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Severe thalassemia alpha diagnosed and prenatally treated in Poland: clinical follow-up of case with more than one hematological disease

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A case report of a patient with severe thalassemia alpha and concomitant hydrops fetalis (BHFS) was published by Skulimowska et al. [1] in the December 2019 issue of "Acta Haematologica Polonica". A hypotrophic female preterm newborn of Vietnamese origin was diagnosed with the most severe type of alpha thalassemia with hemoglobin (Hb) Bart's. No functionally effective chain of alpha globin was produced due to deletion of all four alpha globin genes [2]. In the past this used to be a lethal syndrome, but nowadays intrauterine transfusions and perinatal intensive care offer the chance of a cure. The major adverse long-term outcome is growth retardation and neurodevelopmental delay.

In the neonatal period and the first months of life, the patient was transfusion-dependent and required packed red blood cells (PRBC) transfusion once a month. Chelation therapy was started early due to concomitant iron overload. Aged 8 months, the girl was referred to the pediatric hematology department in February 2014 for further PRBC transfusions. She had continued chelation therapy with deferoxamine, alimentary treatment of cow's milk protein allergy, and insufficient weight gain. At the age of 2 years, thrombocytopenia was noted in routine laboratory tests. A bone marrow biopsy allowed us to diagnose pre-B acute lymphoblastic leukemia (ALL) in August 2015 (Figure 1). The patient started treatment according to the ALL IC 2009 protocol and showed a favorable risk profile. Due to a good prednisone response on day +8 of treatment, low flow cytometric minimal residual disease (FC-MRD) 0.06% on day +15, remission on day +33, and an absence of poor prognostic cytogenetic factors, the patient was treated with a standard risk group therapeutic arm. Hepatosplenomegaly was present, and platelet and PRBC transfusions were performed depending on the laboratory results. Fever of unknown origin, *E.coli* (ESBL+) catheter-related soft tissue infection, *molluscum contagiosum*, mucositis and hepatotoxicity were complications of moderate severity. In April 2016, the child started on maintenance therapy for ALL and continued chelation therapy with the highest concentration of ferritin 3,770 ng/mL. Due to the presence of two coexisting relevant hematological disorders, the patient was referred for a hematopoietic stem cell transplantation (HSCT) procedure in September 2016. This indication had been established as a clinical option for transfusion-dependent thalassemia in accordance with references and case reports [3–5].

A conditioning regimen with treosulfan, fludarabine and tiothepa was administered in March 2017. As prophylaxis of graft rejection and graft-versus-host disease (GvHD), the patient received anti-human thymocyte immunoglobulin (thymoglobuline), cyclosporine A and methotrexate. The donor of peripheral blood hematopoietic stem cells was a 9/10 human leukocyte antigen (HLA)-matched unrelated female. Hematological recovery was stimulated with granulocyte colony-stimulating factor (G-CSF) from day +7, and leukocyte, thrombocyte and neutrophil recovery was observed on day +14. Recurrence of *molluscum contagiosum* and bloodstream infection of *Staphylococcus epidermidis MR* etiology were early complications of the peri-transplant period. Diarrhea with a positive *Clostridioidae* test, treated

