Allogeneic Marrow Transplantation for Acute Nonlymphoblastic Leukemia After First Relapse

By Frederick R. Appelbaum, R. A. Clift, C. Dean Buckner, Patricia Stewart, Rainer Storb, Keith M. Sullivan, and E. Donnall Thomas

Sixty-two patients with acute nonlymphoblastic leukemia in first relapse or second remission were treated with allogeneic marrow transplantation from HLA-matched siblings. In 17 patients (group 1), no attempt at reinduction of remission was made prior to transplantation. In 20 patients (group 2), attempts at inducing a second remission prior to transplantation were unsuccessful; and in 25 patients (group 3), a second remission was achieved. Five of 17 patients (29%) in group 1, 2 of 20 (10%) in group 2, and 5 of 25 (20%) in group 3 are surviving disease-free 2–6 yr after grafting. Early mortality from nonleukemic causes was equal in the 3 groups, but the risk of recurrent leukemia after transplantation was less in patients transplanted without attempts at reinduction (group 1). Among patients transplanted in relapse, those in early relapse (<30% blast cells in the marrow) appeared to do better than patients in florid relapse. The results obtained in group 1 are as good as or better than those achieved in patients transplanted in second or subsequent remission. Thus, for patients with acute nonlymphoblastic leukemia not transplanted in first remission, the optimal time for transplantation would appear to be as soon as possible after the first relapse.

THE SUCCESS of marrow transplantation in the treatment of acute nonlymphoblastic leukemia (ANL) depends in large part on the clinical status of the patient at the time of transplantation. When transplantation is performed during first complete remission, over 50% of patients under the age of 50 yr can be cured.[1-3] The antileukemic regimen is very effective in this setting, and the morbidity and mortality are almost entirely consequences of the toxicity of the therapy. Such therapy is much less effective in eradicating leukemia when patients receive transplants during the later stages of ANL. Thus, only 10%–15% of patients become long-term disease-free survivors when they receive transplants after all conventional measures have failed.[4,5]

It is important to define the results of marrow transplantation for patients with ANL in clinical situations other than during first remission or in drug-resistant relapse. The purpose of this article is to provide such a definition in order to help determine the optimal time to perform transplantation in patients who have undergone an initial relapse. Specifically, we were interested in ascertaining whether or not attempts at second remission induction in patients with HLA-matched siblings were beneficial.

MATERIALS AND METHODS

Between January 1975 and May 1980, 62 patients with ANL in first relapse or second remission received allogeneic marrow transplants from HLA-matched siblings. All patients had previously achieved complete remissions. In 17 patients (group 1), no attempt was made to induce a second remission prior to transplant. In 20 patients (group 2), transplantation was performed after failure to induce a second complete remission with chemotherapy. Twenty-five patients (group 3) were transplanted in second remission. The decision to attempt reinduction or to proceed directly to transplantation was often made by the referring physician in consultation with a member of the Fred Hutchinson Cancer Research Center staff and depended, in part, on the availability of a transplant bed. Many of these patients have been included in previous reports but not evaluated in detail in regards to second remission induction attempts.[4,6-8] Patient characteristics are shown in Table 1.

The technique of marrow transplantation has been described.[9] The preparative regimen used for transplantation always included cyclophosphamide, 60 mg/kg on each of 2 successive days, followed in 3–5 days by the initiation of total body irradiation (TBI). In 14 cases, cytoreductive chemotherapy in addition to cyclophosphamide was given shortly before TBI. TBI delivered from dual cobalt-60 sources at 5–8 rad/min was administered as 1000 rad in a single exposure in 40 cases and as 1200 rad in 200-rad daily fractions over 6 days in 22 cases. Marrow was infused on the last day of TBI (day 0). All patients received post-transplant methotrexate in order to prevent or diminish graft-versus-host disease as described.[10]

Patients were also entered on other protocols involving prophylactic granulocyte transfusions, laminar air flow isolation, and prophylactic antithymocyte globulin. All protocols were reviewed and approved by the Human Subjects Review Committees of the University of Washington and/or the Fred Hutchinson Cancer Research Center.

Data were analyzed as of May 20, 1982.

RESULTS

Seventeen patients with ANL in first relapse were transplanted before any attempt at reinduction (group

From the Fred Hutchinson Cancer Research Center and the University of Washington School of Medicine, Seattle, WA.

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Address reprint requests to Frederick R. Appelbaum, M.D., Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.

