Bone Marrow Transplants May Cure Patients With Acute Leukemia Never Achieving Remission With Chemotherapy


Achieving remission is essential for curing acute leukemia. Over the past 20 years, intensive chemotherapy has increased remission rates.1 Nevertheless, about 30% of adults with acute lymphoblastic leukemia (ALL) and 20% to 40% of children and adults with acute myelogenous leukemia (AML) never achieve remission. Some children with high-risk ALL also fail induction chemotherapy.

Almost all patients with ALL and AML failing to achieve initial remission die of leukemia or its treatment, usually within 6 months. Recently, bone marrow transplants from HLA-identical siblings have been used to treat patients with acute leukemia resistant to intensive induction chemotherapy. The largest reported series included 21 patients, with nine alive and disease-free between 1 and 12 years after transplant.2 This report reviews data from the International Bone Marrow Transplant Registry (IBMTR) for 126 such patients from 49 transplant teams worldwide. These data indicate probable cure of some patients with acute leukemia failing initial intensive chemotherapy.

Materials and Methods

Patients

Between January 1, 1982 and December 31, 1988, the IBMTR received reports of 142 patients with acute leukemia receiving bone marrow transplants from HLA-identical siblings after failing to achieve remission following two or more courses of initial intensive induction chemotherapy. Sixteen patients were excluded because of an intent to perform the transplant before first remission or uncertainty about remission state pretransplant. Thirty-eight study entrants had ALL and 88 had AML. These groups are described separately.

ALL. The median age was 32 years (range, 1 to 50 years); only three patients (8%) were less than 10 years old and seven (18%) were 10 to 19 years old. Twenty-four (63%) were male. Seventeen (45%) had eALL, seven (18%) had T-ALL, four (11%) had B-ALL, and one (3%) had null-AL; nine (24%) cases were unclassified. French-American-British (FAB) classification was available for 22 patients: 11 (50%) were L1, 18 (82%) were L2, and 2 (9%) were L3. Median white blood cell counts (WBCs) at diagnosis were 39 × 10⁹/L (2 to 215 × 10⁹/L). Five patients (13%) had central nervous system leukemia. Although all patients received at least 2 courses of induction chemotherapy, information regarding the exact number of courses received was available for only 18 patients: 10 received 2 courses, 7 received 3 courses and 1 received 4 courses. Median interval from diagnosis to transplant was 4 months (2 to 13 months). Median WBCs pretransplant were 5 × 10⁹/L (<1 to 107 × 10⁹/L); median circulating blasts were 0% (0% to 95%). Median blasts in the bone marrow were 23% (0% to 96%) pretransplant. Fifteen (39%) were believed to be in partial remission. Median performance score before transplant was 80% (30% to 100%); 23 patients (61%) had performance scores less than 90%. Clinically important infection was present at transplant in seven cases (18%).

AML. The median age was 28 years (1 to 52 years); seven (8%) were less than 10 years and 15 (17%) were 10 to 19 years old. Fifty-five (63%) patients were male. Distribution of FAB types was M1, 10 (11%); M2, 23 (26%); M3, three (3%); M4, 27 (31%); M5, nine (10%); M6, six (7%); M7, four (5%); six cases (7%) were unclassified. Median WBC count at diagnosis was 18 × 10⁹/L (<1 to 723 × 10⁹/L). Median interval from diagnosis to transplant was 006-4971/92/8004-0012$3.00/0


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4 months (2 to 22 months). Information regarding the exact number of induction courses received was available for 55 patients: 22 received 2 courses, 18 received 3 courses, 15 received 4 or more courses. Median WBC count pretransplant was $3 \times 10^9/L$ ($<1$ to $208 \times 10^9/L$); median circulating blasts were 2% (0% to 97%). Median blasts in the bone marrow were 25% (0% to 97%). Twenty-six patients (30%) were in partial remission pretransplant. Median performance score was 80% (20% to 100%); 60 (68%) had performance scores less than 90%. Clinically important infection was present at transplant in 22 patients (25%).

**Transplant Regimens**

Transplant regimens were similar for patients with ALL and AML. All donors were HLA-identical siblings. Median donor age was 28 years (1 to 60 years). Sixty-seven donor-recipient pairs (53%) were sex-matched.

Pretransplant conditioning included total body radiation in 105 patients (83%). Most were also administered drugs such as cyclophosphamide, cytarabine, and/or etoposide; two patients received total body radiation only. Twenty-one patients (17%) received busulfan and cyclophosphamide rather than radiation; 20 of these had AML and one had ALL.

Prophylaxis of graft-versus-host disease (GVHD) was cyclosporine with (N = 14) or without (N = 56) methotrexate in 70 subjects (56%), methotrexate without cyclosporine in 38 (30%), T-cell depletion in 15 (12%), and other approaches in 3 (2%).

**Statistics**

Median follow-up was 41 months (4 to 94 months). Actuarial probabilities of relapse, transplant-related mortality (TRM; death in continuous complete remission) and leukemia-free survival (LFS; survival in continuous complete remission) were calculated using life-table methods. Univariate associations between patient-, disease-, and treatment-related factors and relapse, TRM, and LFS were tested using the Lee-Desu statistic. The following variables were examined for their effect on outcome: disease, FAB classification, immune phenotype (for ALL), WBCs at diagnosis, number of cycles of induction chemotherapy, WBCs pretransplant, percent blasts in blood and bone marrow at time of transplant, age, sex, presence of clinically important infection pretransplant, performance score, and interval between diagnosis and transplant. Because of the limited numbers of patients available for study, multivariate analyses were not performed.

