Treatment of Preleukemic Syndromes With Marrow Transplantation

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Thirty patients with advanced preleukemic syndromes were treated with marrow transplantation. Most cases were diagnosed by the presence of peripheral pancytopenia and a diagnostic marrow examination but in 6 of the 30 patients pretransplant chromosome studies were instrumental in establishing the diagnosis. Three patients prepared for transplantation with cyclophosphamide alone recurred with their disease within 6 months of transplantation. The other 27 patients were treated with cyclophosphamide and total body irradiation. Twenty of these 27 patients had preleukemia not associated with prior therapy or severe marrow fibrosis. Thirteen of these 20 are alive and well 9 to 56 months from transplant and 7 died, 4 of interstitial pneumonia, 2 of candida septicemia, and 1 of disseminated zoster. There have been no disease recurrences in this group. The remaining preleukemic patients, which include 3 patients transplanted for preleukemia secondary to prior therapy and 4 patients transplanted for preleukemia associated with severe marrow fibrosis, have all died. Major problems in these patients included disease recurrence (2 cases) and, in those with severe marrow fibrosis, graft failure (2 cases). These results suggest that for patients with life-threatening pancytopenia due to spontaneous preleukemia without severe marrow fibrosis, marrow transplantation can prolong disease-free survival and may result in cure of the disease.

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Submitted April 1, 1986; accepted July 18, 1986.

Supported by Grants Nos. CA 15704, CA 09319, HL 36444 (formerly CA 30924), and CA 18029 from the National Cancer Institute and the National Heart, Lung, and Blood Institute, DHHS. Dr E. Donnall Thomas is a recipient of Research Career Award AI 02425 from the National Institute of Allergy and Infectious Diseases.

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PATIENTS AND METHODS

Thirty consecutive patients with preleukemia were treated between May 1977 and December 1985. In this study we included as “preleukemic” patients with pancytopenia and the presence of myelodysplasia on marrow examination, patients with aplastic marrow and a clonal cytogenetic abnormality of a type associated with hematologic malignancies, or patients with otherwise unexplained myelofibrosis. Table 1 shows the clinical characteristics of the patients. Ages ranged from 4 to 54 years (median 24 years) with 17 males and 13 females. In 3 patients (UPN 2798, 2799, and 2813) preleukemia was apparently therapy related, in 3 cases (UPN 2173, 2855, and 1763) preleukemia occurred in patients with Fanconi’s anemia, and one patient (UPN 1694) had a family history of preleukemia. No cause was identified in the other 23 cases. The median duration of disease from diagnosis to transplantation was 12 months and ranged from 2 to 180 months. All patients received transfusion support prior to referral and 19 had received prior therapy, the most common forms of therapy being steroids (16 patients), androgens (6 patients), and low-dose cytarabine (4 patients). At the time of referral for transplantation all patients required red cell transfusion support, 26 required platelet transfusions, and 25 had a granulocyte count of less than 1,000/cu mm. Peripheral blood and marrow samples were reviewed and classified, when possible, according to the proposals of the French-American-British (FAB) cooperative group.14 Degree of marrow fibrosis was graded according to the criteria of Bauermeister.15 Twenty-one patients had disease that could be classified as myelodysplastic according to the proposed FAB schema including 9 patients with refractory anemia and 12 patients with refractory anemia with excess blasts. Six patients had aplastic marrows but a clonal cytogenetic abnormality. Two patients had unexplained myelofibrosis. A final patient had a normal appearing marrow but severe pancytopenia and trisomy 8.

Marrow samples were processed for chromosome analysis after 1.5 and 24 hours in culture without added mitogens. In 3 patients (UPN 2208, 2254, and 2813) marrow either could not be aspired or no metaphases were present for analysis. Chromosome banding was done using quinacrine mustard for Q bands. Details of the transplant procedure are presented in Table 2. Histocompatibility between donor and recipient was determined by HLA typing and mixed leukocyte culture tests. In 24 cases the donor was an HLA-identical sibling, in 1 case an HLA phenotypically matched father, and in 5 cases a son or sibling mismatched for 1 (2 cases) or 2 (3 cases) antigens. The technique of marrow transplantation has been described.14

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The preparative regimens used prior to transplantation were those we have used for treatment of aplastic anemia (UPN 691, 1042, and 1442) or acute leukemia (the remaining 27 patients).17,18 All patients received posttransplant immunosuppression with either methotrexate (4 cases), cyclosporine (1 case), or a combination of the two (25 cases) in an effort to diminish or prevent graft-versus-host disease (GVHD).19,20

Patients were also entered on other protocols involving laminar air flow isolation and prophylactic systemic antibiotics. All risks of the treatment protocol were fully explained to patients, donors, and relatives. Informed consent was obtained using forms approved by the Investigational Review Board of the Fred Hutchinson Cancer Research Center. Data were analyzed as of July 1, 1986.