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Table 1. Patient Characteristics

Unique Patient Number	Age	Months From First Remission to Relapse	Bone Marrow Status at Transplantation*	Chemotherapy With Cyclophosphamide†	Total Body Irradiation	Post-transplant Survival (Days)	Outcome‡
Group 1							
554	4	3	M3	Ara-C	1,000	19	Aspiration, death
1188	27	4	M2	—	1,200	26	Idiopathic interstitial pneumonia, death
535	14	12	M3	BCNU	1,000	36	GVHD, hepatic failure, death
1193	21	5	M2	—	1,200	40	Idiopathic interstitial pneumonia, death
504	42	12	M3	BCNU	1,000	46	GVHD, infection, death
761	5	18	M2	DMM	1,000	63	CMV interstitial penumonia, death
701	35	7	M3	—	1,000	71	Aspergillus, death
588	19	31	M3	—	1,000	116	Idiopathic interstitial pneumonia, death
578	39	14	M3	—	1,000	151	Idiopathic interstitial pneumonia, death
532	28	12	M3	BCNU	1,000	183	Relapse day 116, death
812	25	7	M3	—	1,200	714	Relapse day 619, death
377	30	12	M3	DNR + ARA-C	1,000	806	GVHD, pulmonary failure, death
1095	21	20	M3	—	1,000	905+	Alive, Karnofsky score 95%
995	17	3	M1§	—	1,200	1,110+	Alive, Karnofsky score 100%
962	10	10	M3	—	1,200	1,171+	Alive, Karnofsky score 90%
930	18	2	M2	—	1,200	1,242+	Alive, Karnofsky score 100%
883	18	11	M2	—	1,200	1,351+	Alive, Karnofsky score 80%
Group 2							
502	22	7	M3	BCNU	1,000	9	Cardiovascular collapse, death
712	50	10	M3	DMM	1,000	14	Pseudomonas septicemia, death
924	27	14	M3	—	1,200	17	Klebsiella septicemia, death
1033	19	9	M3	—	1,200	18	Veno-occlusive disease, death
584	25	10	M3	—	1,000	44	Idiopathic interstitial pneumonia, death
516	23	9	M3	BCNU	1,000	44	CMV interstitial pneumonia, death
551	15	2	M3	Procarbazine	1,000	46	CMV interstitial pneumonia, death
393	11	4	M3	BCNU	1,000	66	Idiopathic interstitial pneumonia, death
396	31	25	M3	—	1,000	68	CMV interstitial pneumonia, death
655	38	6	M3	—	1,000	75	Relapse day 40, death
545	19	13	M2	Ara-C	1,000	89	Cardiomyopathy, death
1294	33	7	M2	—	1,200	117	Idiopathic interstitial pneumonia, death
785	18	7	M3	DMM	1,000	164	Relapse day 138, death
988	25	3	M3	—	1,200	173	Relapse day 169, death
791	15	4	M3	—	1,200	181	Relapse day 59, death
885	11	11	M2	—	1,200	200	Relapse day 72, death
631	19	18	M3	—	1,000	234	Relapse day 220, death
386	10	14	M3	—	1,000	423	Relapse day 366, death
735	28	11	M2	DMM	1,000	1,675+	Alive, Karnofsky score 75%
536	25	13	M2	BCNU	1,000	2,422+	Alive, Karnofsky score 100%
Group 3							
965	11	9	M1	—	1,200	17	Idiopathic interstitial pneumonia, death
832	17	4	M1	—	1,000	37	Idiopathic intersititial pneumonia, death
745	22	13	M1	—	1,000	39	Idiopathic interstitial pneumonia, death
970	17	15	M1	—	1,200	47	Idiopathic interstitial pneumonia, death
743	15	3	M1	—	1,000	59	Relapse day 51, death
1352	29	9	M1	—	1,200	67	GVHD, hepatic and renal failure, death
901	23	8	M1	—	1,200	72	Veno-occlusive disease, GVHD, death
926	21	7	M1	—	1,200	86	Disseminated candida, death
941	19	9	M1	—	1,200	86	GVHD, infection, death
840	24	8	M1	—	1,000	92	GVHD, infection, death
1320	30	11	M1	—	1,000	93	CMV pneumonia, death
1285	28	17	M1	—	1,200	123	GVHD, infection, death
977	27	4	M1	—	1,000	137	Relapse day 102, death
980	16	14	M1	—	1,200	206	Relapse day 190, death
951	22	9	M1	—	1,000	276	Encephalopathy
1023	24	6	M1	—	1,000	301	Myelopathy
1348	20	11	M1	—	1,000	317	Cardiomyopathy
1302	24	8	M1	—	1,000	501+	Relapse day 387
763	2	7	M1	—	1,000	824	Relapse day 131, death
1098	17	24	M1	—	1,000	858+	Alive, Karnofsky 60%, chronic GVHD
905	23	2	M1	—	1,200	957	Relapse day 746, death
978	16	4	M1	—	1,200	1,101+	Alive, Karnofsky 90%
789	30	7	M1	—	1,000	1,417+	Alive, Karnofsky 70%, chronic GVHD
674	27	3	M1	—	1,000	1,836+	Alive, Karnofsky 100%
566	3	4	M1	—	1,000	2,223+	Alive, Karnofsky 100%

