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Allogeneic Marrow Transplantation from HLA-Identical Siblings in the Acute Leukemias: Baltimore Experience

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A. Introduction

Allogeneic bone marrow transplantation in the treatment of acute leukemia has shown remarkable therapeutic progress in recent years. Long-term remissions and possible cure rates of 50% or higher have been obtained by a number of centers in acute nonlymphocytic leukemia (ANL), particularily when patients were transplanted in their first remission [1–9]. Most reported series of allogeneic marrow transplantation in acute lymphocytic leukemia (ALL) performed in the second remission have shown long-term disease-free survival of 20%–30%. Data for patients in their third and subsequent remissions are less good [10–14]. The recent report from the Memorial Sloan Kettering group [15] and the Baltimore group [16] has shown a therapeutic improvement over the previously reported series of ALL transplanted in their second remission. In the present communication, we wish to update our results of allogeneic marrow transplantation in patients with ANL and ALL who received marrow grafts from genotypically HLA-identical siblings.

B. Material and Methods

I. Informed Consent

All protocols were reviewed and approved by The Johns Hopkins University Institutional Review Board.

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II. Patient Selection

To be eligible for these studies, patients had to have a diagnosis of ANL or ALL confirmed by examination of a marrow aspirate. In addition, for ANL, they had to have a negative history for central nervous system leukemia and, for both ANL and ALL, a spinal fluid free of leukemic cells on cytocentrifuge examination at admission. All data were analyzed as of 15 April 1984.

A total of 27 patients with ANL were transplanted in their first remission and 28 patients in their subsequent remissions and early relapse; 18 patients with ALL were transplanted to the second remission and 16 in their third remission. The characteristics of each patient group are noted in Table 1.

III. Marrow Grafts

Marrow aspiration was performed under general anesthesia. The technical aspects of

Table 1. Characteristics of patients with ANL and ALL

Diagnosis	Remission	Number	Median age (range) (years)
ANL	1st	27	24 (9–41)
ANL	2nd, 3rd, and early relapse	28	25 (5–39)
ALL	2nd	18	13 (3–31)
ALL	3rd	16	12 (6–22)

the marrow collection and administration were as described previously [17].

IV. Preparation for Engraftment

Patients with ANL were prepared with oral busulfan (BU) given in divided doses over a 4-day period for a total dose of 16 mg/kg. This was followed by cyclophosphamide (CY) given intravenously (i.v.) at a dose of 50 mg/kg for four consecutive daily doses. Patients with ALL were prepared with CY given i.v. at a dose of 50 mg/kg for four consecutive daily doses followed by low dose rate total body irradiation (TBI) of 300 rad/day for four consecutive daily doses (lungs shielded for the third dose). All patients received one intrathecal injection of methotrexate (10 mg/m^2, but not more than a total of 12 mg) before cytoreductive therapy.

V. Treatment After Marrow Grafting

Patients were given CY or cyclosporine prophylactically to prevent graft-versus-host disease. Prophylaxis for central nervous system leukemia was given 50–80 days after marrow transplantation as five intrathecal doses of methotrexate (10 mg/m^2) over 10–14 days.

C. Results

Analysis by Kaplan-Meier plots for patients with ANL revealed an actuarial 3-year disease-free survival and median duration of living survivors (range) for patients transplanted in the first remission of 44% and 33.4 months (2.4–61.3 months) respectively. Similar analysis of patients transplanted in second and subsequent remission and early relapse revealed an actuarial 3-year disease-free survival of 43%. The median survival for the survivors was 15.7 months with a range of 4.9–46.5 months. The 3-year probability of disease-free survival (for both groups of ANL patients combined) for those aged 20 years or younger and older patients was 61% and 35%, respectively. There was only one leukemic relapse in this entire series. This occurred 1 year after transplantation in a 36-year-old male transplanted in his third remission. Of 18 patients with ALL transplanted in their second remission, 9 survive in continuous remission from 1.2 to 49 months (median 19.2 months). The probability of a 2-year disease-free survival is 48%. There have been no relapses in this group. Of 16 patients (6 in continuous remission) with ALL transplanted in their third remission, 8 survive for 2.3–46.8 months (median 22.3 months) with a projected 2-year survival of 46%. Six relapses were seen. The projected 2-year probability of remission was 44%. The causes of deaths in both the ANL and ALL series of patients were similar. Some 80% of the deaths were related to graft-versus-host disease and viral infections.

