Successful fludarabine-based hematopoietic stem cell transplantation in a pediatric patient with idiopathic CD4+ lymphocytopenia.


Abstract: Idiopathic CD4+ lymphocytopenia (ICL) is a rare immunodeficiency disease with severe CD4 T-cell depletion, leading to serious opportunistic infections. The optimal treatment of ICL has not been determined, especially in severe form of the disease. Here, we report an eight-yr-old girl with ICL who was successfully treated with fludarabine-based conditioning HSCT. To the best of our knowledge, this is the first pediatric ICL case that was treated by HSCT. Allogeneic HSCT with a reduced intensity condition (RIC) regimen may be a feasible and curative treatment option in ICL patients with recurrent life-threatening complications.

ICL is a rare PID first defined in 1992 by the Centers for Disease Control and Prevention (1). It has been characterized by CD4+ T-lymphocyte depletion (absolute CD4+ T-lymphocyte level <300 mL or <20% of total lymphocytes at a minimum of two separate time points at least six wk apart), no serological evidence of HIV infection, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T-cells. Most cases of ICL are adults, but some ICL have been described in children (2–4).

Here, we report the first child with ICL who has been successfully treated by fludarabine-based HSCT.

Case report
An eight-yr-old girl with diagnosis of ICL was referred to our center as a potential candidate for HSCT due to frequent life-threatening infections (respiratory infections and meningitis). She had a three-yr history of widespread molluscum contagiosum lesions as she was five yr old. She had been receiving IVIG treatment every three wk. She was under antifungal treatment for more than six months during the last year because of proven pulmonary aspergillosis. Because of resistant chronic sinusitis, she underwent endoscopic surgery to drain the sinuses three months before transplantation. At admission, she had bronchiectasis due to recurrent pulmonary infections.
She had been diagnosed with ICL by the Immunology, Asthma & Allergy Research Institute, Tehran, after rule out of all other immune deficiencies. Anti-HIV antibody tests and HIV DNA polymerase chain reaction test were done on two separate blood samples with two months interval to rule out HIV infection. Expression of HLA class I and II, CD4 transcription and expression, Th-POK sequence, LCK sequence, and expression and transcription of p56lck were carried out to rule out other immune deficiencies. Several peripheral blood flow cytometry studies showed CD4+ T-cells of 3–12% (<20% of total T-cells (1)) and CD4+/CD8+ ratio of less than 1/3.

As her parents were first cousins, we did an extended family search, and finally, her 68-yr-old maternal grandfather was completely matched with her in high-resolution HLA typing. The conditioning protocol for PIDs was approved by the institutional review board, and written informed consent was obtained from the parents. She received a RIC regimen consisting of fludarabine, 30 mg/m², administered intravenously on five consecutive days (days –8 to –4), melphalan, 70 mg/m², intravenously on two consecutive days (days –3 and –2), and antithymocyte globulin (Atgam; horse), 10 mg/kg for four consecutive days (days –4 and –1). The donor received subcutaneous injections of G-CSF as mobilizing agent at doses of 5 µg/kg daily from day –4 to –1. The total nucleated and CD34+ cell dose infused was 8.4 × 10⁹/kg and 6.7 × 10⁹/kg, respectively.

Cyclosporine (1.5 mg/kg/day IV) was administered as GVHD prophylaxis from day –1 and followed by 3 mg/kg IV from day +7. It was switched to an equivalent oral dose (9 mg/kg) after discharge from hospital and tapered off after six months of treatment. Acyclovir, trimethoprim-sulfamethoxazole, and amphotericin B were given as infection prophylaxis. IVIG (0.5 g/kg weekly) was administered at day –9. She received G-CSF from day +8.

The patient was successfully treated for *Staphylococcus* bacteremia on day +3. Neutrophil engraftment occurred on day +10 and platelet engraftment on day +11. She developed grade III acute GVHD of the skin on day +12 and was successfully treated with corticosteroids, which were weaned off by day +120 without GVHD recurrence. She received pre-emptive gancyclovir for CMV antigenemia on day +27. Studies demonstrated >95% donor chimerism for all studies after day +15. Post-transplant CD4+ percentage and CD4+/CD8+ ratio normalized and remained in the normal range based on multiple peripheral blood flow cytometry. The last lab studies in +36-month post-transplantation showed WBC of 10.8 cells/µL, neutrophil count of 5616 cells/mm³, CD4+ of 2857 cells/mm³, and CD8+ of 1632 cells/mm³ (ratio = 1.75).

Following treatment, her respiratory symptoms were resolved, and her pulmonary function tests were significantly improved. The bronchiectasis changes recorded on high-resolution computed tomography of her chest remained stable, and the focal infiltrates resolved. No serious infection has developed during the 36-month follow-up period. She has normal growth and development now.

**Discussion**

ICL is a rare PID in which there is an unexplained deficit of CD4 T-cells and is usually detected after the occurrence of an opportunistic infection. Several hypotheses have been suggested as a potential mechanism for CD4 depletion, including increased T-cell apoptosis, defective cytokine production, regenerative failure of hematopoietic stem cell precursors, biochemical failure of the CD3-T-cell receptor pathway by p56 Lck kinase alteration, impaired thymic T-cell maturation, and CD4 T-cell autoantibody (4, 5).

Clinical presentations vary widely from asymptomatic to life-threatening situations caused by frequent opportunistic infections, as shown in our patient. The bronchiectasis in pediatric PID patients can be halted or improved after treatment (6), as shown in our patient.

Current treatment of ICL is mainly symptomatic and consists of prevention and treatment of opportunistic infections. However, some experimental approaches have been suggested to enhance CD4 T-cell counts. A few reports showed that administration of interferon gamma in ICL patients resulted in clinical recovery from mycobacterial and cryptococcal infections (7, 8). Also, interleukin-2 has been suggested to increase CD4 counts and improve the outcome in ICL patients (9–11).

Allogeneic HSCT for aplastic anemia in an ICL patient resulted in complete restoration of immune function and was suggested as a potentially curative therapy for ICL (12). Recently, a 40-yr-old ICL patient has been treated with allogeneic HSCT (13). He received fludarabine plus low-dose total-body irradiation as the conditioning regimen.

Myeloablative conditioning regimen may be accompanied by the risk of mortality in PID patients, especially with the existence of comorbid conditions. The RIC regimen may lead to more occurrence of mixed chimerism and graft rejection (14–16), but is well tolerated and associated with high rates of engraftment, reduced
transplantation-related mortality (17–19), shorter inpatient hospital stays, and reduced need for transfusions (20). Despite the use of a RIC regimen, the patient achieved and retained a stable full chimerism. She received only one unit of packed red blood cells and one unit platelet transfusion and was discharged from hospital on day +16.

In conclusion, allogeneic HSCT can be considered as a potentially curative treatment in ICL patients with recurrent life-threatening complications. The severity of these complications must be balanced with the risks of transplantation.

Conflict of interest

The authors declare no competing financial interests.

Authors’ contributions

AAH – concept/design, data analysis/interpretation, critical revision of the article; AH – data collection/analysis, drafting the article; ZP and MN – data collection/interpretation; AG – approval of the article.

References


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All in-text references underlined in blue are linked to publications on ResearchGate, letting you access and read them immediately.