Yes</td>
<td>Dead, day 201</td>
<td>Blast crisis</td>
<td>—</td>
</tr>
</tbody>
</table>
agents. All patients signed informed consents approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota.

Preparation and GVHD Prophylaxis

Patients were prepared for bone marrow transplantation with cytosine arabinoside, 25 mg/sq m bolus (day -9) then 100 mg/sq m/day intravenously (day -8, day -7), cyclophosphamide, 60 mg/kg/day intravenously (day -6, day -5), and fractionated total body irradiation at a dose of 280 cGy/day (day -3, day -2, day -1). On day 0, the patients received marrow from their major histocompatibility loci matched sibling donors. As prophylaxis against graft-versus-host disease (GVHD), all patients received antithymocyte globulin, 15 mg/kg every other day (days 8-20), and with the monoclonal antibody OKT3. All patients received low-dose methotrexate, 10 mg/m²/day for 12 days then 5 mg/m²/week. Patients 172-245 received this series received donor marrow that had been incubated in vitro with the monoclonal antibody OKT3.11 Patients 172-245 received antithymocyte globulin, 15 mg/kg every other day (days 8-20), and prednisone, 40 mg/sq m/day (days 7-21).12 Patient 255 received OKT3 infused in vivo.

RESULTS

Fifteen of sixteen patients demonstrated hematologic evidence of engraftment, reflected by a rise in the peripheral blood absolute neutrophil count of greater than 5 x 10³/liter at a median of 24 days (range 18-48 days). One patient (no. 234), a 42-year-old insulin-dependent diabetic in fourth “chronic phase,” died at day 19 without evidence of engraftment. Normal bone marrow chromosomes without evidence of leukemic cells were found in 14 of the 15 evaluable patients after BMT. One patient (no. 219) transplanted in second “chronic phase” manifested only persistence of abnormal chromosomes in all metaphases after transplant.

GVHD was evaluated using a previously designed clinical and pathologic grading system.11 Three of 15 evaluable patients did not develop any evidence of acute GVHD. One patient developed mild acute GVHD, 8 developed moderate GVHD, and 3 developed severe GVHD. All cases of mild or moderate GVHD resolved with therapy. All 3 cases of severe GVHD resulted in death from secondary infection.

Six of 15 evaluable patients have relapsed. All 6 patients were female. Three of the 6 have died in blast crisis. One patient, transplanted in second chronic phase (no. 219), demonstrated persistent cytogenetic abnormalities in all marrow metaphases at day 39 and died in blast crisis at day 150. One patient (no. 255) developed cytogenetic evidence of relapse at day 100 and died in blast crisis at day 201. A third patient (no. 188) relapsed into blast crisis at day 381 and died in blast crisis at day 334.

Three additional patients had developed the reappearance of the Ph¹ chromosome after earlier post-BMT analyses revealed only normal marrow metaphases. Patients 194, 200, and 238 demonstrated a mixture of normal metaphases of donor sex and Ph¹ metaphases of recipient sex at days 540, 98, and 85, respectively. All three patients are well, require little or no therapy, and have normal activity levels at 550, 515, and 319 days after transplantation.

All three patients who have relapsed and died in blast crisis presented with marrow cytogenetic changes in addition to the Ph¹ chromosome. The three patients who have manifested marrow cytogenetic evidence of relapse, but survive in chronic phase, possessed only the Ph¹ chromosome in the marrow in pretransplant evaluations.

Five patients received elective splenectomy because of symptoms related to splenomegaly. The median day to engraftment in the splenectomized and nonsplenectomized group was 24 days. The range in the splenectomized group (18-48 days) was greater than in the splenectomized group (19-27 days). Four of six patients have relapsed in the splenectomized group. No significant differences in severity of GVHD, relapse, and survival between the two groups can be found in this small series.

Four patients survive free of clinical hematologic or cytogenetic evidence of recurrent disease at 501-732 days. Disease duration ranged from 10 to 62 mo prior to BMT in these patients. One of the 4 patients had elective splenectomy prior to BMT. This patient also had two Ph¹ chromosomes in all marrow metaphases. One patient had mild GVHD, and the remaining three had moderate GVHD. Two patients had experienced a blast crisis and were in second or third “chronic phase,” while the two others were transplanted before entering blast crisis.

DISCUSSION

The natural history of CML poses a problem in the use of allogeneic BMT as therapy. Intervention during the unpredictably long, relatively trouble-free chronic phase may expose patients to premature morbidity and mortality associated with toxicity of the preparative regimen, with GVHD, and with immunosuppression.

Delay of transplantation until signs of acceleration occur may be desirable; however, this approach is not without hazard. A uniform definition of the accelerated phase has not been accepted.2 Delay of BMT might allow patients to slip into a refractory blast crisis without warning. Delay might also jeopardize the outcome of BMT because of increased tumor burden, cumulative toxicity of low-dose therapy, or compromised health related to intercurrent illness during chronic phase.

In this study, allogeneic BMT performed during the accelerated phase of CML eradicated evidence of the malignant clone and established normal hematopoiesis in most patients. This approach was associated with a high relapse rate, which may be the consequence of a
preparative regimen containing a relatively low dose of total body irradiation, chosen deliberately to reduce toxicity. Relapse may also be related to the advanced state of disease in these patients. All three patients who have progressed to blast crisis and to death possessed marrow chromosome abnormalities in addition to the Ph1 chromosome prior to BMT.

Evidence of relapse, however, has not been synonymous with progression to blast crisis and to death in our series. Three patients who have demonstrated cytogenetic evidence of relapse are surviving without hematologic or clinical evidence of disease, without obvious progression of disease, and with normal activity levels at 319, 515, and 550 days post-BMT. Of interest, splenectomy did not protect against relapse in this setting.

The long-term curative potential of this approach and the relative merits of intervention during chronic or during accelerated phase have yet to be determined. Studies directly comparing allogeneic transplantation in chronic phase and in accelerated phase are underway at our institution.

REFERENCES

Allogeneic bone marrow transplantation as treatment for accelerating chronic myelogenous leukemia

PB McGlave, DC Arthur, D Weisdorf, T Kim, A Goldman, DD Hurd, NK Ramsay and JH Kersey