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Bone Marrow Transplantation in Leukemia

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A. Introduction

Studies in the mid-1950s using rodent models led to recognition that living bone marrow cells could be transplanted from one animal to another (reviewed in [18]). The clinical applications for replacement of marrow damaged by disease or its therapy were immediately apparent. However, more than a decade of research was required before the principles of transplantation biology, human tissue typing, and the supportive care of the patient without marrow function were sufficiently established for marrow grafting for therapeutic purposes to become a realistic clinical modality.

The underlying concept of marrow transplantation is to destroy malignant cells without regard for marrow toxicity with restoration of marrow function by transplantation of normal marrow cells. The goal is to achieve a maximum anticancer effect without the limitations imposed by the marrow toxicity which characterizes most therapeutic agents.

B. Allogeneic Marrow Transplants

I. Rationale for Chemoradiotherapy

In early studies of patients with acute leukemia in end-stage relapse, it was considered necessary to administer total body irradiation (TBI) as quickly as possible in the hope that a marrow graft would be functional before the patient died of problems related to marrow failure. Accordingly, 1000-rad TBI was administered over a period of approximately 4 h [19]. The TBI caused the sudden destruction of large numbers of leukemic cells, resulting in acute toxic reactions. To spread the destruction of leukemic cells over a longer time period and to kill more leukemic cells, the Seattle team initiated the use of a large dose of cyclophosphamide before the TBI [20]. The basic regimen consisted of cyclophosphamide 60 mg/kg body wt. on each of 2 days followed 3 days later by the administration of 1000-rad TBI. There is now an extensive experience with this regimen in a number of marrow transplant centers. The greatest experience has been with an allogeneic marrow graft from an HLA-identical sibling given within 24 h after the TBI. The clinical experience in Seattle with this basic regimen, in some patients combined with additional chemotherapeutic agents, is summarized.

II. Transplantation for Acute Leukemia in End-Stage Relapse

Fifty-four patients with acute nonlymphoblastic leukemia (ANL) and 46 patients with acute lymphoblastic leukemia (ALL) were given cyclophosphamide 60 mg/kg×2, 1000 rad TBI, and marrow from HLA-identical siblings [20]. There were many early deaths from advanced illness and subsequent deaths from graft-versus-host disease (GVHD), opportunistic infection, and recurrence of leukemia. However, six patients with ANL and seven patients with ALL are alive in unmaintained remission 6–10 years later. Although the fraction of long-term survivors is low, these patients are unique in that no other form of therapy has resulted in prolonged unmain-

tained disease-free survival in relapsed patients. Actuarial analysis demonstrates a flat long-term disease-free plateau and provides evidence that these patients are cured of the disease.

III. Transplantation for ANL in First Remission

Since some patients in the end stage of the disease could be cured by combined chemoradiotherapy and allogeneic marrow transplantation, we initiated studies of marrow grafting in patients with ANL in first remission [21]. When these studies were begun, there were almost no reports describing median remission durations longer than 1 year. It seemed ethically acceptable therefore to carry out these studies in these patients. The first group of 19 patients was reported 3 years ago, and three additional patients were transplanted while that report was in press. Twelve of these 22 (55%) are alive in unmaintained remission 4–6 years after transplantation. Only one patient has significant chronic GVHD with a Karnofsky score of 80%.

IV. Transplantation for ALL in Second or Subsequent Remission

Patients with ALL who relapse have a grim prognosis. Subsequent remissions can frequently be induced but tend to be short in duration. We initiated a study for patients with ALL in second or subsequent remission in order to carry out the marrow graft when the patient was in good condition and when the possibility of cure might be increased because of the minimal burden of leukemic cells in the body [22]. Of the first 22 patients, the median remission duration after grafting was 1 year, and six patients became long-term survivors. The apparent cure rate of 27% is a significant achievement, but we were disappointed by the fact that leukemia recurred in eight of these patients. A Kaplan-Meier analysis indicated that 60% of these patients would suffer a relapse of leukemia if other causes of death were eliminated. In a subsequent study it was shown that marrow transplantation in remission was superior to chemotherapy for patients with ALL who have relapsed at least once [11].