**RESULTS**

**ALL**

The actuarial probability of LFS at 3 years was 23% (95% confidence interval, 12% to 40%) (Fig 1A). LFS was higher in patients less than 30 years old than in older patients (37% [18% to 61%] v 9% [2% to 34%]; P < .02). Patients without clinically significant infection at transplant had higher 2-year LFS (28% [14% to 47%] v 0%; P < .03). Other potential prognostic variables (listed above) were not significantly associated with LFS.

The 3-year probability of persistent or recurrent leukemia was 59% (38% to 77%) (Fig 1B). There was no significant association between relapse and other potential prognostic variables.

The 3-year probability of TRM was 44% (25% to 64%). TRM was significantly higher in patients older than 30 years than in younger patients (80% [43% to 96%] v 13% [4% to 37%]; P < .004) and in persons with performance scores less than 90% (57% [34% to 77%] v 26% [7% to 64%]; P < .02). No other potentially prognostic variables significantly affected TRM.

**AML**

The 3-year probability of LFS was 21% (14% to 31%) (Fig 1A). It was higher in patients with less than 25% blasts in the bone marrow pretransplant than in persons with higher blast counts (32% [18% to 47%] v 12% [1% to 13%], P < .008). LFS was higher in patients transplanted after two to three courses of induction therapy than in those receiving four or more courses (24% [10% to 38%] v 13% [1% to 33%], P < .04). It was slightly higher in persons with performance scores ≥90% (P < .03). Other potential prognostic variables (listed above) did not significantly influence LFS.

The 3-year actuarial probability of persistent or recurrent...
higher risk of relapse in patients with versus those without circulating blasts (73% [57% to 89%] v 48% [26% to 70%], P < .05) and in those with greater than 25% blasts in the bone marrow compared to those with ≤25% blasts (78% [60% to 100%] v 46% [26% to 66%], P < .005). Relapse was also more common in men than women (77% [60% to 88%] v 43% [24% to 64%]; P < .03). There was no significant impact of other potential prognostic variables studied.

Three-year TRM was 44% (32% to 57%). TRM was lower in patients transplanted after two to three courses of induction chemotherapy than in those receiving four or more courses (34% [17% to 51%] v 53% [27% to 79%], P < .02). No other variables examined were associated with TRM.

**Causes of Death**

Ninety-four patients died between 1 week and 37 months (median 4 months) posttransplant. Most (53%) deaths were from persistent or recurrent leukemia. Other causes of death were interstitial pneumonia (11%), GVHD (6%), interstitial pneumonia and GVHD (13%), infection (9%), and other causes (8%).

**DISCUSSION**

There is no effective therapy for patients with acute leukemia failing to achieve initial remission after intensive chemotherapy. Most die of resistant leukemia, usually within 6 months. In contrast, the 3-year probability of LFS was 21% (15% to 29%) in 126 transplant recipients with comparable disease.

Superiority of transplants over chemotherapy is related to improved antileukemia efficacy. One hundred thirteen of 115 evaluable (surviving ≥ 21 days with engraftment) transplant recipients in this study achieved remission. The 3-year actuarial relapse rate was 62% (51% to 72%) and was similar in ALL and AML. No potential prognostic factors at diagnosis, like FAB type or WBCs, correlated with relapse. This is not surprising because all patients failed prior intensive chemotherapy. Such persons are typically considered to have high-risk leukemia regardless of prognostic factors at presentation. Another consideration is that different risk factors for relapse may operate in transplants because the major antileukemia effect of allogeneic transplant is immune-mediated rather than a direct result of high-dose therapy. Interestingly, relapse in these 126 patients receiving an average of only three courses of chemotherapy was similar to relapse in over 700 patients with advanced acute leukemia reported to the IBMTR who received extensive prior therapy. These data suggest that leukemia resistance may be intrinsic, rather than the consequence of prior treatment. The higher relapse rate in AML patients with greater than 25% blasts in the marrow after two or more cycles of induction may simply reflect identification of a subgroup with greater resistance to treatment.

We have reported transplant outcomes at 3 years; however, 29 patients are alive without leukemia 4 months to more than 7 years posttransplant (median 3.4 years). Only three relapses occurred among 27 patients at risk more than 2 years after transplant, and no relapse occurred among 19 patients at risk more than 3 years. Consequently, it seems that many patients reported here as 3-year survivors may achieve long-term LFS or even cure.

Improved results of transplants in patients failing to achieve remission with intensive chemotherapy require effective methods of decreasing relapse and TRM. The former may be achievable by better antileukemia pretransplant conditioning and by a better balance between GVHD and immune-mediated antileukemia effects. Reduced TRM is also approachable by improved pretransplant conditioning regimens as well as better GVHD and interstitial pneumonia prophylaxis and careful patient selection. Patients with ALL who are over 30 years old may not be good candidates for this salvage procedure because their probability of LFS at 3 years was less than 10%. Because transplants were more effective in persons with higher performance scores and in those receiving fewer than four cycles of induction chemotherapy, earlier identification of patients unlikely to achieve remission with chemotherapy would be helpful as well as early identification of histocompatible donors.

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Additional patient-, treatment-, and transplant-related data are available from the authors.

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Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy