

Case report

Unrelated bone marrow transplantation for leukocyte adhesion deficiency

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Summary:

The severe form of leukocyte adhesion deficiency type I (LAD-I) usually leads to death early in life. Allogeneic haematopoietic transplantation is the only cure. Unrelated transplantation has been reported only once. We describe three children with LAD-I transplanted with T cell non-depleted bone marrow from unrelated HLA-matched donors. All patients engrafted, one of them at second transplant. One patient developed grade I and one grade II acute GVHD. Two patients are alive, one of them with a decrease in CD11/CD18 expression. Early referral for HLA-matched unrelated BMT is a reasonable option for patients with LAD-I lacking an HLA-matched related donor.

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Leukocyte adhesion deficiency type 1 (LAD-I) is a rare autosomal recessive disorder characterized by defective leukocyte adhesion to endothelial cells and defective migration to inflammatory sites. LAD-I is caused by mutations in the gene encoding the $\beta 2$ -integrin CD18 on chromosome 21, resulting in absent or markedly reduced expression of CD11a/CD18 (LFA-1), CD11b/CD18 (MAC-1, CR3) and CD11c/CD18 (p150,95). In the severe form of the disease, leukocytes express less than 1% of normal levels of CD18. Patients have severe bacterial infections and usually die before 10 years of age.¹ The only cure for patients with severe LAD-I is hematopoietic stem cell transplantation.² Published experience refers mainly to related bone marrow transplantation, with T cell depletion being performed in HLA-mismatched donor-recipient pairs.^{3–7}

In this report, we review our experience with HLA-matched unrelated BMT for the correction of LAD-I between 1992 and 1998. Three LAD-I patients without HLA-identical siblings were diagnosed and treated at Hôpital Sainte-Justine during that period. In all cases, leukocyte CD11a, CD11b and CD18 expression was less than 1% of normal levels. One patient was transplanted in another medical center (Hôpital Maisonneuve-Rosemont). HLA typing was performed by standard serological methods for HLA-A and -B, and by molecular biology for DR β 1. Bone marrow was not T cell-depleted. Post transplant engraftment was assessed by monitoring neutrophil and platelet counts and by leukocyte cell surface expression of CD11a, CD11b and CD18 using flow cytometry.

Case reports

Patient 1

A boy presented with necrosis of the upper lip, sterile abscess at a vaccination site, and thumb abscess with marked leukocytosis (up to 79×10^9 WBC/l) in the first 4 months of life. Leukocyte CD11/CD18 expression was less than 1% of normal levels. He was 1 week old at first infection and 1 year old at diagnosis. He had no HLA-identical sibling. He was admitted several times a year because of recurrent bacterial infections. Most of them were severe, including abscesses, pneumonia, cellulitis, stomatitis, septicemia, laryngitis and bilateral pneumonia. Chronic ileocolitis developed, associated with splenomegaly and pancytopenia. Treatments included antibiotics and, on one occasion, granulocyte transfusions. In 1992, at the age of 8 years, he was transplanted with an HLA-matched unrelated bone marrow. Pre-transplant first generation hepatitis C serology was negative. The conditioning regimen was busulfan p.o. (total dose 16 mg/kg) and cyclophosphamide (total dose 200 mg/kg). The total nucleated cell dose was 4.8×10^8 /kg. No prophylactic antibacterial antibiotics were given. GVHD prophylaxis comprised short-course methotrexate, cyclosporin and methylprednisolone. GM-CSF was administered on days +1 to +26. BMT was complicated by *Staphylococcus epidermidis* and *Pseudo-*

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monas spp. sepsis, acute renal failure and haemorrhagic cystitis. The neutrophil count was $>0.5 \times 10^9/l$ on day +18 with normal expression of CD11/CD18, and the platelet count was $>50 \times 10^9/l$ on day +22. Grade II acute skin GVHD was diagnosed on day +42, and responded to increased immunosuppressive therapy which was stopped on day +180. Hepatitis C was diagnosed 1 year after transplantation. Retrospective screening of the granulocyte donors with second generation hepatitis C serology found that one of them was positive. The corresponding transfusion was given before transplantation and the donor's serology was negative at that time. Despite α -interferon treatment, cirrhosis developed with portal hypertension and esophageal varicosities. He was 16 years old at last follow-up, 8 years after BMT. His height was below the 5th centile, he had developmental delay with a deficit in concentration and attention, and academic difficulties. He had normal leukocyte expression of CD11/CD18 and did not develop any major infection after engraftment.

