CONCISE REPORT

Bone Marrow Transplantation for Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia


We report the treatment outcome of allogeneic bone marrow transplantation in ten patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Six patients are alive and well for 6 to 30 months (median 19 months) after transplantation. Four patients died with transplant related complications. In view of the poor prog-

PHILADELPHIA CHROMOSOME (Phi)-positive acute lymphoblastic leukemia (ALL) is a variant of ALL that is associated with an exceptionally poor prognosis. Although complete remissions (CR) are readily attained with remission induction chemotherapy in ~70% of adult patients with this disorder, median remission duration is <1 year. In addition, long-term, disease-free survival is rare even when intensification and maintenance regimens that have been successful in other variants of ALL are administered. To overcome the resistant nature of the abnormal clone involved, bone marrow ablation with high-dose radiochemotherapy followed by bone marrow transplantation (BMT) has been used in some patients. We report our experience using allogeneic BMT as a treatment for ten adult patients with Phi-positive ALL.

MATERIALS AND METHODS

Preparation for BMT consisted of fractionated total body irradiation (FTBI) with 1320 cGy (11 × 120 cGy on day –7 through day –4 at a dose rate of 15 cGy/min) in eight patients and of single-dose total body irradiation (STBI) with 750 cGy at 26 cGy/min on day –5 in one patient. This was followed on day –3 by intravenous (IV) administration of cyclophosphamide (CY) at a dose of 100 mg/kg in three patients or etoposide (VP16) at a dose of 60 mg/kg in six patients. For technical reasons, one patient was treated with busulfan (BU) at 16 mg/kg given over 4 days (day –7 through day –4) followed by CY at 60 mg/kg administered on day –3 and day –2. Supportive care was provided as previously described. The BMT procedure from the histocompatible sibling donors was carried out on day 0 following a generally practiced method. To prevent graft-versus-host disease (GVHD), patients received either cyclosporine A/prednisone (CSA/PSE) or methotrexate/prednisone (MTX/PSE); details of the two drug schedules, investigated in a prospective randomized GVHD study, were reported recently.

Patients: Between October 1984 and October 1986, 10 patients with Phi-positive ALL were accepted for BMT at the City of Hope National Medical Center. At the time of entry, patients were assigned a unique patient number (UPN). Initially the WBC cell count of these patients ranged from 400 to 350,000/μL. The distribution of immunophenotypes of ALL was as follows: null type (1 patient), common ALL antigen (CALLA) positive (3 patients) and pre-B type (6 patients). Because these patients were referred to us from eight different leukemia centers, their initial chemotherapy had contained various drug combinations. The patients had been treated with the following chemotherapeutic agents: daunorubicin (9 patients), vincristine (9 patients), PSE (8 patients), L-asparaginase (6 patients), cytosine arabinoside (5 patients), MTX (5 patients), 6-mercaptopurine (4 patients), 6-thioguanine (2 patients), and CY (2 patients). Eight patients had attained CR within 4 to 8 weeks after beginning remission induction therapy, whereas 2 others had failed repeated remission induction attempts. When the preparatory regimen was administered, 4 patients were in first CR, 2 had failed to enter CR, 1 was in first relapse, and 3 were refractory to reinduction attempts. All clinical research protocols have been approved by the Institutional Review Board of the City of Hope Medical Center. Patient entry to the study was contingent upon prior written informed consent.

RESULTS

By the end of the first month following BMT, all patients showed signs of engraftment, documented by appropriate genetic marker analysis. One patient (UPN 323) has become a mixed lymphohematopoietic chimera. Five patients showed no signs of acute GVHD, whereas in two patients GVHD was mild (grade 1) and in three patients it was moderate to severe (grades II through IV).