*M1, remission marrow. M2, <30% blasts. M3, ≥30% blasts.

†Abbreviations: Ara-C, cytosine arabinoside. DNR, daunomycin. DMM, dimethyl myleran. BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea.

‡Abbreviations: GVHD, graft-versus-host disease. CMV, cytomegalovirus.

§Patient had extramedullary relapse.

1). There are 5 long-term survivors (29%) at 905, 1110, 1171, 1242, and 1351 days, and their current status is included in Table 1. The other 12 patients died between days 19 and 806. Of these, 5 died with interstitial pneumonitis, 3 with graft-versus-host disease, 2 with infectious complications, and 2 with recurrent leukemia.

Two of 20 patients with refractory leukemia (group 2) are long-term survivors at 1675 and 2422 days after transplantation. Eleven patients died of nonleukemic causes during the first 120 days after transplant, including interstitial pneumonitis in 6 cases, septicemia in 3 cases, and veno-occlusive disease and cardiomyopathy in 1 case each. Seven patients developed recurrent leukemia 40–366 days from transplant, and all subsequently died of leukemia-related problems.

Among the 25 patients transplanted in second remission, 5 remain disease-free at 858, 1101, 1417, 1836, and 2223 days from transplantation. A sixth patient is alive at day 501 but relapsed at day 387. Five other patients relapsed between days 51 and 746 and died of leukemia-related causes. Fourteen patients died between days 17 and 317 of causes unrelated to leukemia. Five patients died with severe graft-versus-host disease associated with infections or hepatic complications, and 5 patients died of interstitial pneumonitis. One patient died with a disseminated candida infection, 1 patient died with an encephalopathy at day 276, 1 patient died of a myelopathy of unknown etiology at day 301, and 1 patient died of cardiomyopathy at day 317.

Figure 1 shows the post-transplantation survival curves for the three groups plotted according to the method of Kaplan and Meier.[11] Although survival appears best among patients not subjected to reinduction chemotherapy (29% versus 22% in patients transplanted in second remission and 10% in patients with refractory leukemia), the differences in overall survival between the groups are not statistically significant ($p = 0.14$).

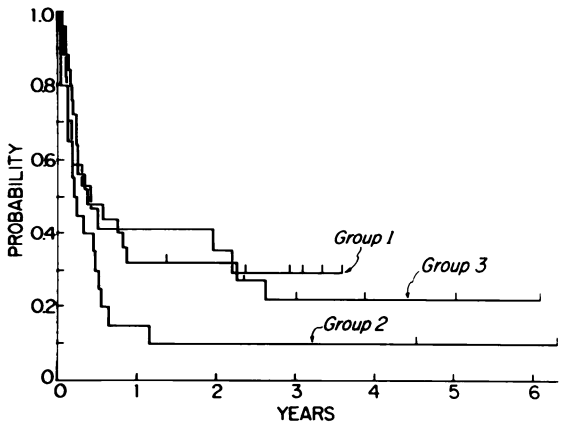

Fig. 1. Kaplan-Meier product limit estimates of the probability of survival of patients transplanted without reinduction (group 1), having failed reinduction (group 2), and in second remission (group 3).

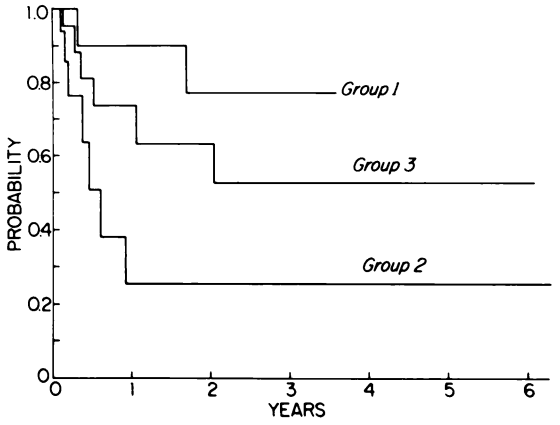

Fig. 2. Kaplan-Meier product limit estimates of the probability of being in remission (patients dying of nonleukemic causes having been censored from the groups) for patients transplanted without reinduction (group 1), having failed reinduction (group 2), and in second remission (group 3).