Patient 2

A 45-day-old girl presented with omphalitis, *Pseudomonas* spp. septicemia, oral candidiasis, failure to thrive and marked leukocytosis (up to 80×10^9 WBC/l). Leukocyte CD11/CD18 expression was less than 1% of normal. She was 2 weeks old at first infection, and 1 month old at diagnosis. She had no HLA-identical sibling. At the age of 8 months, she was admitted to the ICU because of respiratory failure caused by aspiration pneumonia, leading to a diagnosis of tracheo-oesophageal fistula, possibly due to a local infection. She received multiple granulocyte transfusions. She was transplanted in 1998 at the age of 12 months with marrow from an HLA-matched unrelated male donor, while still under mechanical ventilation. The conditioning regimen was busulfan (total dose 15 mg/kg) administered via jejunostomy, cyclophosphamide (total dose 200 mg/kg), etoposide (total dose 900 mg/m²), and 2 mg/kg antithymocyte globulin (ATG) (Thymoglobulin; Sangstat, Fremont, CA, USA) i.v. once daily on days -2, -1, +1 and +2. The total nucleated cell dose was 7.3×10^8 /kg. GVHD prophylaxis was short-course methotrexate and cyclosporin. She received granulocyte transfusions until engraftment. Transplantation was complicated by severe *Escherichia coli* sepsis. Neutrophil count was $>0.5 \times 10^9/l$ on day +15, but without expression of CD11/CD18. All leukocytes were of female origin by chromosomal FISH analysis, confirming non-engraftment. Inadequate administration of busulfan by jejunostomy was suspected, and a second bone marrow transplant was performed on day +74 using cryopreserved marrow (7.2×10^8 nucleated cells/kg) from the original donor. The conditioning regimen of the second transplant was busulfan (total dose 21 mg/kg) administered by jejunostomy under direct medical supervision, cyclophosphamide (total dose 200 mg/kg), etoposide (total dose 900 mg/m²), and ATG (Atgam, Upjohn, Kalamazoo, MI, USA) 30 mg/kg in two divided doses daily i.v. on days -2, -1, +1 and +2. GVHD prophylaxis was a short course of methotrexate and cyclosporin. Neutrophil count was $>0.5 \times 10^9/l$ and platelet count was $>50 \times 10^9/l$ on day +22, with normal leukocyte CD11/CD18 expression, and 100%

leukocytes of donor origin by FISH analysis. Grade I acute GVHD was diagnosed by skin biopsy on day +30, which was responsive to steroids. Gastric hemorrhage led to partial gastrectomy, complicated with *Pseudomonas aeruginosa* sepsis. She was finally discharged on day +130, but was readmitted because of aspiration pneumonia, leading to death 149 days after the second transplant. Necropsy showed massive aspiration pneumonia, attributed to the persistent tracheo-oesophageal fistula. There was no sign of GVHD at necropsy and leukocyte expression of CD11/CD18 was normal before death.

