Complete Recovery of Hemopoiesis Following Bone Marrow Transplant in a Patient With Unresponsive Congenital Hypoplastic Anemia (Blackfan-Diamond Syndrome)

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Allogeneic bone marrow transplantation (BMT) was carried out on a 5-year-old boy with congenital hypoplastic anemia (CHA), who did not respond to corticosteroids and who was displaying signs of progressive hemosiderosis. Pretransplant preparation had to be modified because respiratory failure and cerebral edema supervened. This preparatory regimen consisted of busulfan (2 mg/kg for four days), cyclophosphamide (50 mg/kg for one day), and a dose of 750 rad. All blood products were irradiated to a dose of 1,500 rad prior to transfusion. The technique used in the bone marrow transplantation was the same as that used by Thomas et al.

Congenital Hypoplastic Anemia (CHA) is a childhood disease that is characterized by a marked reduction in red cell precursors in the bone marrow. Although most of these patients respond to corticosteroids, and some may enjoy spontaneous remission, about 20% require periodic transfusion and die prematurely as a result of hemosiderosis. It has also been reported that neoplasms may occur even in patients in remission.

This article describes a patient with CHA who failed to respond to corticosteroids, but who was successfully treated by BMT.

MATERIALS AND METHODS

Routine hematologic, chemical, and microbiologic studies were carried out using standard methods in the clinical laboratories of the M. Valdecilla Medical Centre. HLA-A, B, C antigen typing was performed by the Terasaki microdroplet lymphocyte cytotoxicity test. One-way mixed lymphocyte cultures were performed according to the method of Bach and Bach. Red cell phenotypes were established by standard serologic techniques. Metaphase chromosomes were obtained from bone marrow samples and examined using C' and G' banding techniques. Total body irradiation from a single cobalt 60 source was administered at a rate of 5 rad/min to a midline somes were obtained from bone marrow samples and examined using C' and G' banding techniques. Total body irradiation from a single cobalt 60 source was administered at a rate of 5 rad/min to a midline.

CASE REPORT

The patient was a 5-year-old boy who was found to be severely anemic at 2 months of age. His reticulocyte count was 0%. A bone marrow examination disclosed erythroid hypoplasia. CHA was diagnosed, and a complete recovery was obtained after treatment with prednisone (2 mg/kg daily) for 30 days. Four months later, the patient relapsed and failed to respond to four further courses of prednisone (2 mg/kg daily) of one month each. Finally, the patient required red cell transfusions twice a week. At the time of his BMT, he had received 89 transfusions of packed, not frozen, RBC from random donors not directly related to him. Iron chelation therapy was not done prior to transplant.

At 5 years of age, the patient displayed indirect signs of iron overload: hepatomegaly, skin pigmentation, elevation of SGOT, SGPT, and lactate dehydrogenase (LDH), hypersideremia and hyperferritinemia, and a positive glucose tolerance test. It was then determined that he and his 10-year-old sister were HLA identical and unreactive in mixed lymphocyte culture (stimulation index .94), so a BMT was proposed. Informed consent was obtained from the parents. At 6 months of age, the patient had suffered a thrombosis of the superior sagittal sinus, which had resulted in a hydrocephalus and slight corticocerebral atrophy, but the neurologic examination on admission was otherwise normal. Except for anemic findings, his cardiovascular status was normal.

Laboratory investigations gave the following results: white blood cell count, 6.5 x 10^6/L; neutrophils, 74%; platelet count, 250 x 10^6/L; hemoglobin, 5.3 g/dL; reticulocytes, 0%; SGOT, 150 mU/mL; SGPT, 214 mU/mL; LDH, 425 mU/mL; fasting blood glucose, 120 mg/dL. After the administration of 30 g of glucose, blood glucose at 30, 60, and 120 minutes was 190 mg/dL, 220 mg/dL, and 150 mg/dL respectively. Total bilirubin was 1 mg/mL; serum iron, 289 μg/dL; total iron-binding capacity (TIBC), 310 μg/dL; and serum ferritin, 2,020 μg/mL. Aspirated bone marrow was practically devoid of red cell precursors (Fig 1A). The red cell phenotypes of donor and recipient displayed antigenic differences in the Rh (Ee) and P systems. The patient had anti-HLA-A2 antibody. No other evidence of isoinmunization due to previous blood transfusion was detected.

Pretransplant preparation started with busulfan (2 mg/kg daily for four days). It was intended to be followed up with cyclophosphamide, 50 mg/kg daily for four days, and donor buffy coat, but the first dose of cyclophosphamide and the subsequent hyperhydration (3 L/24 h) were followed by an episode of hydric retention with cerebral edema, convulsions, profound coma, and acute respiratory failure due to pulmonary edema, which was not of cardiac origin. The cyclophosphamide was withdrawn, and the patient was artificially ventilated and treated with mannitol and diuretics. No further cyclophosphamide was given because of the inappropriate antidiuretic hormone (ADH) secretion induced by the
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Graft-versus-host disease (GVHD) was prevented by treatment with methotrexate, according to the Seattle protocol, until the 103rd day. Following the transplant, the patient was given irradiated random packed red blood cells and platelets, which were HLA compatible, from voluntary family donors whenever needed.

The clinical course is shown in Fig 2. The period of induced aplasia was the same as in other BMTs performed at this hospital and was uneventful except for two episodes of fever, which responded rapidly to antibiotics. The white cell count of peripheral blood was $10^9/L$ on day 23 and the reticulocyte count was 5% (of red cells) on day 40. On day 90, hemoglobin was 12.5 g/dL and the reticulocyte count was $60 \times 10^9/L$. A bone marrow sample obtained on day 66 was moderately hypocellular, and the myeloid:erythroid ratio was 2:1, with 26% normal erythroblasts (Fig 1B). The red cell phenotype obtained on day 150 was identical to that of the donor (Table 1) and a female karyotype was present on day 180 in all the metaphases examined in the bone marrow (Table 2). No anti-HLA-A2 antibody was found when sought on day 180. On day 650, the hemoglobin was 14.4 g/dL. No evidence of acute or chronic GVHD has developed, and the clinical condition is good. The patient did not require transfusions after day 35.

DISCUSSION

In a previous BMT for CHA, the patient died on day 55, even though erythropoiesis had been reestablished. The present case shows that this procedure can restore sustained normal hemopoiesis and that the procedure should, therefore, be considered for patients with CHA who do not respond to drugs and who need frequent transfusions.

As some of these patients may go into spontaneous remission, it is difficult to be certain at what point BMT should be undertaken. It is evident that the iron overloading of the tissues in these patients will increase according to increasing age. On the other hand, it is well known that the incidence of GVHD is higher in adults. Therefore, we think that once the patient is refractory to treatment, early intervention would reduce the iron overload of the tissues and the risk of GVHD.
patients if cyclophosphamide alone is used. This incidence can be reduced by increasing the number of stem cells transfused (donor buffy coat), by irradiating the lymph nodes of the whole body, or by adding antithymocyte globulin (ATG) and procarbazine to the standard cyclophosphamide regimen.

Total body irradiation is an effective means of achieving both the destruction of the marrow and immunosuppression. However, irradiation may have damaging effects, including carcinogenesis. As we wished to avoid irradiation in this 5-year-old child, we selected a regimen of busulfan-cyclophosphamide and donor buffy coat.

Busulfan, which is a potent myeloablative agent, but which has few other toxicities, has been suggested by the studies of Santos et al. The dosage of busulfan used in this patient regularly induces aplasia without producing other toxicities, in particular, those related to the lungs.

The appearance of a possible cyclophosphamide-induced toxicity obliged us to change the planned regimen, so we used total body irradiation, with both the lungs and brain protected. No toxicity has developed and the patient is leading a normal, active life.

The question of optimum pretransplant regimen in this setting remains unsolved. In spite of these difficulties, we believe that BMT is a useful procedure for the treatment of unresponsive CHA, especially if it is performed in the first years of life.

ACKNOWLEDGMENT

The authors wish to acknowledge Dr Carlos Pérez Clausell, who referred this patient, and the invaluable help of the nursing staff of the bone marrow transplant unit, who took excellent care of this patient.

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