

Bone Marrow Transplantation for the Treatment of Leukemia*

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Marrow transplantation from a syngeneic (monozygous twin) or allogeneic [homologous leucocytic antibody (HLA)-identical sibling] donor allows the administration of aggressive antileukemic therapy without regard to marrow toxicity. Until 1975 marrow transplantation was carried out only in patients with advanced relapse after failure of all other therapy. Six of sixteen patients given syngeneic marrow grafts and 13 of 100 patients with allogeneic marrow grafts are still in remission after 5½–10 years (Thomas et al. 1977a,b). An actuarial survival curve according to the method of Kaplan and Meier of the first 100 patients grafted in Seattle after treatment with cyclophosphamide (60 mg/kg/day × 2) and total body irradiation (1000 rad at 5–8 rad/min) showed three periods of interest: (1) during the first 4 months the slope was steep because many patients died due to advanced illness, graft-versus-host disease, infections (in particular interstitial pneumonias), and recurrent leukemia; (2) from 4 months to 2 ys the curve showed a much slower rate of decline, primarily due to death from recurrent leukemia; and (3) from 2 to 10 years the curve was almost horizontal with a negligible loss of patients and no recurrent leukemia. This flat portion of the curve corresponded to 13% of the patients, and it is likely that the majority of these survivors are cured of their disease (Thomas et al. 1977b).

A number of transplant groups, including our own, made attempts at reducing the

incidence of leukemic relapse after transplantation by added chemotherapy. This approach proved to be toxic, lengthened the period of maximum pancytopenia, and failed to reduce the rate of recurrent leukemia. Survival after these various approaches proved to be similar to that seen after the cyclophosphamide/total body irradiation regimen used in Seattle.

Current approaches at reducing leukemic relapse and improving long-term survival in patients transplanted with acute leukemia in relapse have involved the use of higher doses of total body irradiation by means of fractionation. Perhaps these efforts are futile, since in an exponential killing process it is difficult to kill the last leukemic cell. Some of the apparent cures may have occurred because of destruction of leukemic cells by immune reactions of the grafted cells against non-HLA antigens and/or leukemia-associated antigens of the host. Such a possibility is suggested by the observation of a graft-vs-leukemia effect in man (Weiden et al. 1979).

The demonstration that a treatment regimen is effective in the otherwise refractory end stage patient with acute leukemia constitutes a rational basis for its application earlier in the course of the disease. Accordingly, the Seattle group initiated a study in early 1976 of treating patients with acute nonlymphoblastic leukemia by marrow grafting in first or subsequent remission and those with acute lymphoblastic leukemia in second or subsequent remission using the basic conditioning regimen of cyclophosphamide and total body irradiation used since 1971. We assumed that patients with leukemia in remission would be more readily cured, since the number of leukemic cells in the body could be expected to be small and cells

* This investigation was supported by Grant Numbers CA 18029, CA 15704, and CA 18221, awarded by the National Cancer Institute. U.S.-Dept. of Health, Education and Welfare

should not have become resistant to therapy. Moreover, previous experience had shown that patients in good clinical condition and with good blood cell values at the time of transplantation had a much better chance of surviving the transplantation procedure.

A. Acute Nonlymphoblastic Leukemia in First or Subsequent Remission

Patients with acute nonlymphoblastic leukemia have a poor prognosis with chemotherapy. The median duration of the first remission is approximately one year and only 15%–20% of the patients are alive at 3 years. A Kaplan-Meier plot of survival with a logarithmic ordinate for the fraction of patients surviving usually shows no evidence of a plateau (Powles et al. 1980b). Our past observation that marrow transplantation could lead to an operational cure of 13% of end stage refractory patients made it ethically acceptable to consider marrow grafting for acute nonlymphoblastic leukemia in first remission. The first 19 patients were transplanted between March 1976 and March 1978 at a median of 4 months following initial treatment or 2½ months following the achievement of the first complete remission (Thomas et al. 1979b). Of the 19 patients, 12 are alive in continued unmaintained remission with a functioning marrow graft between 27 and 48 months after transplantation. Nine of the twelve are entirely well, while three have mild chronic graft-vs-host disease with Karnofsky performance scores of 80%–90%. A Kaplan-Meier plot of the probability of survival shows a plateau at 65% with the long-term survivors far out on the plateau and presumably cured of their disease. Six of the nineteen patients died from graft-vs-host disease and/or interstitial pneumonia.

