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Case report

Successful unrelated bone marrow transplantation for Shwachman–Diamond syndrome

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Summary:

A 5-year-old boy with Shwachman–Diamond syndrome underwent unrelated HLA-identical bone marrow transplantation for severe pancytopenia. Conditioning was with busulfan, thiotepa and cyclophosphamide plus rabbit anti-lymphocyte serum. Engraftment for neutrophils and platelets was observed on days +18 and +41, respectively. Transplant-related side-effects were mild and transient. After a follow-up of 32 months, the patient is alive and enjoys a normal life, off any immunosuppressives. Immunological and hematological reconstitution is complete while other phenotypic characteristics (pancreatic insufficiency, short stature, femur dysostosis) are stable. Although experience in this field is scarce, we speculate that bone marrow failure in Shwachman–Diamond syndrome (even if not linked to the appearance of clonal disorders or leukemic transformation) is an indication for bone marrow transplantation and may be associated with a better outcome.
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Marrow dysfunction including neutropenia, marrow aplasia, myelodysplasia and leukemic transformation are well known features of Shwachman–Diamond syndrome (SDS), a rare recessive autosomal disorder of infancy that is also characterized by pancreatic insufficiency, metaphyseal dysostosis and short stature.[1] Very limited information has been published on the long-term survival range in SDS. A projected median survival time of 35 years has been reported[2] but this figure could be an over-simplification. SDS was first described only 35 years ago and the true long-term survival is unknown. However, the development of pancytopenia and leukemia significantly reduce survival, infections and hemorrhage being the major causes of death.[2]

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Supportive treatment with antibiotics and transfusion, and correction of malabsorption with oral pancreatic enzymes, currently allow prolonged survival without modifying the natural evolution of the disease.[1,2] Allogeneic stem cell transplantation is a valuable option when clonal disorders such as leukemic transformation, myelodysplasia or severe marrow aplasia develop[3,4] but experience in this field is very limited due to the rarity of the disease and the lack of clear-cut indications concerning the optimum timing of transplantation. We report a successful unrelated identical bone marrow transplant (BMT) in a 5-year-old boy who developed marrow aplasia after initial marrow dysplasia. The patient is alive and well after a follow-up of 32 months. We speculate that the reduced incidence of transplant-related mortality, the recent availability of larger panels of volunteer bone marrow donors and a growing cord blood bank could provide a better chance of long-term survival for SDS patients with severe (even if not clonal) hematologic complications.

Case report

A diagnosis of SDS was made in a 5-month-old boy with exocrine pancreatic insufficiency and steathorrea, failure to thrive, malnutrition, hepatosplenomegaly, diffuse eczema, metaphyseal dysostosis of the femur, normochromic, normocytic anemia (7.9 g/dl), intermittent mild–severe neutropenia (0.3–0.66 $\times$ 10^9cells/l), thrombocytopenia (37–57 x 10^9 cells/l) and impairment of neutrophil function. The boy was born at 40 weeks gestation after a normal pregnancy, weight 3080 g (10th percentile), length 46 cm (3rd percentile). During his first 4 months of life he was admitted to hospital for three episodes of sepsis and failure to thrive. Pancreatic insufficiency was demonstrated by the quantitative pancreatic stimulation test. After an overnight fast and a bolus infusion of secretin and cholecystokin-pancreozymin, pancreatic juice was collected by aspiration over a 30-min period with a monolumen tube inserted into the duodenum. Pancreatic enzyme output (determined as output/30 min/kg) under stimulation was clearly pathological: trypsin 1.7 IU (normal value, (n.v.) $>$28.9); chymotrypsin 4.46 IU (n.v. $>$28.6); lipase 21.25 IU (n.v. $>$160.9); amylase 42.5 IU (n.v. $>$1800, but the secretion of this latter enzyme is negligible in children who are less than 6 months old and is related to diet).

Bone marrow aspirate confirmed hypoplasia with dysplastic changes and hemoglobin electrophoresis revealed an elevated Hb F. Cytogenetic analysis was attempted twice but was unsuccessful both times due to the low number of metaphases observed. No FISH analysis was performed.

Other causes of bone marrow dysfunction such as Fanconi anemia, Pearson syndrome and viral infections, and other causes of malabsorption (celiac disease, cystic fibrosis) were excluded. The eczema was associated with a cow's milk allergy and resolved when this was withdrawn from the diet.

The patient was started on supportive treatment based on the administration of oral pancreatic enzymes, vitamins (A, E, D), granulocyte colony-stimulating factor, erythropoietin, and as required, platelet, blood transfusions and intravenous broad-spectrum antibiotics.

Three years later the patient developed severe aplasia (biopsy proven) requiring frequent platelet and red cell transfusions and proved refractory to any myeloid or erythroid growth factor. A high level of serum ferritin was consistent with progressive iron overload and he was started on deferoxamine. Bone marrow transplantation seemed to provide the only chance of definitive cure for the acquired marrow aplasia. Being an only child, a search for unrelated volunteer donors was started through the national and international registries. A phenotypically HLA A, B, DR-identical donor was found within 6 months and the patient was admitted to hospital for transplantation. Typing was performed by serology for HLA class I antigens and by serological and molecular techniques for HLA class II antigens. The donor was a 33-year-old CMV negative male, with a minor ABO incompatibility (donor/recipient ABO Rh group: 0+/A+).

