CONCISE REPORT

Marrow Transplantation for Children in First Remission of Acute Nonlymphoblastic Leukemia: An Update

By Jean E. Sanders, E. Donnall Thomas, C. Dean Buckner, Nancy Flournoy, Patricia S. Stewart, Reginald A. Clift, Lawrence Lum, William I. Bensinger, Rainer Storb, Frederick R. Appelbaum, and Keith M. Sullivan

Thirty-eight children between the ages of 0.8 and 17 years with acute nonlymphoblastic leukemia in first remission induced by chemotherapy were given cyclophosphamide, total body irradiation, and bone marrow transplants from HLA-matched donors. Six patients died of pneumonia, one died of metabolic problems, and one died of chronic graft-*v*-host disease complications. Five patients relapsed between six months and 3.2 years after transplantation. Three of the five died of leukemia, one survives with leukemia three years after transplantation, and one survives in remission off treatment following chemotherapy for 22 months. Twenty-five survive in continuous remission from 1.7 to 8.4 years after transplantation, and the actuarial analysis shows a disease-free survival rate of 64%, with a plateau extending from 3.5 to 8.4 years. All lead normal lives.

MARROW transplantation for patients with acute nonlymphoblastic leukemia (ANL) in first remission has been reported by several transplant teams.[1-5] In 1981 we reported 13 children with ANL who received transplants while in first remission.[6] This report presents a follow-up of those children and describes 25 additional children who received transplants for ANL in first remission.

MATERIALS AND METHODS

Thirty-eight consecutive children 0.8 to 17 years of age with ANL in first remission received transplants at the Fred Hutchinson Cancer Research Center between March 1976 and August 1983 and were analyzed as of April 1, 1985. All patients had the diagnosis of ANL and its subtypes determined by French-American-British (FAB) classification by referring institutions. Twenty-one were subtype acute myeloid leukemia (M1,M2), two were acute promyelocytic leukemia (M3), eight were acute myelomonocytic leukemia (M4), and seven were acute monocytic leukemia (M5). In most instances, original marrow slides were sent with the patient for confirmation of diagnosis and subtype. Remission status was confirmed by examination of the bone marrow and spinal fluid on admission. The remission induction treatment varied with the referring institution. The interval between diagnosis and referral was one to eight months (median, four). All marrow donors were siblings who were genetically HLA identical.[7]

Preparation for engraftment consisted of two doses of intrathecal methotrexate (MTX)(3 to 12 mg), cyclophosphamide (60 mg/kg for two doses), and total body irradiation (TBI).[7] Seven patients received 9.20 Gy and eight received 10 Gy TBI in a single exposure, and 23 patients received 12 Gy given as 2 Gy/d for six consecutive days. Marrow infusion was performed immediately following the last dose of TBI. Prophylaxis for acute graft-*v*-host disease (GVHD) consisted of MTX in 33 patients and cyclosporine in five.[7,8] Post-transplant intrathecal MTX was given to 29 patients. Protocols and consent forms were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center. The grading of acute GVHD, diagnosis of chronic GVHD, and treatment of both have been discussed elsewhere.[7,9]

RESULTS

All 38 patients achieved engraftment as shown by rising peripheral blood counts and by marrow studies, and as confirmed in 20 patients by blood genetic markers.

Figure 1 shows the probability of survival and disease-free survival.[10] Twenty-seven are surviving 1.7 to 8.4 years after transplantation. Twenty-five have been in continuous complete remission and have not received maintenance chemotherapy. Median remission duration has not been reached, and the actuarial analysis shows a disease-free survival rate of 64% (95% confidence interval of 48% to 80%), with a plateau extending from 3.5 to 8.4 years.

All five relapses after transplantation were in the bone marrow. Figure 1 also shows the probability of relapse. Three patients died of leukemia. One patient who relapsed was treated with cytosine arabinoside, 5-azacytidine, and daunomycin for 22 months and remains in second remission now six months after discontinuation of chemotherapy. The fifth patient was treated with the vincristine, adriamycin, prednisolone, cytosine arabinoside regimen,[11] achieved remission but relapsed four months after discontinuation of chemotherapy, and is alive with leukemia 36 months after transplantation. Four of the five who relapsed were under age 5 at the time of transplantation and two of these had M1,M2 subtype and two had M4 subtype. The fifth patient had M1,M2 subtype and was 13 years old.

Nine patients developed grade II or III acute GVHD which responded to treatment with steroids, antithymocyte globulin, or cyclosporine. Chronic GVHD occurred in nine patients, six with de novo onset, three after grade II or III acute GVHD. Eight of these nine have completely responded to immunosuppressive therapy.[9] Seven have Karnofsky scores of 100% and one has a score of 90%. One remains on treatment for chronic GVHD and has a Karnofsky score of 90%.

Eight patients died of transplant-associated complications. Seven deaths occurred within the first 100 days after trans-

From the Division of Oncology, Departments of Pediatrics and Medicine, Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle.

Supported in part by National Cancer Institute grants No. CA 18029 and CA 15704. E.D.T. is a recipient of a Research Career Award No. AI 02425 from the National Institute of Allergy and Infectious Diseases.

Submitted April 16, 1985; accepted May 16, 1985.

Address reprint requests to Dr Jean E. Sanders, Division of Oncology, Fred Hutchinson Cancer Research Center, 1124 Columbia St, Seattle, WA 98104.