Of particular interest is the fact that only 1 of the 19 patients has had a recurrence of leukemia. Forty-eight patients have now been transplanted in first remission, and again recurrence has been limited to that single patient. Evidently the chemo-radiotherapy regimen used is capable of eradicating the leukemic cell population in most of these patients. In contrast, patients grafted in second remission have a leukemic recurrence rate of 35%.

More recently, the Seattle results in acute

nonlymphoblastic leukemia in first remission have been confirmed by reports from the marrow transplant teams at the City of Hope in Duarte, California (Blume et al. 1980) and at the Royal Marsden Hospital in Sutton, Surrey, England (Powles et al. 1980a).

B. Acute Lymphoblastic Leukemia in Second or Subsequent Remission

Approximately 50% of the patients with acute lymphoblastic leukemia, particularly children, can be cured by combination chemotherapy. However, once marrow relapse has occurred, only 5% of the patients treated with conventional chemotherapy are alive at 2 years after relapse (Chessels and Cornbleet 1979). Transplantation of patients with this disease in second or subsequent remission would entail the risk of losing some of them early after grafting due to grafts-vs-host disease and/or infections. However, this risk seemed acceptable if other patients could be “cured” of their disease.

The first 22 patients were grafted between April 1976 and December 1977 (Thomas et al. 1979a). Three patients died of interstitial pneumonia within three months of transplantation. Eleven patients died of recurrent leukemia within 27 months of grafting. The latest relapse was in the central nervous system of a patient who had active central nervous system leukemia at the time of grafting. The median survival of this group of transplanted patients was 1 year compared to the 6–8 months usually observed after combination chemotherapy. Eight patients are surviving between 32–41 months after transplantation in unmaintained remission. Seven of the eight are without problems and one has moderately severe chronic graft-vs-host disease with a Karnofsky performance score of 70%. It is clear that recurrent leukemia was the major problem in patients with acute lymphoblastic leukemia transplanted in second or subsequent remission. These recurrences were in cells of host type indicating that the conditioning regimen was ineffective in eradicating residual leukemic cells in approximately 50% of the patients. Further improvement in survival in patients with acute lymphoblastic leukemia hinges on the development of new preparative regimens.

C. Chronic Myelogenous Leukemia

The Seattle team has carried out six marrow grafts from monozygous twins for chronic myelogenous leukemia in blast crisis and one of these patients continues to be in unmaintained remission with disappearance of the Philadelphia chromosome 53 months after transplantation. Four of 22 patients with chronic myelogenous leukemia in blast crisis treated by marrow grafts from HLA identical siblings are alive in unmaintained remission 8, 15, 27, and 31 months after grafting, while the remainder died either of transplantation associated complications or of recurrent blast crisis.

In an attempt to improve the results in patients with chronic myelogenous leukemia, a study was initiated during the chronic phase of the disease for those patients who had a healthy monozygous twin (Fefer et al. 1977). The objective was to eradicate the Philadelphia chromosome positive clone by chemotherapy and total body irradiation and, thus, to prevent the transformation into blast crisis and cure the disease. An initial group of four patients was treated with a combination of dimethylbusulfan, cyclophosphamide, and total body irradiation followed by marrow infusion. Complete hematologic and cytogenetic remissions were induced in all four. One patient has relapsed 30 months after transplantation and is now back in the original state of chronic myelogenous leukemia. The other three are clinically, hematologically, and cytogenetically normal 36, 39, and 44 months after transplantation. It is possible that the Philadelphia chromosome positive clone has been eradicated. Obviously a longer follow-up of these three patients and of seven similar patients grafted since the initial report is in order.

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