

## Allografting

# Transfusion-dependent congenital dyserythropoietic anemia type I successfully treated with allogeneic stem cell transplantation

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### Summary:

Until recently, therapy for patients with severe congenital dyserythropoietic anemia (CDA) has been limited to blood transfusions and chelation therapy. Three children with transfusion-dependent CDA type I underwent allogeneic stem cell transplantation (SCT) from matched sibling donors. Conditioning was with cyclophosphamide 50 mg/kg/day for 4 days, busulphan 4 mg/kg/day for 4 days, and antithymocyte globulin (ATG) 30 mg/kg for four doses pre-SCT. All patients engrafted and are alive, and transfusion independent. To our knowledge, this is the first report of successful SCT in the management of CDA type I.

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### Patients and methods

From November 1995 to September 1999, three patients (two boys and one girl) with blood transfusion-dependent CDA type I received allogeneic SCT at KFSH&RC. Two patients were diagnosed at 2 months of age; the third was diagnosed at 6 months. Diagnosis was confirmed by demonstrating the dyserythropoietic megaloblastic changes in the form of intercytoplasmic and internuclear bridging between separated erythroblasts, binucleation and erythroid hyperplasia.

Ages at SCT were 1.8, 10 and 4.4 years. All patients had been transfusion dependent prior to SCT. Serum ferritin levels prior to SCT were 530, 1469, 1890  $\mu\text{g/l}$ , respectively and thus only the last two patients had required chelation therapy with deferoxamine. All patients had hepatosplenomegaly at presentation; one had undergone splenectomy pre-SCT because of increased transfusion requirements. All had borderline elevated liver function tests and mild hyperbilirubinemia. No liver biopsies were done. Patients had not had any other medications prior to SCT.

Donors were HLA-identical siblings and had normal blood counts. Cytomegalovirus (CMV) serology indicated that one patient was CMV-seronegative and all donors were CMV-seropositive. Harvested bone marrows were not manipulated; the CD34-positive cell counts were 7.3, 4.7 and  $11 \times 10^6/\text{kg}$  of recipient body weight for each of the three patients, respectively. Conditioning therapy consisted of busulfan (BU) 4 mg/kg p.o. in divided doses daily on days -10, -9, -8 and -7 (total dose of 16 mg/kg), cyclophosphamide (CY) 50 mg/kg once daily i.v. on days -5, -4, -3 and -2 (total dose of 200 mg/kg). Antithymocyte globulin (ATG) was given i.v. at a dose of 30 mg/kg on days -5, -4, -3 and -2 (total of four doses).

Graft-versus-host disease (GVHD) prophylaxis was cyclosporin A in two patients and cyclosporin A and methotrexate in the third.

All patients were treated in HEPA filtered rooms and were isolated until their absolute neutrophil count (ANC) was greater than  $0.5 \times 10^9/\text{l}$  for 3 consecutive days. One patient received CMV IVIG (seronegative recipient and seropositive donor) at a dose of 4 ml/kg on day -2 and 1 ml/kg weekly post SCT for six doses. The other two patients (CMV-seropositive) were given IVIG every 2 weeks at a dose of 0.5 g/kg from day -4 until day +90.

The congenital dyserythropoietic anemias (CDA) are a rare group of disorders of unknown etiology characterized by marked ineffective erythropoiesis, secondary hemochromatosis and specific cytopathologic findings in the nucleated erythrocytes on bone marrow examination. Three types have been identified. CDA type I can manifest during the neonatal period or at any age thereafter up to middle age. The severity of anemia is variable in different patients. Patients may also have jaundice, hepatosplenomegaly and dysmorphic features such as syndactyly, absence of phalanges, and dysplastic nails.<sup>1,2</sup> The bone marrow typically shows megaloblastoid erythroid hyperplasia and nuclear chromatin bridges between erythroblasts. Until recently, the management of this disorder has been limited to blood transfusions when needed and chelation therapy as necessary.

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All patients received acyclovir 45 mg/kg/day from day -3 to day +28. All blood products were leukocyte-filtered and irradiated.

## Results

Engraftment was defined as an increase in the ANC to  $\geq 0.5 \times 10^9/l$  for 3 consecutive days. All patients engrafted at 20, 22 and 16 days post SCT. The days for a self-sustaining platelet count of  $\geq 20 \times 10^9/l$  were 24, 24 and 33 days post SCT for the three patients, respectively. Bone marrow examination post SCT showed that all the abnormal morphological changes were reversed in all patients, with evidence of normal trilineage hematopoiesis. One patient developed acute GVHD (grade III) of the gut but responded to steroids. One patient developed chronic GVHD of the skin 1 year post SCT and is currently on therapy, and his symptoms are under control. All three patients are alive and transfusion independent at 5, 2.5 and 2 years, respectively.

## Discussion

The severity of anemia in CDA type I depends on the degree of ineffective erythropoiesis. One study of a large group of such patients found that 48% of affected infants required blood transfusions during the first month of life; all but two became transfusion-independent thereafter.<sup>1</sup>

Earlier studies have suggested that serum erythropoietin levels in affected patients are lower than expected for the degree of anemia. A recent trial of recombinant human erythropoietin over 18 weeks in eight patients with CDA type I failed, however, to show any significant effect on the hemoglobin levels.<sup>3</sup>

More promising is the role of interferon- $\alpha_2$  in the management of this disease since it has been shown to have a beneficial effect on these patients. Five cases were reported to have shown a hematological response to this modality, with an increase in hemoglobin levels and reduction in bilirubin levels.<sup>4,5</sup> More cases have been reported lately with comparable satisfactory responses to interferon therapy.<sup>6,7</sup> Although all the reported cases seemed to respond favorably to interferon, one concern about this modality is that despite the clinical improvement, the erythroblasts on bone marrow examination continued to show internuclear chromatin bridges and other dysplastic changes<sup>4</sup> raising serious questions about the long-term outcome of the treated patients. Furthermore, continuous maintenance on interferon therapy appears to be necessary to uphold the response.

SCT may be curative for patients with hemoglobinopathies.<sup>8,9</sup> In patients with thalassemia major, outcome has been shown to be influenced by the presence of hepatomegaly, portal fibrosis, and ineffective chelation therapy before SCT. Class I patients have none of these risk factors, class II patients have one or two, and class III patients have all three risk factors. Conditioning regimens using busulfan and cyclophosphamide have resulted in excellent outcomes, with a probability of disease-free survival of 91%, 83%, and 58% for thalassemic children in class I, II and III,

respectively.<sup>8,9</sup> Furthermore, SCT has been successfully performed in other congenital anemias with dyserythropoiesis; we have recently reported three patients with hereditary sideroblastic anemia who underwent allogeneic SCT successfully using a similar conditioning regimen.<sup>10</sup> Others have reported similar successful cases.<sup>11,12</sup> More recently, Iolascon *et al*<sup>13</sup> reported successful stem cell transplantation in one case of severe, type II congenital dyserythropoietic anemia.

In our series, we transplanted three children with transfusion-dependent CDA using busulfan and cyclophosphamide for conditioning. ATG was added to help reduce the risks of graft rejection. All patients engrafted and tolerated the transplantation with no major toxicity. Our patients did not receive interferon prior to SCT. We now believe, however, in light of the emerging data about its efficacy in the management of this disorder, that a trial of interferon- $\alpha_2$  is warranted before embarking on an aggressive therapeutic modality such as SCT.

SCT appears, nonetheless, to offer a more radical solution to the problem and may be considered as one of the therapeutic options for patients with transfusion-dependent CDA type I.

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