The transplant was carried out in an isolation room equipped with HEPA filtration. The patient received standard prophylaxis against bacteria (penicillin and pefloxacin), fungi (nystatin mouthwashes and oral fluconazole), and herpes virus (acyclovir), until engraftment or discharge. Heparin was administered up to day +21 as veno-occlusive disease prophylaxis. The conditioning regimen consisted of busulfan 4 mg/kg (orally, days −10, −9, −8, −7), thiotepa 6 mg/kg (day −6), cyclophosphamide 50 mg/kg (days −5, −4, −3, −2) and rabbit antilymphocyte serum 3.75 mg/kg (days −5, −4, −3, −2). Cyclosporin A (from day −1 to day +180, 3 mg/kg, intravenously for 3 weeks and then 6–10 mg/kg, orally) and low-dose methotrexate (15 mg/m^2 day +1, 10 mg/m^2 days +3 and +6) were administered as GVHD prophylaxis.

The patient received a total of 7.14×10^8/kg unmanipulated bone marrow nucleated cells. Neutrophil and platelet engraftment were observed on day +18 and day +41, respectively. Total transfusion requirement was 4 units of red cells and 9 units of platelets. According to the Bearman *et al*[5] criteria, major problems before engraftment were grade III mucositis and two episodes of fever of unknown origin. The patient was discharged home on day +29 post transplant. No acute or chronic GVHD was observed. Two episodes of CMV reactivation were diagnosed by detection of CMV pp65 antigenemia on days +54 and +96, respectively, and both were successfully treated with foscarnet. Cyclosporin A was tapered slowly from 6 to 12 months post transplant. Full hematological engraftment was demonstrated by the recovery of normal blood counts, normal bone marrow hemopoiesis, change of blood group, and chimerism analysis. The latter was performed by PCR of variable number of tandem repeat (VTNR). Results were always consistent with full donor chimerism. After a follow-up period of 32 months, the patient is alive and well with normal immunological and hematological reconstitution. Other clinical characteristics such as pancreatic insufficiency, short stature and moderate impairment of cognitive performance are still present. A longer follow-up period is needed to assess the benefit, if any, of bone marrow transplant on the phenotype of patients with SDS.

Discussion

Hematologic abnormalities occur commonly in SDS patients. Recently, Ginzberg *et al*[6] reported an incidence of neutropenia, anemia and thrombocytopenia of 98%, 42% and 34%, respectively, in a series of 88 cases of SDS. Another quite common finding is pancytopenia, which has been described in about 20% of patients between 1 and 6 years of age.[2] Moreover, an increased risk of leukemic transformation (in particular acute myeloid leukemia) has been observed in SDS patients, often preceded by a myelodysplastic phase and associated with clonal cytogenetic abnormalities of chromosome 7.[7,8]

The involvement of bone marrow significantly affects survival, severe infections and hemorrhage being the main reported causes of death. In addition, the prognosis of acute myeloid leukemia associated with abnormalities of chromosome 7 is very poor because of the low response rate to chemotherapy.[8]

Allogeneic bone marrow transplantation is the only definitive treatment for severe bone marrow dysfunction or clonal disorders, but, to date, the experience has been very limited in Shwachman–Diamond patients. Including this report, only 11 cases of allogeneic transplant have been reported in the literature.[3,4,9–14] Indications for transplantation were marrow aplasia (five cases), myelodysplastic syndrome (three cases) and acute myeloid leukemia (three cases). Only five of 11 were alive at follow up, and four of them were disease-free survivors with follow-ups ranging from 9 months to 5 years. Unrelated allogeneic bone marrow transplants were performed on four of 11 patients, and two of these are alive and long-term survivors. Both survivors were transplanted for marrow aplasia whereas the other two patients were transplanted after a clonal stem cell disorder had already developed. Both died, one due to graft rejection/relapse, and the other of severe graft-versus-host disease.

Two major factors can influence the successful outcome of allogeneic BMT: transplant-related mortality and rejection or relapse.

Regarding the first point, severe early toxicity with cardiomegaly, myocardial fibrosis and cyclophosphamide–associated cardiomyopathy have been described in SDS patients.[13] This worrying cardiac toxicity appears inexplicable and emphasizes the need for more research into the pathogenesis of the disorder. However, a long history of

blood transfusions with iron overload before BMT could increase the risk of severe cardiac as well as hepatic toxicity. In the present case, severe iron overload was prevented by treatment with deferoxamine. On the other hand, the conditioning regimen, based on three alkylating agents without total body irradiation, was tolerated very well with limited toxicity and rapid and sustained engraftment.

Regarding the risk of rejection/relapse, a crucial point is the reason for and the timing of transplantation. The use of allogeneic BMT once clonal marrow disorders or secondary leukemic transformation have already developed may be associated with a low probability of success. These disorders usually have a less favorable outcome in most series of non-SDS patients.[15]

On the basis of these observations, we would suggest that BMT be considered for severe pancytopenia or marrow aplasia in SDS as soon as they develop.

The current availability of a large panel of volunteer donors and of cord blood banks increases the chances of identifying an alternative source of hematopoietic stem cells for the transplant, when no donor has been identified in the family. This could translate into a higher number of patients who could benefit from allogeneic BMT. Moreover, improvement in HLA molecular typing allows optimum matching with a decreased risk of graft rejection and graft-versus-host disease.[16]

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