The incidence of nonleukemic deaths among the three groups was not significantly different, with approximately equal proportions of patients dying of interstitial pneumonitis, graft-versus-host disease, and infectious complications in each of the three groups. However, there was a major difference in the frequency of relapse among the three groups. Based on methodology compensating for competing causes of death, the probability of relapse was 23% in group 1, 74% in group 2, and 47% in group 3; these differences are statistically significant ($p = 0.035$) (see Fig. 2).[12]

Although most patients in group 1 were in florid relapse at the time of transplantation, six patients did have either M1 or M2 marrows (<30% blasts), and three of these are long-term survivors.

DISCUSSION

This article concerns all patients transplanted from HLA-matched siblings for ANL in first relapse or second remission between January 1975 and May 1980 in Seattle. As in any retrospective analysis of nonrandomized data, the results should be viewed with caution. Although the groups are very similar in diagnosis, age, months from first remission to relapse, and clinical status at the time of transplantation, there may be differences among the groups not readily apparent to us that may have influenced the outcome.

We have previously shown that 12% of patients with leukemia who have failed remission induction or therapy after relapse can be cured by a regimen of cyclophosphamide, TBI, and allogeneic marrow trans-

plantation.[13] This finding was established in patients transplanted before 1976 at a time when chemotherapy regimens were less effective than today. The more recent results, reported here in chemotherapy-resistant first relapse, are similar to the previous experience. Clearly, a small but significant proportion of patients with drug-resistant leukemia can be cured with marrow transplantation. Therefore, for ANL patients younger than 50 yr with suitable marrow donors, the problem is not whether to perform marrow transplantation but the timing of this intervention.

In the present study, 29% of patients transplanted after first relapse before any attempts at inducing a second remission with chemotherapy are alive and free of disease from 2 to 6 yr after transplantation. Among patients transplanted in Seattle, this result is as good as or better than those achieved in patients transplanted after attempts at inducing a second remission regardless of the outcome of that attempt. Although these findings do not *prove* that the optimal time for transplantation for patients not transplanted in first remission is as soon as possible after relapse, there are good reasons to postulate this. First, few, if any, patients with ANL who relapse after achieving a complete remission can be cured with chemotherapy. Second, some patients with HLA-matched sibling donors will die or become too ill to transplant as a consequence of remission-induction attempts. Third, there appears to be no advantage to transplanting patients in second remission over transplantation in first relapse. Fourth, there may be an advantage to transplanting patients in early relapse as opposed to transplanting patients with florid disease in that 3 of 6 patients with M1 or M2 marrows are long-term survivors compared to 2 of 11 with M3 marrows within group 1.

It is of additional interest that the probability of relapse after transplantation was significantly greater in groups 2 and 3 than in group 1. This implies that exposure to further chemotherapy after initial relapse enhances resistance to the preparative regimen whether or not the chemotherapy is successful in reducing the leukemic burden prior to transplantation.

A question that is not answered by this study is when is the optimal time to transplant patients with newly diagnosed ANL. We and others have demonstrated that transplantation for patients less than age 50 with ANL in first remission results in a greater proportion of long-term disease-free survivors than does conventional chemotherapy.[3,14] In most studies, approximately 50%–60% of patients with ANL transplanted in first remission will become long-term survivors compared to approximately 20% of patients treated with conventional chemotherapy.[3,14,15] If 20% of patients treated with conventional therapy are long-term survivors and if 30% of those who relapse can be salvaged by transplantation in first relapse, then the composite cure of these two groups might approach that achieved by transplantation in first remission. Transplant results are age-dependent, with patients under age 20 having a 70% survival and those over 30 having a 35% survival.[16] Thus, there may be subpopulations of patients for whom transplantation in first relapse rather than in first remission is particularly appropriate, such as those over age 30.

There are, however, problems associated with the concept of marrow transplantation in first relapse. First, some patients with ANL in relapse have a very rapidly progressive disease and thus would require careful follow-up in order to assure that the disease is diagnosed early. Second, even with early diagnosis, marrow transplantation might not be able to be carried out rapidly unless a donor had been previously identified and finances arranged. Third, a transplant bed might not be available unless the referring physician and the transplant center had an arrangement to insure rapid transfer of the patient. Thus, some patients with ANL in first relapse will continue to require chemotherapy prior to transplantation in an attempt to keep them in reasonable clinical condition while a transplant is being arranged. However, based on this retrospective analysis, except for solving certain logistical problems, we could identify no advantage to transplanting patients with ANL in second remission over transplantation in first relapse.

