CONCISE REPORT

Reversal of Acute ("Malignant") Myelosclerosis by Allogeneic Bone Marrow Transplantation


A 28-yr-old woman with acute malignant myelosclerosis received, as primary treatment, ablative chemotherapy and total body radiation therapy followed by bone marrow transplantation from her histocompatible brother. The patient is now well more than 15 mo after bone marrow transplantation, with normal peripheral blood counts, a normal bone marrow, no evidence of graft-versus-host disease, and is on no therapy. In light of the poor results obtained with conventional chemotherapy in this disease, bone marrow transplantation may represent the treatment of choice for patients who have an appropriate donor.

Acute ("MALIGNANT") MYELOSCLEROSIS (AMS) is a uniformly fatal hematologic disorder characterized by pancytopenia and a fibrotic, unexpireable bone marrow in which all three cellular elements are hyperplastic and immature. Normal and abnormal megakaryocytes and their precursors are particularly prominent, splenomegaly is almost always absent, and peripheral red cell morphology is usually unremarkable. Utilizing supportive care only, survival from diagnosis is always less than 1 yr and usually less than 6 mo. Moreover, no form of conventional chemotherapy has been shown to be effective, prompting at least one author to suggest the use of bone marrow transplantation as primary therapy for this disease.

Ablative chemoradiotherapy, followed by either syngeneic or allogeneic bone marrow transplantation, has been applied successfully to a number of hematologic disorders as well as to some primary immunologic deficiencies and to other serious nonmalignant diseases. In some instances in which bone marrow fibrosis was a prominent feature, transplantation has led to a reversal of that fibrosis, suggesting that bone marrow sclerosis might merely by reactive and secondary to malignant infiltration.

We report here the case of a 28-yr-old woman (unique patient number 67) with AMS who successfully received high-dose chemoradiotherapy followed by allogeneic bone marrow transplantation as primary therapy for her disease.

CASE REPORT

A 28-yr-old mother of two presented in March 1980 with a 2-wk history of increasing fatigue and unexplained fever. She had been exposed to no toxins, had ingested no drugs, and had no previous history of illness. Physical examination demonstrated mild purpura, no lymphadenopathy, and no hepatosplenomegaly. There was no obvious source for her fevers. White blood cell count was 1300/μl (12% neutrophils); platelets 18,000/μl, reticulocytes 0%. There were no circulating myeloblasts. Red cell morphology was unremarkable. An attempted marrow aspiration was unsuccessful, but a core biopsy was diagnostic of acute malignant myelosclerosis (Fig. 1 A and E).

Without any prior therapy, the patient was prepared for bone marrow transplantation from her ABO and HLA-identical, mixed lymphocyte culture compatible brother. The pretransplantation regimen consisted of cytosine arabinoside 5 mg/kg on days 8 and 3, cyclophosphamide 80 mg/kg on day −5, and 1000 rads of total body irradiation on day −1. On the day of transplantation, day 0, she received 2.8 × 10^6 nucleated cells/kg. Her posttransplantation course was uneventful (Fig. 2). While receiving prophylactic granulocytes, her pretreatment fevers disappeared, and except for a short episode of fever requiring antibiotics, she had no further posttransplantation problems. For graft-versus-host disease prophylaxis, methotrexate was given during the first 100 days posttransplantation and prednisone was administered throughout the first year.

Peripheral blood counts reached 1000 white cells/μl on day +24, 50,000 platelets/μl on day +31, and 10 g/dl of hemoglobin (untransfused) on day +48 after transplantation.

Serial bone marrow biopsies showed return of qualitatively and quantitatively normal bone marrow (Fig. 1 A–D), with progressive clearing of fibrosis (Fig. 1 E–H). The bone marrow on day +100 was aspirable and microscopically normal. Further biopsies through day +354 revealed no abnormal reticulin fiber content. All bone marrow metaphases after bone marrow transplantation were of male karyotype.

A transient interstitial pulmonary infiltrate was noted during the tenth month after transplantation. There was no elevation in cytomegalovirus antibody titer and no other causative organism was identified. Lung biopsy was not performed. The patient's clinical status and chest x-ray returned to normal while receiving 0.4 mg/kg of prednisone as well as co-trimoxazole. Currently, the patient is more than 15 mo after bone marrow grafting for AMS; she is well, has normal peripheral blood counts (WBC 7000/μl (49% neutrophils), no evidence of graft-versus-host disease, and is on no therapy. In light of the poor results obtained with conventional chemotherapy in this disease, bone marrow transplantation may represent the treatment of choice for patients who have an appropriate donor.

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Fig. 1. The top row are hematoxylin and eosin stains of bone marrow biopsies from (A) diagnosis, (B) day +15 after transplantation, (C) day +100 after transplantation, and (D) day +360 after transplantation. The bottom row (E–H) are the corresponding reticulin stains relating to the marrows directly above. The diagnostic marrow shows a panmyelosis with many abnormal megakaryocytes and their precursors and many other immature forms. The day +15 marrow is totally aplastic after ablative therapy. The days +100 and +360 marrows show progressive and then total clearing of reticulin fiber content. (Magnification for all photomicrographs ×320).

**DISCUSSION**

Using conventional chemotherapy, investigators have demonstrated resolution of bone marrow sclerosis in such diverse diseases as Hodgkin's disease, metastatic breast carcinoma, and acute leukemia. Following bone marrow transplantation for chronic granulocytic leukemia, fibrosis has likewise been shown to be reversible. Moreover, there is accumulating evidence that the fibrosis associated with some of these processes may not be part of the malignant process but rather secondary to the primary malignancy, and therefore might be expected to improve with resolution of the malignant proliferation. Thus, in chronic myelogenous leukemia and in chronic and acute myelofibrosis, the marrow fibroblasts have been shown to be distinct from the malignant clone by both chromosomal and biochemical markers. The successful reversal of the sclerosis in our case confirms the nonpermanent nature of this process and supports the argument that the fibrosis associated with many bone marrow malignancies is a reactive phenomenon.

The success of this case also demonstrates the usefulness of ablative measures followed by bone marrow transplantation as primary therapy. To date, all conventional therapies for AMS have been totally ineffective in changing the dismal prognosis of this disease. It appears, however, that increasing the ablative nature of the therapy for this disorder leads to a more complete and lasting response. It can also be envisioned that other bone marrow dyscrasias with...
Fig. 2. The patient's pre- and posttransplantation course. Day 0 is the day of transplantation. TPN, total parenteral nutrition. PCV, packed cell volume. WBC, white blood cell count or WBC transfusions. PLT, platelet count or platelet transfusions. ARA-C, cytosine arabinoside. CTX, cytoxan (cyclophosphamide). TBI, total body irradiation. MTX, methotrexate.

poor prognosis might be similarly amenable to primary therapy with bone marrow transplantation. Bone marrow transplantation may represent the treatment of choice for patients with AMS under the age of 45 who have histocompatible donors.

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