**RESULTS**

The results are summarized in Table 2. Three patients (UPN 2798, 2799, and 2813) were transplanted for therapy-related preleukemia, 2 after chemoradiotherapy for Hodgkin's disease, and 1 after prolonged busulfan therapy for polycythemia vera. All three died within 3 months of transplant, one of persistent disease, one of septic shock, and one of venoocclusive disease of the liver and candida septicemia. Four patients were transplanted for preleukemic syndromes characterized by extensive marrow fibrosis. None of these 4 survive with one patient dying of recurrent disease, 2 with graft failure associated with either bleeding or infection, and one of idiopathic interstitial pneumonia. Twenty patients were transplanted for preleukemia which was neither therapy related nor associated with extensive marrow fibrosis. Thirteen of these 20 patients are alive without either clinical or cytogenetic evidence of disease from 9 to 56 months after transplant. The seven patients who failed therapy included 4 cases of interstitial pneumonia (3 idiopathic and one associated with cytomegalovirus; CMV), 2 cases of candida septicemia, and one case of disseminated herpes zoster infection. None of the 20 patients suffered a recurrence of their disease.

In addition to the apparently important influences of the preparative regimen, etiology of disease, and presence of marrow fibrosis, patient age seemed to influence survival.

### Table 1. Pretransplant Clinical Characteristics of 30 Patients With Preleukemic Syndromes

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age</th>
<th>Sex</th>
<th>Duration (mo)</th>
<th>Previous Treatment</th>
<th>Hgb</th>
<th>WBC</th>
<th>PMN</th>
<th>Plt</th>
<th>Cell*</th>
<th>Fibrosis</th>
<th>Morph</th>
<th>Cytogenetics</th>
<th>CMV Traf</th>
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</thead>
<tbody>
<tr>
<td>691</td>
<td>9</td>
<td>F</td>
<td>39</td>
<td>A,S</td>
<td>9.4</td>
<td>3,800</td>
<td>468</td>
<td>2,000</td>
<td>1+</td>
<td>0</td>
<td>AA</td>
<td>45,XX-7</td>
<td>-</td>
</tr>
<tr>
<td>1042</td>
<td>30</td>
<td>M</td>
<td>2</td>
<td>-</td>
<td>5.0</td>
<td>3,125</td>
<td>668</td>
<td>9,700</td>
<td>4+</td>
<td>0</td>
<td>RAEB</td>
<td>45,XY-7</td>
<td>-</td>
</tr>
<tr>
<td>1442</td>
<td>34</td>
<td>F</td>
<td>3</td>
<td>S</td>
<td>7.3</td>
<td>1,800</td>
<td>120</td>
<td>13,000</td>
<td>1+</td>
<td>0</td>
<td>AA</td>
<td>46,XX,del(2q22q23)</td>
<td>+</td>
</tr>
<tr>
<td>1688</td>
<td>13</td>
<td>M</td>
<td>28</td>
<td>S,P</td>
<td>5.5</td>
<td>1,400</td>
<td>84</td>
<td>20,800</td>
<td>0+</td>
<td>0</td>
<td>RA</td>
<td>45,XY-7</td>
<td>-</td>
</tr>
<tr>
<td>1636</td>
<td>54</td>
<td>M</td>
<td>3</td>
<td>S</td>
<td>5.2</td>
<td>2,200</td>
<td>320</td>
<td>3,000</td>
<td>1+</td>
<td>0</td>
<td>RAEB</td>
<td>46,XY-5,-6,-7,-17,-21, +mar(1-4)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: UPN, unique patient number; A, androgens; S, steroids; P, pyridoxine; ATG, antithymocyte globulin; Endo, endotoxin; LDAC, low-dose cytarabine; CRA, cis retinoic acid; HDAC, high-dose cytarabine; CSP, cyclosporine; AA, aplastic anemia; RAEB, refractory anemia with excess blasts; RA, refractory anemia; MF, myelofibrosis; NA, marrow not aspirable.

*0, acellular; 1, markedly hypocellular; 2, mildly hypocellular; 3, monocellular; 4, hypercellular.

†Patients treated for a prior malignancy; UPN 2798 with busulfan; UPN 2799 and 2813 with nitrogen mustard, vincristine, prednisone, procarbazine, and irradiation.

‡Presence (+) or absence (−) pretransplant of antibody to cytomegalovirus.
The health of the 13 disease-free survivors is excellent. All have normal hematologic function and 12 of the 13 are off all medications with Karnofsky scores of 90% to 100%. One patient has developed bronchial asthma posttransplant without other evidence of chronic graft-vs-host disease. He requires no immunosuppressive therapy.

**DISCUSSION**

Despite recent advances in the management of patients with preleukemic syndromes, in particular the use of low-dose cytarabine, patients with preleukemia are generally considered to be incurable and most of these patients die with bleeding, infection, or acute leukemia. The success of high-dose chemotherapy or chemoradiotherapy followed by marrow transplantation as treatment for various marrow disorders prompted us to study this approach in patients with preleukemic syndromes.

The first 3 patients were given cyclophosphamide alone as a preparative regimen, similar to the way in which patients with aplastic anemia are prepared for transplantation. Although all three demonstrated evidence of engraftment of donor marrow, in all three the malignant clone recurred suggesting that cyclophosphamide alone, or combined with any allogeneic reactivity of the engrafted marrow, is inadequate to eradicate the abnormal cell population. According-
matched donors. Since recurrent disease has not been a major problem and since irradiation presumably contributed to the observed toxicities, the use of lower doses of TBI or lung shielding might be considered in patients undergoing transplantation for preleukemia.

Results in the small group of patients with preleukemia secondary to previous therapy were less encouraging. One patient never cleared his abnormal cell population and the other 2 died of transplant-related complications. This unfavorable experience is apparently not universal. Gyger et al reported a 22-year-old man who developed preleukemia following chemoradiotherapy for Hodgkin's disease who received an HLA-identical marrow graft from his sister following treatment with busulfan and cyclophosphamide. He was reported to be alive in remission 311 days posttransplant.21

Results in the 4 patients transplanted for preleukemia associated with extensive marrow fibrosis were discouraging. None of these patients is alive, one having relapsed and 3 having died of transplanted-related complications. Further, in 3 of these 4 patients normal peripheral blood counts were never achieved despite evidence for lymphoid engraftment and in 2 of these 3, pancytopenia was the cause of death. There are several case reports that demonstrate that engraftment can be achieved in some patients with severe marrow fibrosis.22-26 But, as case reports, these studies did not compare the outcome of transplantation in patients with and without marrow fibrosis. The question of the effect of severe marrow fibrosis on engraftment prompted us to review our wider experience with transplantation in patients with marrow fibrosis of any etiology. As recently reported by Rajantie et al, patients transplanted for preleukemia, chronic myelogenous leukemia, or acute leukemia with coexistent extensive marrow fibrosis frequently have difficulty with engraftment as evidenced by a graft failure rate of 33% and slower myeloid and platelet engraftment in those who do engraft when compared to age- and disease-matched control patients with little or no fibrosis.27

The experience reported here emphasizes the importance of marrow cytogenetic results in deciding on treatment of patients with pancytopenia. Six of the 30 patients described here were thought on initial morphologic examination of the marrow to have aplastic anemia. In each case marrow cytogenetics showed a clonal chromosomal abnormality establishing the diagnosis of preleukemia, including 3 cases of monosomy 7, one case of trisomy 8, one case with 46,XX,i(3)(q26;q21q26), and one case with 48XY,-7,+8,+21,+22.

Patients with preleukemia and life-threatening pancytopenia, in general, do poorly. The results reported here, particularly in those patients with de novo preleukemia without severe marrow fibrosis, suggest that if an appropriate donor is available, marrow transplantation should be strongly considered.

REFERENCES


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