REFERENCES

1. Thomas ED, Buckner CD, Clift RA, Fefer A, Johnson FL, Neiman PE, Sale GE, Sanders JE, Singer JW, Shulman H, Storb R, Weiden PL: Marrow transplantation for acute nonlymphoblastic leukemia in first remission. N Engl J Med 301:597–599, 1979

2. Blume KG, Beutler E, Bross KJ, Chillar RK, Ellington OB, Fahey JL, Farbstein MJ, Forman SJ, Schmidt GM, Scott EP, Spruce WE, Turner MA, Wolf JL: Bone-marrow ablation and allogeneic marrow transplantation in acute leukemia. N Engl J Med 302:1041–1046, 1980

3. Powles RL, Clink HM, Bandini G, Watson JG, Spence D, Jameson B, Kay HEM, Morgenstern G, Hedley D, Lumley H, Lawson D, Barrett A, Lawler S, McElwain TJ: The place of bone-marrow transplantation in acute myelogenous leukaemia. Lancet 1:1047–1050, 1980

4. Thomas ED, Buckner CD, Banaji M, Clift RA, Fefer A, Flournoy N, Goodell BW, Hickman RO, Lerner KG, Neiman PE, Sale GE, Sanders JE, Singer J, Stevens M, Storb R, Weiden PL: One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood 49:511–533, 1977

5. Gale RP: Clinical trials of bone marrow transplantation in leukemia, in Gale RP, Fox CF (eds): Biology of Bone Marrow Transplantation. New York, Academic, 1980, pp 11–27

6. Buckner CD, Clift RA, Thomas ED, Sanders JE, Hackman R, Stewart PS, Storb R, Sullivan KM: Allogeneic marrow transplantation for patients with acute non-lymphoblastic leukemia in second remission. Leuk Res 6:395–399, 1982

7. Buckner CD, Clift RA, Thomas ED, Sanders JE, Stewart PS, Storb R, Sullivan KM, Hackman R: Allogeneic marrow transplantation for acute non-lymphoblastic leukemia in relapse using fractionated total body irradiation. Leuk Res 6:389–394, 1982

8. Badger C, Buckner CD, Thomas ED, Clift RA, Sanders JE, Stewart PS, Storb R, Sullivan KM, Shulman H, Flournoy N: Allogeneic marrow transplantation for acute leukemia in relapse. Leuk Res 6:383–387, 1982

9. Thomas ED, Storb R: Technique for human marrow grafting. Blood 36:507–515, 1970

10. Thomas ED, Storb R, Clift RA, Fefer A, Johnson FL, Neiman PE, Lerner KG, Glucksberg H, Buckner CD: Bone-marrow transplantation. N Engl J Med 292:832–843, 895–902, 1975

11. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958

12. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE: The analysis of failure times in the presence of competing risks. Biometrics 34:541–554, 1978

13. Thomas ED: Bone marrow transplantation, in Burchenal JH, Oettgen HF (eds): Cancer: Achievements, Challenges, and Prospects for the 1980s, vol 2. New York, Grune & Stratton, 1981, pp 625–638

14. Appelbaum FR, Cheever MA, Fefer A, Greenberg PD, Glucksberg H, Buckner CD, Thomas ED: A prospective study of the roles of bone marrow transplantation and maintenance therapy in adult acute nonlymphocytic leukemia. Nineteenth International Cancer Congress, Seattle, 1982 (abstr)

15. Rai KR, Holland JF, Glidewell OJ, Weinberg V, Brunner K, Obrecht JP, Preisler HD, Nawabi IW, Prager D, Carey RW, Cooper MR, Haurani F, Hutchison JL, Silver RT, Falkson G, Wiernik P, Hoagland HC, Bloomfield CD, James GW, Gottlieb A, Ramanan SV, Blom J, Nissen NI, Bank A, Ellison RR, Kung F, Henry P, McIntyre OR, Kaan SK: Treatment of acute myelocytic leukemia: A study by Cancer and Leukemia Group B. Blood 58:1203–1212, 1981

16. Thomas ED, Clift RA, Buckner CD for the Seattle Marrow Transplant Team: Marrow transplantation for patients with acute nonlymphoblastic leukemia who achieve a first remission. Cancer Treat Rep 66:1463–1466, 1982