CONCISE REPORT

Marrow Transplantation for Patients With Acute Lymphoblastic Leukemia: A Long-Term Follow-up

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Twenty-two patients with acute lymphoblastic leukemia in second or subsequent remission and 26 with acute lymphoblastic leukemia in relapse were given cyclophosphamide (60 mg/kg on each of 2 days), total body irradiation (920 rad), and marrow transplants from HLA-identical siblings. With a minimum follow-up of more than 5 yr, an actuarial analysis shows a survival and apparent cure of 27% of the patients transplanted in remission and 15% of the patients transplanted in relapse.

MARROW TRANSPLANTATION was initially undertaken for patients with acute leukemia in the end-stages of the disease, after failure of combination chemotherapy.[1] In the first series of such patients reported from Seattle, 12% are living in unmaintained remission 7–11 yr after transplantation and appear to be cured.[2,3] Since patients with acute lymphoblastic leukemia (ALL) who relapse on combination chemotherapy are not cured even though additional remissions can be achieved, we undertook marrow transplantation during the second or subsequent remission. In this journal, we reported the first series of 22 such patients along with a concurrent series of 26 patients with ALL transplanted in relapse.[4] This article presents a long-term follow-up of those patients.

MATERIALS AND METHODS

The patients were consecutively entered on study between April 1976 and December 1977, and the present analysis was carried out in May 1983. The selection of the patients, the patient characteristics, and the marrow transplant procedure were described in detail in the previous article.[4]

RESULTS

Figure 1 shows a Kaplan-Meier analysis of the probability of disease-free survival for the two groups of patients ($p = 0.02$). Six of the 22 patients transplanted in remission became long-term disease-free survivors, although one patient (Unique Patient Number [UPN] 644), indicated by the open circle, was censored at the time of death in an automobile accident. Four of the 26 patients transplanted in relapse are long-term disease-free survivors. Seven of the living patients have Karnofsky performance scores of 100%. One (UPN 582) has a score of 80% due to a monoarthritis of the left ankle. One (UPN 694) has a score of 75% due to chronic obstructive pulmonary disease. Figure 2 shows a Kaplan-Meier analysis of the probability of being in remission for the two groups of patients ($p = 0.11$).

Table 1 lists the characteristics of the 10 patients with long-term unmaintained remission. Nine suffered their first relapses while on chemotherapy. One (UPN 678) was being treated on a Children's Cancer Study Group protocol and was randomized to stop therapy after 1 yr. She relapsed off therapy.

DISCUSSION

Since some patients in end-stage relapse of ALL could apparently be cured with high-dose chemoradiotherapy and marrow transplantation, we undertook marrow grafts for patients in second or subsequent remission since patients in remission would be in good clinical condition with a minimum body burden of leukemic cells, perhaps not yet refractory to therapeutic agents. The present study shows an improved survival for patients transplanted in remission as compared to those transplanted in relapse. The difference in survival is mainly due to a reduced incidence of deaths from nonleukemic causes for the patients transplanted in remission. Unfortunately, the probability of relapse in both groups is quite high, suggesting that patients with ALL in remission may still have a rather large, but not detectable, body burden of leukemic cells. Previous therapy followed by relapse may also indicate that the leukemic cells may have acquired resistance to therapy. We[5] and others[6] are currently undertaking marrow grafts for poor-risk patients with ALL in first remission, but it is too early to evaluate the results. Since recurrence of leukemia is the major

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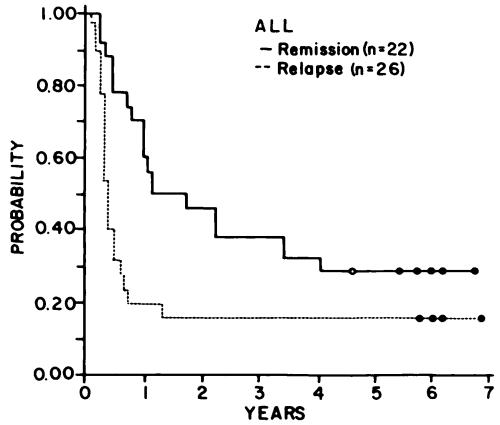

Fig. 1. Probability of disease-free survival. The dots indicate patients surviving, and the open circle indicates a patient who died in an automobile accident while in remission.

problem for patients with ALL transplanted in remission, marrow transplant teams are exploring new regimens directed at this problem.[3,7-9] It will be necessary to follow these current studies for at least 2 yr, since many patients are still at risk for leukemic relapse.

