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 4 days), cyclophosphamide (50 mg/kg for one day), and total body irradiation (750 rad). Hemopoiesis was completely restored and is still maintained 650 days after transplantation. This is the second published report on the use of BMT to treat a patient with CHA, and it is the first time it has resulted in long-term survival. BMT should be considered for patients with CHA who do not respond to corticosteroids.

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 coat, but the first dose of cyclophosphamide and the subsequent cardiocerebral 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 × 10⁹/L; neutrophils, 74%; platelet count, 250 × 10⁹/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/dL; 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 isoimmunization due to previous blood transfusion was detected.

Pretransplant preparation was 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 hydration (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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Fig 1. (A) Patient bone marrow prior to transplantation. Total absence of red cell precursors. (B) Patient bone marrow on day 66 after transplantation. Presence of numerous erythroblasts in different stages of maturation.

drug. Pretransplant preparation was completed by total body irradiation (750 rad) with both lungs and brain protected.

Twenty-four hours later, the patient was given a transfusion of 6 x 10^6 nucleated marrow cells/kg from his HLA-identical sister. The patient was nursed in reversed isolation in a room maintained under slightly positive air pressure.

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 that 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 x 10^6/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.

Fig 2. Clinical course of patient after bone marrow transplantation. ●, busulfan; ●, cyclophosphamide; ●, methotrexate; ●, TBI; ●, carbenicillin; ●, tobramycin; ●, azlocillin; ●, amikacin; ●, packed R.C. Transf.; ●, Plat Transf.
patients if cyclophosphamide alone is used.\textsuperscript{24} This incidence can be reduced by increasing the number of stem cells transfused (donor buffy coat),\textsuperscript{25} by irradiating the lymph nodes of the whole body,\textsuperscript{26} or by adding antithymocyte globulin (ATG) and procarbazine to the standard cyclophosphamide regimen.\textsuperscript{27}

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.\textsuperscript{28} 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.\textsuperscript{29,30} The dosage of busulfan used in this patient regularly induces aplasia without producing other toxicities, in particular, those related to the lungs.\textsuperscript{31,32}

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 pretreatment 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.

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