Bone Marrow Transplantation for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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Philadelphia chromosome (Ph1)-positive acute lymphoblastic leukemia (ALL) has a poor prognosis when treated with conventional chemotherapy. We analyzed the outcome of 67 HLA-identical sibling bone marrow transplants (BMTs) for Ph1-positive ALL reported to the International Bone Marrow Transplant Registry (IBMTR). Twenty-one of 67 (31%) transplant recipients survived in continuous complete remission more than 2 years after transplant. Two-year actuarial probabilities (95% confidence interval) of leukemia-free survival were 38% (23% to 55%) for 33 patients transplanted in first remission, 41% (23% to 61%) for 22 patients transplanted after relapse, and 25% (9% to 53%) for 12 patients failing to achieve remission with conventional chemotherapy. These data indicate that transplants are effective treatment for Ph1-positive ALL.

APPROXIMATELY 5% of children and 20% of adults with acute lymphoblastic leukemia (ALL) have the Philadelphia (Ph1) chromosome resulting from the translocation of the ninth and 22nd chromosomes and fusion of the ABL proto-oncogene with the breakpoint cluster region (BCR) of the 22nd chromosome. The translocation either involves the first exon (minor BCR region) or the second or third exon (major BCR region) of the BCR gene. Minor BCR-ABL fusion occurs exclusively in de novo ALL; major BCR-ABL fusion occurs in both chronic myeloid leukemia and de novo ALL.1-5 There are no consistent clinical or hematological differences between de novo ALL associated with either of these variants.

Ph1-positive ALL has a poor prognosis in children and adults. Although approximately 70% of patients achieve remission with chemotherapy, almost all relapse.6-10 Because of these poor results, bone marrow transplants (BMTs) in first remission have been considered in Ph1-positive ALL.11-13 One report suggests that some patients with Ph1-positive ALL are cured by this approach.13 However, this series included only 10 patients. We analyzed the outcome of 67 patients with Ph1-positive ALL reported to the International Bone Marrow Transplant Registry (IBMTR). The outcome of BMT in first remission was compared with results of transplants in patients with ALL with normal karyotypes after matching for other prognostic characteristics. Results compared favorably with transplants for ALL with no chromosome abnormalities, and suggest that BMT may cure some cases of Ph1-positive ALL.

MATERIALS AND METHODS

Between 1978 and 1990, the IBMTR received 2,039 reports of HLA-identical sibling BMTs for ALL. Results of cytogenetic studies at disease presentation were available for 772 (38%) cases. The Ph1 chromosome was identified in 67 (9%) cases, other chromosome abnormalities in 195 (25%), and normal karyotypes in 510 (66%). Disease characteristics for the 67 cases of Ph1-positive ALL are shown in Table 1. Median age was 28 years (range, 5 to 49); 13 (19%) were less than 16 years old. Thirty-eight (58%) were male. Forty (60%) patients had Karnofsky performance scores less than 90% at the time of transplant. Pretransplant conditioning was with total body radiation and cyclophosphamide in 19 (28%) cases, total body radiation, cyclophosphamide, and other drugs in 20 (30%), total body radiation and drugs other than cyclophosphamide in 19 (28%), and busulfan and cyclophosphamide in nine (13%). Thirteen (19%) patients received methotrexate posttransplant to prevent graft-versus-host disease (GVHD), 29 (43%) cyclosporine, and 13 (19%) combined methotrexate and cyclosporine. Eleven (16%) patients received T-cell–depleted bone marrow with or without additional posttransplant immunosuppression to prevent GVHD, and one patient received no GVHD prophylaxis. Four patients were transplanted between 1978 and 1982, the remainder between 1983 and 1990, with a median follow-up of 36 months (range, 4 to 85 months).

Graft failure was analyzed in patients surviving 21 days or longer in first remission, 41% (23% to 61%) for 22 patients transplanted after relapse, and 25% (9% to 53%) for 12 patients failing to achieve remission with conventional chemotherapy. These data indicate that transplants are effective treatment for Ph1-positive ALL.