0006-4971/85/6602-0036$03.00/0

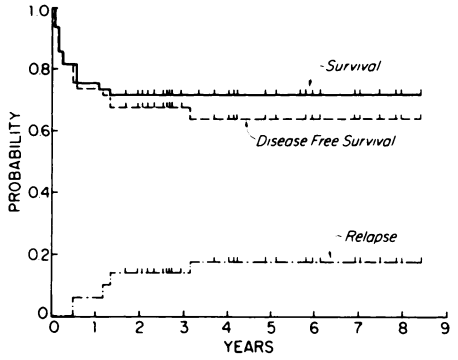

Fig 1. Kaplan-Meier product limit estimates for probability of survival (—), disease-free survival (— — —), and relapse (— · — · —) of children who received transplants for ANL in first remission. The dots indicate living patients.

plantation and were related to severe metabolic abnormalities in one, cytomegalovirus interstitial pneumonia in four, adenovirus interstitial pneumonia in one, and aspergillus pneumonia in one. One patient died 220 days after transplantation, of chronic GVHD complications.

The 25 patients surviving free of relapse have demonstrated growth in both height and weight. Of the 16 who received transplants before puberty, development of secondary sex characteristics has been delayed in five, but has occurred at a normal age for five, and six children are still too young to evaluate. Of the five girls who were postpubertal at the time of transplantation, four developed primary ovarian failure and are receiving hormone supplementation and one girl had menstruation return three years after transplantation. Twenty children have had their endocrine systems evaluated two or more times following transplantation. Bone age and pituitary–adrenal function have been normal. One patient became hypothyroid and is receiving hormone treatment. At this time, ten patients have developed cataracts and four have had them surgically removed.

DISCUSSION

The Kaplan-Meier probability of disease-free survival for these children shows a plateau at 64%. Since more than half are now surviving more than three years posttransplant, it is reasonable to expect that the majority are cured of their disease.

Recent reports indicate improved disease-free survival with intensive combination chemotherapy for one to two years after remission induction.[11,12] According to the German Cooperative Study BFM-78 protocol, 151 children treated for two years had a 52% probability of remaining in first remission, with the longest follow-up being 4.7 years after remission induction and one third of the patients still receiving chemotherapy.[12] Sixty-one children treated for 14 months according to the VAPA regimen had a probability of being in continuous complete remission at three years of 56%, the longest follow-up being seven years.[11] In both studies, extramedullary relapses were not uncommon. None of the children in the present study developed extramedullary leukemia following transplantation and no antileukemic therapy was given beyond day 102, when MTX was discontinued.

Weinstein reported that patients with M5 subtype had significantly shorter remissions as compared to other subtypes.[11] However, the German Cooperative Study, with a larger number of children, could not identify factors predictive of relapse.[12] The Children's Cancer Study Group found that children between the ages of 3 and 10 years had longer remission duration than other age groups.[13] In the current study, age rather than morphological subtype appeared to be significant, with four of the five relapses occurring among eight evaluable children under 5 years of age at the time of transplantation. Among the seven patients with M5 subtype, none have relapsed and five are surviving.

The results of the present study show that allogeneic marrow transplantation is superior to the reported results with prolonged intensive maintenance chemotherapy in achieving long-term disease-free survival for a child with ANL who achieves first remission and has a matched sibling donor. All patients with suitable donors should be offered the option of transplantation while in first remission. These children continue to be observed for adverse effects, which up to the present time are minimal and acceptable.

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, 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, 1980

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

4. Kersey JH, Ramsay NKC, Kim T, McGlave P, Krivit W, Levitt S, Filipovich A, Woods W, O'Leary M, Coccia P, Nesbit ME: Allogeneic bone marrow transplantation in acute nonlymphocytic leukemia: A pilot study. Blood 60:400, 1982

5. Zwaan FE, Hermans J, Barrett AJ, Speck B: Bone marrow transplantation for acute nonlymphoblastic leukaemia: A survey of the European Group for Bone Marrow Transplantation (E.G.B.M.T.). Br J Haematol 56:645, 1984

6. Sanders JE, Thomas ED, and the Seattle Marrow Transplant Group: Marrow transplantation for children with acute nonlymphoblastic leukemia in first remission. Med Pediatr Oncol 9:423, 1981

7. 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, 1975

8. Deeg HJ, Storb R, Thomas ED, Flournoy N, Kennedy MS, Banaji M, Appelbaum FR, Bensinger WI, Buckner CD, Clift RA, Doney K, Fefer A, McGuffin R, Sanders JE, Singer J, Stewart P, Sullivan KM, Witherspoon RP: Cyclosporine as prophylaxis for graft-versus-host disease: A randomized study in patients undergoing marrow transplantation for acute nonlymphoblastic leukemia. Blood 65:1325, 1985

9. Sullivan KM, Storb R, Witherspoon R, Shulman H, Deeg HJ,

Schubert M, Doney K, Appelbaum F, Tsoi M-S, Sale G, Sanders J, McDonald G, Thomas ED: Biology and treatment of chronic graft-versus-host disease, in Gale RP (ed): Recent Advances in Bone Marrow Transplantation. New York, Liss, 1983, p 331

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

11. Weinstein HJ, Mayer RJ, Rosenthal DS, Coral FS, Camitta BM, Gelber RD: Chemotherapy for acute myelogenous leukemia in children and adults: VAPA update. Blood 62:315, 1983

12. Creutzig U, Ritter J, Riehm H, Langermann H-J, Henze G, Kabisch H, Niethammer D, Jürgens H, Stollmann B, Lasson U, Kaufmann U, Löffler H, Schellong G: Improved treatment results in childhood acute myelogenous leukemia: A report of the German Cooperative Study AML-BFM-78. Blood 65:298, 1985

13. Baehner RL, Kennedy A, Sather H, Chard RL, Hammond D: Characteristics of children with acute nonlymphocytic leukemia in long-term continuous remission: A report for Childrens Cancer Study Group. Med Pediatr Oncol 9:393, 1981