CONCISE REPORT

Allogeneic Bone Marrow Transplantation for Chronic Myelogenous Leukemia in Chronic or Accelerated Phase

By Richard Champlin, Winston Ho, Edward Arenson, and Robert Peter Gale

Eight patients with Ph1-positive chronic myelogenous leukemia (CML) in chronic or accelerated phase received high-dose cyclophosphamide, total body irradiation, and bone marrow transplantation from an HLA-identical sibling donor. All patients had prompt engraftment and achieved complete hematologic remission. Six patients remain alive and in continuous remission with a normal bone marrow karyotype 3-20+ mo posttransplant. One patient died from cytomegalovirus interstitial pneumonitis. Only one patient who was transplanted in accelerated phase relapsed 6.5 mo posttransplant and died in blast crisis. High-dose combined modality therapy is capable of producing sustained complete remissions in patients with CML treated during chronic or accelerated phase.

SURVIVAL OF PATIENTS with chronic myelogenous leukemia (CML) has not increased substantially in the past 20 yr. Chemotherapy with busulfan, hydroxyurea, or other drugs may palliate symptoms during the chronic phase of the disease but does not delay transformation to the acute phase (blast crisis) or improve survival.1 Median survival of patients with CML is approximately 3 yr; less than 20% of patients survive 5 yr.2 Because of these results, several investigators have evaluated intensive combination chemotherapy in patients with CML in chronic phase. Some patients have achieved transient complete remissions, but the Philadelphia (Ph1) chromosome positive cells generally recur within 6 mo and survival is not improved.3-6 Once acute phase has developed, all forms of therapy have produced only transient remissions, and median survival is less than 6 mo.1 Approximately half of the patients develop a transient "accelerated phase" characterized by fever, increasing leukocytosis resistant to chemotherapy, progressive anemia and thrombocytopenia, increasing basophilia, and rapidly progressive hepatosplenomegaly. Survival from the onset of accelerated phase is only 3-6 mo in most series.7,8

Because of the disappointing results with both conventional and intensive chemotherapy, several investigators have evaluated bone marrow transplantation as a potential therapeutic modality in patients with CML. Three sources of hematopoietic stem cells have been evaluated: autologous cryopreserved chronic phase blood or bone marrow cells, 9,10 normal bone marrow cells from a genetically identical monozygotic twin,11 or bone marrow cells from and HLA-identical sibling.12-13 Transplants performed during the acute phase have generally been unsuccessful, either because of the inability to completely eradicate the leukemic cells or because of treatment-related complications such as incomplete engraftment, graft-versus-host disease (GVHD), or interstitial pneumonitis.

Recently, Fefer and coworkers10 and others14-16 have reported encouraging results in patients with CML in chronic phase who received a bone marrow transplant from a genetically identical monozygotic twin. Their data indicate prolonged disease-free survival in 17 of 21 patients with CML transplanted in chronic phase. These results suggest that high-dose combined modality therapy may be effective in erradicating Ph1-positive leukemic cells when the transplant is performed during the chronic phase of the disease. Unfortunately, few patients with CML have a genetically identical twin to serve as a donor. Therefore, we sought to determine whether a similar approach, bone marrow transplantation during chronic or accelerated phase, might be effective using bone marrow from an HLA-identical sibling donor.

MATERIALS AND METHODS

Patients with chronic myelogenous leukemia less than 45 yr of age in chronic or accelerated phase were eligible for study entry. Accelerated phase was defined by two or more of the following features: (1) WBC > 20 x 10^9/liter resistant to chemotherapy and associated with a hemoglobin <10 g/dl and platelets <100 x 10^9/liter; (2) rapidly increasing hepatosplenomegaly; (3) fever >38.5°C unrelated to infection for >5 days; or (4) the development of chromosome abnormalities in addition to a single Ph1 chromosome. Patients with >30% blasts and promyelocytes in bone marrow or peripheral blood were not considered to be in chronic or accelerated phase and were not eligible for study entry. Bone marrow...
donors were HLA-A,B,C, and D identical siblings who showed bidirectional nonreactivity in mixed lymphocyte culture. The experimental design of the study was approved by the Human Subject Protection Committee of the UCLA School of Medicine and informed consent was obtained from all patients and their donors.