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remission and relapse were compared using the Lee-Desu statistic.19 Remission was defined as the absence of relapse, treatment-related mortality, and leukemia-free survival (survival in continuous complete remission) were calculated by life-table methods.19 Remission was defined as the absence of disease at medullary and extramedullary sites. Relapse included medullary and extramedullary leukemia recurrences. Probabilities of relapse, treatment-related mortality, and leukemia-free survival between groups were compared using the Lee-Desu statistic.20

Outcome for 33 patients transplanted in first remission was compared with a control group of 33 patients selected from a cohort of 106 patients with ALL with normal karyotypes transplanted in first remission from HLA-identical sibling donors. Controls were matched for age at diagnosis (using cohorts of 2 to 12, 13 to 22, 23 to 32, and > 32 years); leukocyte count at diagnosis (< 30, 31 to 90, 91 to 150, and > 150 × 10⁹/L); and interval from diagnosis to transplant (< 5 or > 5 months). Differences in other patient, disease, and treatment characteristics between Ph⁺-positive and Ph⁺-negative cohorts were tested using chi-square analysis. There were no significant differences between the cohorts in immune phenotype, central nervous system (CNS) leukemia pretransplant, time to first remission, infection pretransplant, patient or donor sex, conditioning regimen, GVHD prophylaxis, or year of transplant.

RESULTS

Transplant outcome. Transplant outcome for the 67 cases of Ph⁺-positive ALL is summarized in Table 2. Among 63 evaluable patients, the incidence of graft failure was 3%. Grade II to IV acute GVHD developed in 20 of 61 (33%) and chronic GVHD in 15 of 49 (31%) patients at risk. Nineteen (28%) patients developed interstitial pneumonia. For 33 patients transplanted in first remission, actuarial probabilities (95% confidence intervals) of relapse (Fig 1A), treatment-related mortality, and leukemia-free survival (Fig 1B) were 34% (17% to 56%), 42% (26% to 60%), and 38% (23% to 55%), respectively. Corresponding actuarial probabilities for 22 patients transplanted after first relapse were 32% (14% to 57%), 40% (22% to 62%), and 41% (23% to 61%), respectively. For 12 patients transplanted after failing to achieve first remission, actuarial probabilities were 57% (25% to 84%), 42% (20% to 68%), and 25% (9% to 53%), respectively.

Twelve of 16 relapses occurred in the bone marrow. The site of relapse was not reported in the remaining patients. Most relapses occurred within 10 months of transplant and no patient relapsed after 16 months. Of 67 patients, 21 survive in continuous complete remission more than 2 years after transplant.

Comparison with Ph⁻-negative ALL. Ph⁺-positive patients tended to have earlier relapses (34% [17% to 56%] v 23% [11% to 42%] at 2 years, Fig 2A) and lower probabilities of leukemia-free survival (38% [23% to 55%] v 66% [49% to 80%] at 2 years, Fig 2B) than the Ph⁻-negative matched controls. They also tended to have more interstitial pneumonia and less acute GVHD. None of these differences were statistically significant. The distribution of causes of death was similar for the two groups.

DISCUSSION

The prolonged leukemia-free survival with no relapses beyond 16 months in this cohort of 67 patients with early to advanced Ph⁺-positive ALL suggests that transplants cure some patients. Interestingly, outcome was similar for patients transplanted in first remission and after relapse. Even among patients who failed to achieve first remission with chemotherapy, a small but significant proportion of Ph⁺-positive ALL patients are alive and disease-free 2 years after transplantation. These findings should encourage the use of BMTs for Ph⁺-positive ALL irrespective of the response to induction chemotherapy. The high transplant-
related mortality for patients in first remission at time of transplant may reflect increased toxicity from use of intensive induction and consolidation chemotherapy in these cases known to have a poor prognosis with conventional chemotherapy.

Because only small numbers of patients were available for study, it was not possible to determine whether the presence of karyotype abnormalities in addition to the Ph1 chromosome or other patient or disease features affected transplant outcome.

No significant difference in outcome was detected between Ph1-positive ALL and ALL patients with normal karyotypes transplanted in first remission. This may reflect the small numbers of patients studied. It was surprising that relapse rates were similar in the two groups (Fig 2A), since Ph1-positive ALL is more resistant to conventional chemotherapy. This may indicate that the mechanism of leukemia cure after transplant is different from conventional chemotherapy either because of more intensive treatment or because of immune-mediated graft-versus-leukemia effects. There were insufficient numbers of patients with Ph1-positive ALL to determine whether GVHD correlated with fewer relapses; this has been demonstrated in larger studies of ALL.21-23

Although data from this relatively small patient group should be interpreted cautiously, they indicate that transplants are effective in this poor-prognosis leukemia.

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