Bone Marrow Ablation Followed by Allogeneic Marrow Grafting During First Complete Remission of Acute Nonlymphocytic Leukemia


Of 33 patients who had undergone allogeneic bone marrow transplantation during first complete remission of acute nonlymphocytic leukemia, 21 patients have now been followed in continued complete remission for 6–64 mo (median >18 mo) without maintenance chemotherapy. The median age of the surviving patients is 27 yr. Transplant-related complications occurring throughout the first year after marrow grafting were fatal in 7 patients, and leukemic recurrence led to the death of 5 patients. The actuarial long-term disease-free survival is 60% and the actuarial remission rate is 79%.

During the past decade, bone marrow transplantation (BMT) has evolved into an important treatment modality for acute leukemia. Chances for disease-free, long-term survival are particularly good if BMT is done during complete hematologic remission. This article deals with 33 consecutive patients with acute nonlymphocytic leukemia who were treated with high-dose radiochemotherapy followed by allogeneic BMT from histocompatible siblings while they were in first complete remission.

MATERIALS AND METHODS

Patients

Between December 1976 and October 1981, 33 patients with acute nonlymphocytic leukemia underwent allogeneic bone marrow grafting after marrow ablative radiochemotherapy. Since the majority of patients had been referred to us from other hospitals, remission induction had not been carried out in a uniform fashion; however, all patients had received daunorubicin and cytosine arabinoside as well as other chemotherapeutic agents using widely applied chemotherapy regimens. The remission status of all patients was confirmed using generally accepted criteria. The 33 patients had the following subtypes of acute nonlymphocytic leukemia according to the French-American-British classification: M1 (4 patients), M2 (13 patients), M3 (3 patients), M4 (9 patients), M5 (3 patients), and M6 (1 patient). One patient had extramedullary leukemia at the time of initial diagnosis as documented by a gastric biopsy. The median time between attainment of the first complete remission and preparation for marrow grafting was 2 mo (range 1–13). The median age of the patients was 28 yr (range 7–41). No patient was excluded from analysis, which was carried out in April 1982.

Methods

All clinical research protocols utilized in this study had been approved by the Institutional Review Board of the City of Hope National Medical Center. Preparation of BMT consisted of cytosine arabinoside (5 mg/kg) on days 8 and 9, cyclophosphamide (1000 mg/kg) on day 5, and total body irradiation on day 1 (day 0 being the day of marrow grafting). Total body irradiation was delivered with a 10 MeV linear accelerator at a dose rate of 7 rad/min as a single median dose of 991 rad (range 931–1037) with a median variation along the midline axis of 5% (range 2%–8%) as monitored with 4 separate sets of 8 thermoluminescent detectors as published earlier. The marrow grafts were obtained from the histocompatible sibling donors as described earlier. The number of nucleated cells grafted was 2.4 x 10^10/kg recipient body weight (range 1.1–3.9). After BMT, the patients were housed in conventional protective isolation rooms for a median of 19 days (range 13–29). Combination broad spectrum antibiotics were given for 19 days (range 0–40). Granulocyte transfusions were administered daily for 14 days (range 0–24); it should be noted that the first 20 patients received daily granulocyte transfusions as a part of a prophylactic granulocyte transfusion study. Single donor platelet concentrates were transfused for a median of 15 days (range 1–32). The median requirement for packed red blood cells was 8 transfusions (range 0–18). Posttransplant management with methotrexate and prednisone to prevent and/or treat acute or chronic graft-versus-host disease (GVHD) was carried out as described recently. GVHD was graded following a generally accepted diagnostic system. The median length of hospitalization, including the week required for preparation for BMT, was 44 days (range 29–99). No maintenance therapy was administered following BMT. Statistical analysis was performed using the method of nonparametric estimation from incomplete observations.

RESULTS

Twenty-one of the 33 patients are surviving in continuous complete remission and have now been followed for 6–64 mo (median >18 mo) following BMT. Actuarial disease-free survival is at 60% (SE 9.2%). Actuarial remission is 79% (SE 8.5%). Regular follow-up bone marrow examinations have not shown any evidence of recurrent leukemia in those 21 patients. Survival in relation to patients' ages is presented in Table 1. The median age of the surviving patients is 27 yr (range 7–36) and 13 of the survivors are older than 20 yr. An actuarial survival and remission analysis is demonstrated in Fig. 1.

In 23 patients, an infection with cytomegalovirus was documented by an antibody titer rise (more than 5 titer steps) and/or virus isolation. Sixteen patients developed an interstitial pneumonia with characteris-
Table 1. Outcome of Marrow Transplantation in Relation to Patients' Ages

<table>
<thead>
<tr>
<th>Patients' Ages (yr)</th>
<th>Patients Transplanted</th>
<th>Patients Alive in CR</th>
<th>Causes of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 10</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>10-19</td>
<td>9</td>
<td>7</td>
<td>Leukemia (2 patients)</td>
</tr>
<tr>
<td>20-29</td>
<td>14</td>
<td>9</td>
<td>Leukemia (2 patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Veno-occlusive disease (1 patient)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CMV-pneumonia (2 patients)</td>
</tr>
<tr>
<td>30-39</td>
<td>8</td>
<td>4</td>
<td>Intracranial bleeding (1 patient)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute GVHD with pneumonia (3 patients)</td>
</tr>
<tr>
<td>40 and older</td>
<td>1</td>
<td>0</td>
<td>Leukemia (1 patient)</td>
</tr>
</tbody>
</table>

During the first 2 mo after BMT, transient mild acute GVHD had been observed in 19 patients. However, 3 patients had severe acute GVHD, which proved to be fatal when cytomegalovirus-associated interstitial pneumonia supervened. One patient has developed chronic GVHD involving the skin at the upper torso without affecting his performance status. One patient has a chronic neuropathy manifested by muscle weakness of the lower extremities that is possibly related to either high-dose radiation exposure or due to a previous herpes zoster infection. The performance status of all survivors is 100% on the Karnofsky scale except for the patient with chronic interstitial pneumonitis (80%) and the patient with chronic neuropathy (80%).

The following transplant-related complications led to the death of 7 patients: intracranial bleeding (1 patient), venoocclusive disease (1 patient), severe acute GVHD with interstitial pneumonia (3 patients), and interstitial pneumonia associated with cytomegalovirus without GVHD (2 patients). Leukemia, which had recurred 5–12 mo after BMT, was responsible for the death of 5 patients. The subtypes of leukemia in these 5 patients were: M1 (1 patient), M2 (2 patients), M4 (1 patient), and M6 (1 patient).

**DISCUSSION**

At the present time, optimum results are obtained with bone marrow transplantation in acute nonlymphocytic leukemia when the procedure is carried out during complete first remission. The reports from several transplant centers suggest that marrow transplantation during the first complete remission represents a therapeutic option with a high probability for long-term unmaintained disease-free survival in patients with acute nonlymphocytic leukemia. The median age of the surviving patients in this report (27 yr) indicates that marrow transplantation can offer a likelihood of prolonged disease-free survival in chil-
dren and younger adult patients undergoing marrow transplantation. The effect of age on the success of BMT is shown in Table 1. Whereas the only cause of death in patients under the age of 20 yr is leukemic relapse, patients over 20 have an increased incidence of BMT-related complications.

It is also noteworthy in this study that none of the surviving patients have developed disabling chronic GVHD. Whether the low dose of prednisone prophylaxis and treatment regimen used is responsible for the low incidence of acute and chronic GVHD needs to be confirmed by further studies. Since GVHD is more likely to develop in older patients, larger studies with older patients need to be continued. In addition, it may be possible to further improve the clinical results of allogeneic bone marrow transplantation by improving the management of the transplant-related problems. Different modes of irradiation, such as dose fractionation or marrow ablation with high-dose chemotherapy alone without irradiation, may reduce the incidence of serious complications such as interstitial pneumonitis. In order to prevent GVHD, in vitro manipulation of the marrow inoculum with T-cell-specific antisera, the use of cyclosporin-A, or combinations of immunosuppressive drugs may decrease the incidence of GVHD and hopefully improve overall survival.

In contrast to the results obtained in first remission patients, the disease-free survival in patients who undergo marrow grafting in second or subsequent remission of acute nonlymphocytic leukemia is approximately 25%. Although this result is inferior to that which can be achieved in first remission patients, it represents a major impact on the survival of patients who would otherwise have had a small chance of long-term survival. This is due primarily to the high probability of subsequent relapse and death from acute leukemia in untransplanted patients. Bone marrow transplantation, therefore, is probably the only curative modality for a substantial number of patients who have had leukemic recurrence either while receiving chemotherapy or after its discontinuation.

The cost of marrow transplantation continues to be considerable. The median total cost (including expenses encountered for marrow procurement) was approximately $57,000 (range $41,000–95,000). With improvement in the prevention or management of transplantation-related complications, it may be possible to decrease the overall cost of the procurement. At the present time, however, the cost of marrow transplantation is quite comparable to that of other modern life-saving medical procedures, such as open heart surgery, long-term hemodialysis, renal transplantation, and the treatment of hepatic failure.

### ADDENDUM

No life-threatening complications which developed during remission induction therapy following initial diagnosis of acute nonlymphocytic leukemia excluded patients from entering the transplantation study. In addition to systemic bacterial infections, other complications occurring during initial induction chemotherapy included: Acute renal failure requiring dialysis (1 patient), respiratory failure necessitating open lung biopsy, intubation and ventilation (1 patient), congestive heart failure (1 patient), and multiple fungal abscesses treated with amphotericin B and splenectomy (1 patient).

This study has by now (12/82) been extended to 43 patients, of whom 23 are alive and in complete remission 4 to 72 mo after BMT. A total of 7 patients have relapsed between 5 to 19 mo after marrow grafting.

### REFERENCES


Bone marrow ablation followed by allogeneic marrow grafting during first complete remission of acute nonlymphocytic leukemia