The pretransplant regimen consisted of cyclophosphamide 60/ mg/kg/day on days −4 and −3, and total body irradiation, 10 Gy in a single dose at a dose rate of 6 cGy/min from a 60Co source on day −1. Bone marrow cells were transplanted on day 0.16 Methotrexate was given at a dose of 15 mg/m² on day +3, +6, +9 and weekly thereafter to day +102 to prevent or modify graft-versus-host disease (GVHD).16 Engraftment was documented by increasing peripheral blood cells, bone marrow morphology, chromosome analysis, and by analysis of red cell antigens and red cell leukocyte isoenzymes.19 There was one or more informative chromosome or gene marker available in each case. GVHD and interstitial pneumonitis were evaluated by previously reported criteria.20,21 Patients without GVHD were classified as grade 0, those with mild GVHD as grade 1, and those with moderate to severe GVHD as grades 2-4. Patients with more than grade 2 GVHD received high-dose corticosteroids: methylprednisolone 600 mg/m² i.v. for 3 days, 300 mg/m² i.v. for 2 days, then prednisone 60 mg/m² tapered as tolerated to control symptoms. Patients were managed in reverse isolation and received oral nonabsorbable antibiotics including vancomycin, colistin, or polymixin B and nystatin. Documented or suspected infections in neutropenic patients were treated with a combination of a semisynthetic penicillin and an aminoglycoside antibiotic. Fungal infections were treated with amphotericin-B. All blood products given posttransplant were irradiated with 15 Gy to prevent unintentional engraftment of viable lymphocytes.

Remission of CML was analyzed by serial peripheral blood counts, leucocyte alkaline phosphatase scores, bone marrow morphology, and cytogenetic analyses at 3-6-mo intervals posttransplant. Chromosomes from at least 15 metaphases were routinely evaluated. Remission and survival data were analyzed by means of the product limit method using program BMDP1L of the UCLA Health Sciences Computing Facility.22

RESULTS

Eight patients with CML in chronic or accelerated phase received high-dose chemoradiotherapy followed by bone marrow transplantation from an HLA-identical sibling donor. Pretreatment characteristics are shown in Table 1. Four patients were in stable chronic phase at the time of transplantation. Three patients were in accelerated phase with fever, increasing hepatosplenomegaly, myelofibrosis, WBC > 20 x 10⁹/liter, hemoglobin <10 g/dl, and platelets <100 x 10⁹/liter. One patient had previously developed myeloid blast crisis but achieved a second chronic phase after receiving intensive chemotherapy with daunorubicin, cytarabine, and 6-thioguanine.23 Median age was 26 yr (range 5-39 yr). All patients had the Ph¹ chromosome; two had additional C or G group abnormalities. All patients were previously treated with busulfan and/or hydroxyurea. One patient also received cyclophosphamide. One patient had undergone splenectomy for control of thrombocytopenia during the accelerated phase.

All eight patients had prompt engraftment and achieved a complete hematologic remission. Cytogenetic analysis of bone marrow cells indicated normal donor karyotypes exclusively; no Ph'-positive cells were observed in over 300 karyotypes studied. One patient died on day 63 of graft-versus-host disease and CMV-related interstitial pneumonitis. She also had severe thrombocytopenia secondary to hypersplenism and a marked hemorrhagic diathesis. Blood product support was uncomplicated in the seven remaining patients. One patient (205) relapsed 6.5 mo posttransplant with Ph¹-positive cells. Blast crisis developed rapidly and she died 2 wk later. One patient (188) developed transient grade 3 acute graft-versus-host disease and one has mild chronic graft-versus-host disease of the skin. Two patients (198, 232) developed idiopathic interstitial pneumonitis 4 and 6 mo posttransplant, which resolved without complications.

Six patients are alive and in continuous complete remission 3-21 mo posttransplant. All are Ph¹-chro-

### Table 1. Bone Marrow Transplantation in Chronic Myelogenous Leukemia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Karyotype</th>
<th>Dx→Tx</th>
<th>Prior Treatment†</th>
<th>Clinical Status</th>
<th>Relapse</th>
<th>Disease-Free Survival (mo)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>166</td>
<td>28/M</td>
<td>46,XY,Ph¹</td>
<td>4.7</td>
<td>B</td>
<td>Chronic</td>
<td>—</td>
<td>20+</td>
<td>Alive 100%</td>
</tr>
<tr>
<td>188</td>
<td>5/F</td>
<td>46,XX,Ph¹</td>
<td>1.2</td>
<td>B</td>
<td>Chronic</td>
<td>—</td>
<td>16+</td>
<td>Alive 100%</td>
</tr>
<tr>
<td>193</td>
<td>24/F</td>
<td>46,XX,Ph¹</td>
<td>4.4</td>
<td>B</td>
<td>Chronic</td>
<td>—</td>
<td>15+</td>
<td>Alive 100%</td>
</tr>
<tr>
<td>247</td>
<td>35/F</td>
<td>46,XX,Ph¹</td>
<td>3.0</td>
<td>B,H</td>
<td>Chronic</td>
<td>—</td>
<td>2+</td>
<td>Alive (90%)</td>
</tr>
<tr>
<td>198</td>
<td>37/M</td>
<td>46,XX,Ph¹</td>
<td>4.4</td>
<td>B,HL,C</td>
<td>Accelerated</td>
<td>—</td>
<td>14+</td>
<td>Alive (100%)</td>
</tr>
<tr>
<td>205</td>
<td>16/F</td>
<td>46,XX,Ph¹</td>
<td>3.3</td>
<td>B</td>
<td>Accelerated</td>
<td>+ (6.5 mo)</td>
<td>7</td>
<td>Dead-blast crisis</td>
</tr>
<tr>
<td>231</td>
<td>20/F</td>
<td>46,XX,Ph¹</td>
<td>2.3</td>
<td>B</td>
<td>Accelerated</td>
<td>—</td>
<td>2</td>
<td>Dead-IPn (CMV)</td>
</tr>
<tr>
<td>232</td>
<td>39/M</td>
<td>47,XY,Ph¹</td>
<td>3.4</td>
<td>B,H</td>
<td>acute→chronic</td>
<td>—</td>
<td>5+</td>
<td>Alive (90%)</td>
</tr>
</tbody>
</table>

