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LETTER TO THE EDITOR

Prompt recovery of recipient hematopoiesis after two consecutive haploidentical peripheral blood SCTs in a child with leukocyte adhesion defect III syndrome

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Leukocyte adhesion deficiency (LAD) type III is a rare syndrome characterized by severe recurrent infections, leukocytosis and increased bleeding tendency. All integrins are normally expressed; yet, a defect in their activation leads to the observed clinical manifestations.[1] This specific genetic abnormality is a combined defect in both upstream and downstream integrin regulatory effectors, namely, CaIDAG-GEFI and Kindlin-3, respectively.[2] Both these effectors have a role in regulating integrin activation in plts and leukocytes. Hematopoietic SCT (HSCT) is the only treatment that might correct this life-threatening disease. Here, we present a report of a prompt recovery of recipient hematopoiesis after two haploidentical HSCTs performed in a 3.5-year-old girl with LAD III disease.

As previously described,[1] this girl was born to second-degree consanguinous parents, and the diagnosis of LAD III was made after several recurrent infections and bleeding episodes since birth and a family history of one sister who died at the age of 15 months after severe infection and massive pulmonary bleeding. In addition, both sisters showed increased bone density on skeletal survey. On admission, she presented with a swelling of her right mandible after a tooth extraction 2 months previously. A biopsy from this lesion revealed sub-acute inflammation with eosinophils, mononuclear infiltration and no malignancy. Wound culture demonstrated pseudomonas, for which she was treated with pipracillin together with tazobactam. Blood count revealed a WBC count of 36×10^9/l, hemoglobin of 10.4 g per 100 ml and a plt count of 354×10^9/l. Bleeding time was >10 min. As she did not have a matched sibling donor, it was decided to perform a haploidentical peripheral blood SCT (PBSCT) from her mother. Peripheral stem cells were collected after priming with G-CSF, and T-cell depletion was performed by a positive selection of CD34+ cells with immunomagnetic beads. Conditioning regimen before the first transplantation included i.v. melphalan 140 mg/m^2, i.v. thiotepa 10 mg/m^2, i.v. fludarabine 200 mg/m^2 and i.v. ATG (Fresenius, Bad Homburg, Germany) 25 mg/m^2. On day 0, she received 18.3×10^6 CD34+ cells/kg. Except for fever and neutropenia, treated with broad-spectrum antibiotic therapy, no other complications occurred. She did not engraft and her own marrow recovered 4 weeks after transplantation.

Given the fact that she recovered from her first transplantation without any toxicity, it was decided to perform another haploidentical PBSCT from her mother. At 68 days after the first transplantation, she started conditioning for the second haploidentical transplantation that included total lymph node irradiation 700 cGy, oral BU 12 mg/kg and i.v. CY 200 mg/kg. On day 0, she received 14.7×10^6/kg CD34+ cells. At 2 weeks after transplantation, there was a rise in leukocyte count. Chimeric examination showed no engraftment of donor cells and a recovery of the patient's own cells. It is noteworthy that, during the second transplant, similar to the first one, no major toxicity occurred except for fever and neutropenia. She was discharged 42 days after the second transplantation with a normal leukocyte count and thrombocytopenia.

Compared with LAD I, in which successful allogeneic matched donor, haploidentical donor[3] and unrelated donor transplantations[4] have been reported, detailed data regarding allogeneic HSCT in LAD III are scarce. Kuijpers *et al*.[5] discussed the natural history and early diagnosis of the LAD I/variant syndrome, a term synonymous with LAD III. They described three patients who underwent HSCT, one of whom died of veno-occlussive disease, yet no details regarding donor type or conditioning regimen were documented. In their recent publication,[6] four patients who underwent HSCT were reported, with only one who survived after SCT.

The prompt recovery of our patient's own hematopoietic stem cells after two consecutive haploidentical transplants is unique. It is noted that all patients, including the present one with LAD III described by Kilic *et al*,[1] had increased bone density on X-ray similar to that seen in patients with osteopetrosis. In a report from the EBMT group on the outcome of HSCT in autosomal recessive osteopetrosis,[7] patients who received a graft from an HLA-haplotype-mismatch related donor had a 5-year disease-free survival of only 24% in contrast to the 73% 5-year disease-free survival found in recipients of a genotype HLA-identical HSCT. Causes of death after HSCT were graft failure and early transplant-related complications. In light of these results, the non-engraftment in our patient could be partially explained by her increased bone density, yet her prompt hematopoetic recovery, even after the second myeloablative regimen given 68 days after the first transplant, is hard to explain. A somewhat similar situation is observed in thalassemia, in which chronic hemolysis results in a compensatory hyperactive marrow manifested as extramedulary hematopoiesis and highly nucleated red cells in peripheral blood. A high rate of rejection and autologous recovery were documented in thalassemia major class 3 after myeloablative conditioning.[8] To increase

the engraftment rate without augmenting treatment-related mortality, a new conditioning regimen was created for class 3 thalassemic patients using 45 days of hydroxyurea and azathioprine, followed by fludarabine, BU and CY, with the incidence of rejection that decreased from 30 to 8% only.[9] The results of BMT from a non-identical sibling or parent in thalassemia major were even worse, with only 45% of patients achieving sustained engraftment. All the three patients who received the three Ag-mismatched graft, failed to engraft.[10] In LAD III patients, a hyperactive marrow is also observed with leukocytosis (resembling the increased nucleated red cells in thalassemia peripheral blood) as being one of the hallmarks of the disease. Both hyperactive BM and osteopetrosis documented in the patient described might account for the prompt hematopoietic recovery after two consecutive haploidentical transplants conditioned either with a reduced-intensity regimen or a myeloablative one.

Although this experience is limited to one patient, the unique clinical picture presented herein, together with the limited success in allogeneic HSCT reported in other patients with the same syndrome, presents a tentative suggestion for future patients to use myeloablative regimens without T-cell-depleted grafts.

Conflict of interest

The authors declare no conflict of interest.

R Elhasid[1,4], SS Kilic[3], M Ben-Arush[1,4], A Etzioni[1,4] and JM Rowe[2,4]
[1]*Department of Pediatric Hemato-Oncology, Rambam Health Care Campus, Haifa, Israel;*
[2]*Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel;*
[3]*Department of Pediatric Immunology, Uludag University School of Medicine, Bursa, Turkey and*
[4]*Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*
E-mail: r_elhasid@rambam.health.gov.il

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