D. Discussion

Our initial series of patients transplanted for ANL following preparative treatment with BU and CY have been previously reported [8]. The present extension of that study with additional time and more patient entry continues to show promise. In particular, the very uncommon relapses (1 of 55 patients) suggests that this regimen may well have a more profound antileukemic effect than other reported treatments. Other possible practical or future advantages for this preparative treatment have been noted previously.

The studies in ALL are not quite so advanced, but already it appears that the transplantation of patients with ALL following the CY–TBI protocol outlined here results in a therapeutic response better than most reported series and at the moment is at least similar to the Memorial–Sloan Kettering experience using hyperfractionated TBI followed by CY [15]. Because of the high relapse rate of ALL patients in the third remission, we are currently preparing patients for transplantation with BU and CY as outlined for ANL.

Graft-versus-host disease and viral infections continue to be a major cause of death. A number of laboratories in transplant centers are intensively investigating

approaches to the prevention and treatment of these complications. Some of these studies already show considerable promise. It is reasonable to assume therefore, that within the next few years disease-free survivals following allogeneic marrow transplantation may increase by 20%–30%.

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References

1. Thomas ED, Buckner CD, Clift RA et al. (1979) Marrow transplantation for acute nonlymphoblastic leukemia in first remission. N Engl J Med 301:597–599
2. Forman SJ, Spruce WE, Farbstein MJ et al. (1983) Bone marrow ablation followed by allogeneic marrow grafting during first complete remission of acute nonlymphocytic leukemia. Blood 61:439–442
3. Powles RL, Morgenstern G, Clink HM et al. (1980) The place of bone-marrow transplantation in acute myelogenous leukaemia. Lancet 1:1047–1050
4. Kersey JH, Ramsey NKC, Kim T et al. (1982) Allogeneic bone-marrow transplantation in acute non-lymphocytic leukemia: A pilot study. Blood 60:400–403
5. Zwaan FE, Hermans J, for the E.B.M.T. Leukaemia Working Party (1982) Bone-marrow transplantation for leukaemia. European results in 264 cases. Exp Hematol 10 (suppl 10):64–69
6. Mannon P, Vernant JP, Roden M et al. (1980) Marrow transplantation for acute nonlymphoblastic leukemia in first remission. Blut 41:220–225
7. Gale RP, Kay HEM, Rimm AA et al. (1982) Bone-marrow transplantation for acute leukaemia in first remission. Lancet 2:1006–1009
8. Santos GW, Tutschka PJ, Brookmeyer R et al. (1983) Marrow transplantation for acute non-lymphocytic leukemia following treatment with busulfan and cyclophosphamide. N Engl J Med 309:1347–1353
9. Dinsmore R, Kirkpatrick D, Flumenberg N, Gulati S, Kapoor N, Brochstein J, Shank B, Reid A, Groshen S, O'Reilly R (1984) Allogeneic bone-marrow transplantation for patients with acute non-lymphocytic leukemia. Blood 63:649–656
10. Thomas ED, Sanders JE, Flournoy N et al. (1979) Marrow transplantation for patients with acute lymphoblastic leukemia in remission. Blood 54:468–476
11. Johnson FL, Thomas ED, Clark BS, Chard RL, Hartmann JR, Storb R (1981) A comparison of marrow transplantation to chemotherapy for children with acute lymphoblastic leukemia in second or subsequent remission. N Engl J Med 305:846–851
12. Scott EP, Forman SJ, Spruce WE et al. (1983) Bone-marrow ablation followed by allogeneic bone-marrow transplantation for patients with high-risk acute lymphoblastic leukemia during complete remission. Transplant Proc 15:1395–1396
13. Kendra JR, Joshi R, Desai M et al. (1983) Bone-marrow transplantation for acute lymphoblastic leukemia with matched allogeneic donors. Exp Hematol 11 (suppl 13):9 (abstract)
14. Woods WG, Nesbitt NE, Ramsey NKC et al. (1983) Intensive therapy followed by bone-marrow transplantation for patients with acute lymphocytic leukemia in second or subsequent remission: Determination of prognostic factors (A report from the University of Minnesota Bone Marrow Transplantation Team). Blood 61:1182–1189
15. Dinsmore R, Kirkpatrick D, Flomenberg N et al. (1983) Allogeneic bone-marrow transplantation for patients with acute lymphoblastic leukemia. Blood 62:381–388
16. Santos GW (1983) Allogeneic and syngeneic marrow transplantation for acute lymphocytic leukemia (ALL) in remission. Blood 62:229
17. Thomas E, Storb R (1970) Technique for human marrow grafting. Blood 36:507–515