Patient 3

A boy presented at 4 days of age with axillary adenitis, and oral and perineal candidiasis. In the first 3 months of life, he had several episodes of upper respiratory tract infections and impetigo, and marked leukocytosis (up to 126×10^9 WBC/l). Leukocyte CD11/CD18 expression was less than 1% of normal levels. He was 4 days old at first infection, and 4 years old at diagnosis. He had no HLA-compatible sibling. Further infections were abscessed *Pseudomonas* pneumonia, chronic periodontitis, bronchiectasies, perianal abscess, epiglottitis, cutaneous granulomas, typhlitis with septic shock leading to subtotal colectomy and ileostomy. He underwent HLA-matched unrelated bone marrow transplantation in 1998 at the age of 12 years. The conditioning regimen was busulfan p.o. (total dose 20 mg/kg), cyclophosphamide (total dose 200 mg/kg), etoposide (total dose 900 mg/m²), and 2 mg/kg ATG (Thymoglobulin; Sangstat) i.v. once daily on days -2, -1, +1 and +2. Total nucleated cell dose was 3×10^8 /kg. No prophylactic antibacterial antibiotics were given. GVHD prophylaxis consisted of cyclosporin and short course methotrexate. The transplant was complicated with *Enterobacter faecalis* septicemia. The neutrophil count was $>0.5 \times 10^9/l$ on day +28, with normal leukocyte expression of CD11/CD18. The platelet count was $>50 \times 10^9/l$ on day +41. GVHD never developed. He was 15 years old at last follow-up, 3 years after BMT. Physical examination was normal. A slight obstructive syndrome was observed in his pulmonary function tests. Last examination of CD11/CD18 expression revealed that only 60% of leukocytes expressed CD11/CD18. No serious infection has developed since engraftment.

Discussion

There are few published reports on bone marrow transplantation for correction of LAD-I. Since 1977, when Camitta *et al*⁷ first reported two infants transplanted for LAD-I, only one team reported more than two cases, all of them of related BMT.³⁻⁵ To our knowledge, there is only one case of related cord blood and one case of unrelated bone marrow transplantation reported to date.^{8,9} Here, we report three cases of unrelated T cell non-depleted BMT in children with LAD-I.

The outcome of these transplants has to be interpreted in the light of the clinical condition at the time of BMT. All three patients experienced life-threatening infections before

transplantation. The only death was related to an oesophago-tracheal fistula caused by a pre-transplant infection, and not to the transplant procedure itself. Hepatic sequelae in patient 1 were probably related to a pre-transplant hepatitis C-positive granulocyte transfusion, and thus would have been avoided with an earlier transplant. Serious and complex pre-transplant infections, as expected in these patients within the first months of life, enhance the risk of post-transplant complications. This report thus stresses the importance of early referral to transplantation units for patients with the severe form of LAD-I even in the absence of HLA-matched sibling donors.

Thomas *et al*⁵ reported 14 transplants using one-haplo-type HLA-mismatched ($n = 8$), partially HLA-matched ($n = 1$) or HLA-matched ($n = 5$) related donors. Ten patients were alive and well 12 months to 12 years following BMT. Five out of 14 patients did not engraft. Two of our patients (patients 1 and 3) engrafted rapidly. Last CD11/CD18 results for patient 3 may indicate the potential for late rejection. Patient 2 engrafted after a second transplant. Failure of the first transplant was probably the result of inadequate busulfan administration, and could have been prevented by the use of i.v. busulfan or pharmacokinetic monitoring.

In the series reported by Thomas *et al*,⁵ GVHD was a major complication, which occurred in more than half of the patients and led to death in three cases. Two of our patients received ATG as part of the conditioning regimen from day -2 to day $+2$. The third patient received methyl-prednisolone after transplant. None of the grafts were T cell depleted. Two of the three patients developed grade I or II GVHD. In both cases, GVHD was easily controlled by increasing immunosuppression. Thus, T cell depletion does not seem mandatory in these unrelated transplants.

In our experience, HLA-matched unrelated bone marrow transplantation is an acceptable treatment for patients with the severe form of LAD-I, who lack an HLA-matched related donor. Because serious pre-transplant infections may compromise final outcome, patients with severe LAD-I must be referred promptly to a transplant center, even in the absence of an HLA-matched related donor. In our small number of patients, T cell depletion of the graft was unnecessary in HLA-matched unrelated transplants.

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