Six patients are currently alive and in continued CR for 6 to 30 months (median 19 months) after BMT. The performance status of the six surviving patients is 80 to 100 (median 100); one of them (UPN 271) has mild chronic GVHD. Four patients died within the first 4 months following marrow grafting: 2 with GVHD and interstitial pneumonitis (IP), 1 with polymicrobial infection, and 1 with a combination of veno-occlusive disease (VOD), bleeding, and fungemia. Details of the ten BMT recipients on this study are shown in Table 1.
Table 1. Bone Marrow Transplantation for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>UPN</th>
<th>Initial WBC/µl</th>
<th>Immuno-phenotype</th>
<th>DX → CR</th>
<th>CR → BMT</th>
<th>Status at BMT</th>
<th>Blasts in BM (%)</th>
<th>Preparatory Regimen</th>
<th>GVHD Prophylaxis</th>
<th>Acute GVHD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>264</td>
<td>8,900 CALLA</td>
<td>4 3 1.CR</td>
<td>FTBI/CY</td>
<td>CsA/PSE</td>
<td>Alive in CCR, day + 892</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>271</td>
<td>1,500 Null</td>
<td>4 5 1.CR</td>
<td>FTBI/CY</td>
<td>CsA/PSE</td>
<td>Alive in CCR, day + 836</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>323</td>
<td>7,400 PRE-B</td>
<td>4 2 1.CR</td>
<td>FTBI/CY</td>
<td>CsA/PSE</td>
<td>Alive in CCR, day + 523</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>397</td>
<td>2,900 PRE-B</td>
<td>4 2 1.CR</td>
<td>FTBI/VP16</td>
<td>CsA/PSE</td>
<td>Died with polymicrobial infection on day + 63</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>304</td>
<td>4,600 CALLA</td>
<td>NA NA IF</td>
<td>FTBI/VP16</td>
<td>MTX/PSE</td>
<td>Died with GVHD/IP and sepsis on day + 121</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>306</td>
<td>350,000 PRE-B</td>
<td>4 4 1.RIF</td>
<td>FTBI/VP16</td>
<td>MTX/PSE</td>
<td>Alive in CCR on day + 892</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>309</td>
<td>315,000 PRE-B</td>
<td>NA NA IF</td>
<td>STBI/VP16</td>
<td>CsA/PSE</td>
<td>Alive in CCR, day + 335</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>353</td>
<td>400 CALLA</td>
<td>8 14 1.RIF</td>
<td>BU/CY</td>
<td>CsA/PSE</td>
<td>Died with VOD, Gl bleeding, and fungemia on day + 36</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>355</td>
<td>8,550 PRE-B</td>
<td>4 3 1.REL</td>
<td>FTBI/VP16</td>
<td>CsA/PSE</td>
<td>Died in CCR on day + 311</td>
<td></td>
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</tr>
<tr>
<td>392</td>
<td>20,000 PRE-B</td>
<td>6 22 1.REL</td>
<td>FTBI/VP16</td>
<td>CsA/PSE</td>
<td>Died in CCR on day + 171</td>
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</table>


Abbreviations: UPN, unique patient number; DX, diagnosis; NA, not applicable (because patient failed to attain CR); IF, induction failure; RIF, reinduction failure; REL, relapse; STBI, single-dose total body irradiation; VP16, etoposide; CCR, continued CR.

DISCUSSION

Six of 10 patients with Phl-positive ALL were transplanted successfully with marrow from histocompatible siblings, whereas four patients died with BMT-related complications. Three of the four patients who had undergone BMT during first CR are surviving; the other three survivors were in more advanced stages of their disease when preparation for BMT was begun.

There are several caveats regarding our study: The patient group under study is relatively small and the observation time is still limited to 6 to 30 months. Neither can we conclude from our data the preparatory regimen to recommend. This issue must be addressed in future studies.

Nevertheless, our data, which require confirmation by other transplant centers, can be viewed as encouraging. Indeed, considering the poor prognosis for patients with this variant of ALL, BMT performed early during the course of this disease may currently be the treatment of choice if a suitable donor is available.

REFERENCES

Bone marrow transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia

SJ Forman, MR O'Donnell, AP Nademanee, DS Snyder, PJ Bierman, GM Schmidt, JL Fahey, AS Stein, PM Parker and KG Blume