‡B, busulfan; H, hydroxyurea; L, leukopheresis; S, splenectomy; TAD, 6-thioguanine, cytarabine, daunorubicin; V, vinblastine; P, prednisone.

$Karnofsky score.22$

§GVHD, graft-versus-host disease; CMV, cytomegalovirus; IPn, interstitial pneumonia.

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mosome-negative. Surviving patients have a Karnofsky performance status of 90%–100%.

DISCUSSION

High-dose combined modality therapy and bone marrow transplantation during acute phase of CML has been largely unsuccessful. Treatment failures have been primarily due to resistant leukemia or transplant-related complications, including drug and radiation toxicity, GVHD, and interstitial pneumonitis. In contrast to these disappointing results in acute phase, our data indicate that high-dose chemoradiotherapy and bone marrow transplantation from an HLA-identical sibling donor is capable of inducing sustained complete remissions in patients with chronic myelogenous leukemia transplanted in chronic or accelerated phase. Seven of eight transplanted patients survived the immediate posttransplant period, and six are alive in continuous complete hematologic remission 3–20 mo posttransplant. Actuarial survival is 70%; only one patient who was transplanted in accelerated phase relapsed.

These results using HLA-identical sibling donors are comparable to those achieved following bone marrow transplantation from a genetically identical twin. In addition, transplantation from an HLA-identical sibling rather than an identical twin may confer an advantage due to a possible antileukemic effect of graft-versus-host disease. This effect has been reported in patients receiving allogeneic HLA-identical bone marrow transplants for acute leukemia.24–26

Preliminary data from several centers also indicate favorable results in patients with CML in chronic phase receiving bone marrow transplants from HLA-identical sibling donors.27–30 Twenty-three of 29 patients transplanted in chronic phase survived >6 mo; actuarial survival is 70% at 1.5 yr, with no reported relapses. Results have been less satisfactory in patients transplanted in the accelerated phase. Five of 18 patients survived 6 mo or more. Only one patient has relapsed, but 11 died within 6 mo of transplantation from transplant-related complications, including toxicity, GVHD, and interstitial pneumonitis. Actuarial survival for patients transplanted in accelerated phase is 24% at 2 yr.12,27–30 These results, although disappointing, compare favorably with those achieved with "conventional therapy" of the accelerated phase.8

Allogeneic bone marrow transplantation may be associated with substantial early morbidity and mortality. Although only one of eight patients in this study died due to posttransplant complications, one would anticipate a 30%–40% early mortality rate from transplant-related complications based on transplant data in other disorders.31,32 This risk must be weighed against the 25% annual risk to CML patients of entering blast crisis.5 Although a number of prognostic factors have been reported in patients with CML,7,33 most of these are controversial, and there is currently no reliable means to identify high-risk patients prior to clonal evolution in the karyotype or the clinical development of accelerated or acute phase. If bone marrow transplantation proves effective in permanently eradicating the leukemic cells, then overall survival of transplant patients would exceed that of chronic phase patients receiving conventional treatment after approximately 2–3 yr.

In conclusion, high-dose chemoradiotherapy and bone marrow transplantation from an HLA-identical sibling is capable of producing sustained hematologic remissions in patients with CML in chronic phase. Results of transplantation in accelerated phase have been less satisfactory, with a higher incidence of treatment-related deaths in the early posttransplant period. Clearly, these data are preliminary. Bone marrow transplantation must be evaluated in controlled trials involving large numbers of patients with extended follow-up before its routine use can be recommended. Nevertheless, this approach should be considered as a possible therapeutic alternative in young patients with chronic myelogenous leukemia in chronic or accelerated phase who have an HLA-identical sibling donor.

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