It is difficult to compare the results of the present study with results of chemotherapy, because there are no reports of groups of patients with ALL who have relapsed at least once and who were then treated with chemotherapy and followed for more than 5 yr. It is generally agreed that relapse during therapy dashes hopes for long-term disease control.[10,11] Recent reports indicate no change in this poor prospect. Chessels and Cornbleet reported 34 patients with ALL who relapsed and were treated with prednisone, vincristine, L-asparaginase, and daunorubicin.[12] Although the complete remission rate was 96%, the median duration of remission was only 13 wk. In a recent report, the Children's Cancer Study Group described 30 patients with ALL who achieved second remissions and were then treated with a regimen of vincristine, methotrexate, and L-asparaginase.[13] The predicted median duration of remission was 57 wk, with 10 patients (33%) in continuous hematologic remission at 1 yr and 3 (10%) at 2 yr. They concluded that "a modified Capizzi regimen is the most effective regimen reported to date for maintaining second and subsequent remission in childhood ALL."

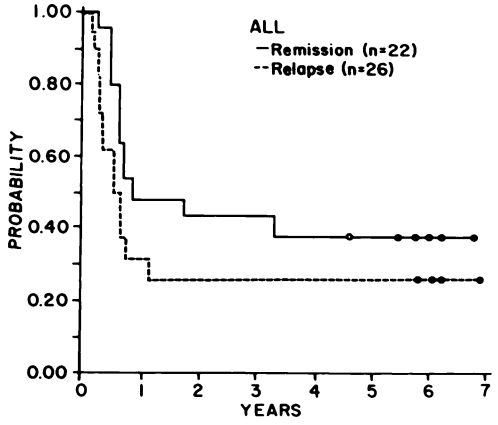

Fig. 2. Probability of being in remission.

Table 1. Characteristics of the Patients in Remission

Patient Status at Transplant	Unique Patient Number	Age at Transplant (yr)	Number of Marrow Remissions Before Transplant	Duration of First Remission (mo)
Remission	592	4	2*	28
	644	8	3	26
	653	5	2	25
	678	8	4*	4
	721	9	2†	20
	752	13	3	28
Relapse	582	18	2	24
	664	7	2	6
	679	25	1	8
	694	20	1	7

*History of central nervous system disease.

†Active central nervous system disease at time of transplant.

Patients who relapse after therapy is stopped may have a long second remission with chemotherapy.[10] Rivera described 13 such patients of whom 2 were long-term survivors and in remission 39 and 51 mo after therapy was stopped for the second time.[14] In the subsequent series of 17 children who relapsed off therapy, all subsequently relapsed after a second remission, but two had remission durations of more than 48 mo and more than 78 mo.[14] In the next 23 patients, the median second remission duration was 14 mo, with 9 remaining in remission after 19–50 mo.[14] Not all reports agree with a good prognosis for these patients. For example, Sallan and Hitchcock-Bryan described 15 patients with ALL who relapsed off therapy after first remissions of 32–61 mo.[15] After intensive treatment with combination chemotherapy, they observed a median duration of disease-free survival of only 11 mo, with the longest remission being 43 mo.

In a prospective study, patients with ALL in second or subsequent remission were given marrow transplants if a matched sibling was available or were treated with combination chemotherapy in the absence of suitable donors.[16] Now, with a follow-up of 3–6 yr, all 21 patients treated with chemotherapy have relapsed, and only 1 is alive, while 8 of 24 marrow transplant recipients continue in unmaintained remission. The results of this prospective study, the long-term follow-up of the patients presented in this report, and the cure of some patients transplanted in end-stage relapse show clearly that marrow transplantation offers the best chance of long-term remission and cure after a patient with ALL has had a relapse in the marrow.

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