V. Transplantation for Chronic Myelogenous Leukemia (CML) in Blast Crisis

Our initial efforts to carry out marrow transplantation in patients in blast crisis after failure of chemotherapy were unsuccessful [6]. Of 12 patients, only one had a remission beyond 1 year, and he died at 16 months of recurrent leukemia. In the more recent series of patients in which the marrow graft was undertaken before combination chemotherapy had been administered, the results have improved ([7] and unpublished). These studies involved the usual two doses of cyclophosphamide followed by fractionated irradiation, either 1200 rad or 1575 rad. Eight of 22 patients are alive in remission from 4 to 48 months after grafting.

VI. Transplantation for CML in Chronic Phase

CML in chronic phase is not actually a "chronic" disease. The median survival time is 2 or 3 years, and there are no cures by conventional therapy. We began studies of this disease in a series of 12 patients who had cytogenetically normal identical twins to serve as marrow donors [8]. Dimethyl myeleran, 5 mg/kg, was administered before the regimen of cyclophosphamide and 1000-rad TBI. One patient died of an interstitial pneumonia, one died of cytogenetic relapse and subsequent blast crisis, and two are living and well but have had recurrence of the Philadelphia chromosome. Eight patients are living, well, and cytogenetically normal 24–68 months after transplantation.

Encouraged by an apparent ability to eradicate the abnormal clone of leukemic cells in most patients, we began a study of marrow grafting for patients with CML in chronic phase with HLA-identical siblings as donors [7]. The first three patients were prepared with cyclophosphamide followed by 1000-rad TBI, and one patient is living and well 35 months later. Two patients died early, one of interstitial pneumonia and one of GVHD.

The current study for CML patients in chronic phase consists of the two doses of cyclophosphamide followed by 200-rad irradiation on each of 6 days; patients are

then randomized to receive methotrexate or cyclosporine for prevention of GVHD. Thirteen patients have been entered on the study. Four died of interstitial pneumonia, and nine are living with a graft and without the Philadelphia chromosome 5–20 months after grafting. A preliminary report from the Toronto marrow transplant team describes 11 patients with CML in the accelerated phase [12]. The preparative regimen usually included cytosine arabinoside (100 mg/m^2 per day×5), cyclophosphamide (60 mg/kg per day×2), and 500-rad TBI. Seven patients were alive without the Philadelphia chromosome 2–26 months after grafting. Another preliminary report from the UCLA marrow transplant team described five patients with CML in chronic or accelerated phase prepared with the two doses of cyclophosphamide and 1000-rad TBI and given HLA-identical sibling marrow [4]. All five were alive and without the Philadelphia chromosome 6–15 months posttransplant. Although a longer follow- up period will be necessary, it appears that more than half of the patients with CML can be cured of the disease but that some patients will die early of complications of the transplant procedure.

VII. Recurrence of Leukemia

The recurrence of leukemia after marrow transplantation for patients with ANL in first remission is a relatively minor problem since only 10% of these patients are destined to have a recurrence as determined by an actuarial analysis. The long-term survival and apparent cure rate is 50%–60%. For all other types of leukemia, when relapse has occurred at least once, whether the patient is transplanted in remission or in relapse, recurrence of leukemia has been observed in approximately 60% of the patients. The long-term disease-free survival and apparent cure rate is approximately 10%–30% [1, 3, 9].

Seven cases of recurrence of leukemia in the donor-type cells have been reported (reviewed in [16]). Two of these recurrences were an immunoblastic lymphosarcoma type, one associated with Epstein-Barr viruses. The other occurrences have been of the original leukemic type, including both ALL and ANL. In a study of recurrent leukemia in patients with a donor of opposite sex, the Seattle group has recognized three recurrences in donor cells among 54 such transplants. Thus, it appears that approximately 5% of the recurrences may be expected to be in the donor-type cells. The mechanism of these recurrences in donor-type cells is, of course, unknown. Present speculations suggest that some type of transfection may be involved.