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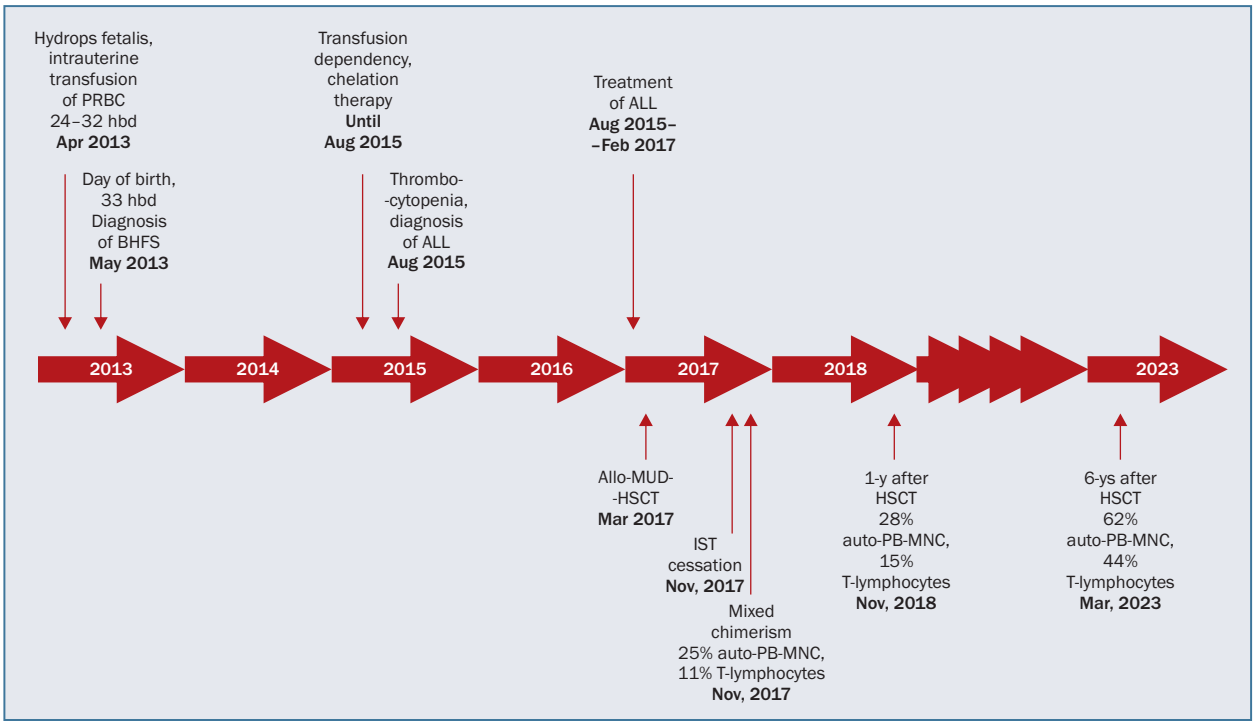

Figure 1. Timeline — horizontal arrows indicate subsequent years: 2013 to 2023; vertical arrows place event on timeline; ALL — acute lymphoblastic leukemia; allo-MUD-HSCT — allogeneic matched unrelated donor hematopoietic stem cell transplantation; auto-PB-MNC — autologous peripheral blood mononuclear cells; BHFS — hemoglobin Bart's hydrops fetalis syndrome; hbd (hebdomas) — week of pregnancy; IST — immunosuppressive therapy; PRBC — packed red blood cells

with metronidazole, and then prolonged probably due to dysbacteriosis (negative viral tests and bacterial cultures) was observed as a late complication. Secondary hypothyroidism was compensated with levothyroxine. Immunosuppressive therapy (IST) was completed in November 2017 on day +239. During the post-transplant period, an increasing mixed chimerism was noted. On IST cessation it was 41% of autologous signal in bone marrow (BM), 25% in peripheral blood mononuclear cells (PB-MNC), and 11% in T-lymphocytes. FC-MRD of ALL at that time was negative. One year after HSCT, autologous signal increased to 28% in PB-MNC and 15% in T-lymphocytes. Six years after HSCT, autologous signal reached 62% in PB, 44% in T-lymphocytes, and 89% in CD15+ cells. The patient is transfusion-independent with normal red blood cell (RBC) and Hb with constantly dropping ferritin concentration and an actual value of 508 ng/mL. Despite mixed chimerism the patient remains in a stable complete hematological remission of ALL.

Early molecular diagnostics, intrauterine transfusions and perinatal intensive care decrease the mortality risk in newborns with severe hemoglobinopathies.

In transfusion-dependent patients, the consequences of iron overload significantly influence quality and duration of life. Growth retardation and neurodevelopmental delay are strictly associated with low Hb levels [6]. HSCT is an optimal treatment in BHFS, but the results are best if performed at an early age [7]. Clinical experience is limited due to a very small number of patients. HSCT is a clinical option in transfusion-dependent thalassemia [8]. There is a high risk of complications such as GvHD, mixed chimerism and further potential secondary graft failure, but the procedure gives a chance for transfusion-independency, prolongation of lifespan, and improved quality of life.

A case report history of ALL as a second hematological disease is unique. The available data and our case support favorable results of HSCT in alpha thalassemia major. International collaboration is needed in order to share experiences, encourage research and improve outcomes.

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Authors' contributions

ASB, MMS — manuscript writing. ASB, MMS, MC — data acquisition. All authors — data check and final approval.

Conflict of interest

The authors declare no conflict of interest.

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Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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