VIII. Acute GVHD

Acute GVHD involves the skin, the liver, and the gut as target organs and is associated with severe immunodeficiency [18]. Approximately 60% of the patients receiving a marrow transplant from an HLA-identical sibling and treated postgrafting with methotrexate will show no evidence of GVHD or only grade I GVHD. Forty percent will have more severe GVHD with multiple organ involvement. Treatment of acute GVHD has been attempted with prednisone, antithymocyte globulin, cyclosporine, cyclophosphamide, and various monoclonal antibodies. The response to treatment is variable and unpredictable.

IX. Chronic GVHD

About one-third of the patients who live beyond 100 days postgrafting will display some evidence of chronic GVHD. Chronic GVHD typically presents a scleroderma-like involvement of the skin associated with sicca. Chronic GVHD may also involve the liver or the gut. About 80% of the patients with chronic GVHD will respond to therapy with azathioprine and prednisone or cyclophosphamide and prednisone [17].

X. Opportunistic Infections

Patients with a marrow graft from an HLA-identical sibling are profoundly immunodeficient in the first 100 days after grafting, and 1 year is required for full recovery of immunologic function [14]. The presence of GVHD, either acute or chronic, is associated with further suppression of immune function. During the period of immunodeficiency, patients are susceptible to infection with a broad range of bacterial, viral, and fungal infections [13].

XI. Graft Versus Leukemia

It has long been known from studies in rodents that an allogeneic graft may have an antileukemic effect [2]. With better survival of patients with GVHD, it has now been possible to show that the presence of GVHD indicates a lower incidence of recurrence of leukemia after grafting [23].

XII. Cyclosporine

Cyclosporine is a fungus-derived antibiotic with profound immunosuppressive properties without marrow toxicity. Preliminary and uncontrolled trials of this agent indicate that it is of value in preventing GVHD and in treating established GVHD [15]. A prospective trial has been underway in Seattle for past 1½ years. Patients are randomized to treatment with cyclosporine after grafting in comparison to the standard postgrafting methotrexate regimen. With some 60 patients entered into the study, the survival curve of the two groups is not statistically significantly different.

XIII. Monoclonal Antibodies

Many monoclonal antibodies which react with various epitopes on the surface of T cells are now available. Since GVHD is presumed to be mediated by T cells, it is reasonable to attempt to prevent GVHD by in vitro treatment of the donor marrow with monoclonal anti-T cell antibodies as well as the in vivo administration of these antibodies for the treatment of established GVHD. Although the use of monoclonal antibodies is being studied in many marrow transplant centers, definitive reports have not yet appeared.

XIV. Haploidentical Marrow Donors

The Seattle Marrow Transplant Team began 5 years ago a cautious exploration of family-member donors with one HLA haplotype genetically identical with the patient and the other HLA haplotype phenotypically identical at two of the three major HLA loci [5]. Some 80 patients with leukemia have now been transplanted from donors of this type and, overall, the results are much more a reflection of the type and stage of the disease than of the transplant donor.

XV. Unrelated Donors

Three years ago the Seattle Transplant Team carried out a transplant for a patient with ALL using a totally unrelated donor [10]. The transplant was successful, and the recipient had no GVHD. This case illustrated the feasibility of using as a donor a completely unrelated individual.

C. Summary

Marrow grafting is now an established treatment for patients under the age of 50 with acute leukemia and a suitable marrow donor. For all patients who have relapsed at least once, marrow grafting offers the possibility of cure of approximately 20%–30% of these patients, which cannot be achieved by any other regimen yet reported. Although still somewhat controversial, it appears that marrow grafting is also the treatment of choice for younger patients with ANL in first remission since approximately 50%–60% of these patients can be cured. The problems associated with marrow grafting are largely those of failure to eradicate the malignant disease and of transplantation immunobiology. Progress is being made on solving these problems, and the ever-increasing number of marrow transplant centers involved in the study of these problems promises rapid progress in this field.

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