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# Successful Salvage Haploidentical Bone Marrow Transplantation in a Child With Hemophagocytic Lymphohistiocytosis, When the Previously Matched Unrelated Donor Tested Positive for SARS-CoV-2 on the Day of Stem Cells Collection

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## ABSTRACT

The coronavirus disease 2019 pandemic has made us adjust our standards and cope with unpredictable circumstances affecting the whole world, including the medical field.

A 2-year-old boy diagnosed with X-linked lymphoproliferative disease type 2 with concomitant positive polymerase chain reaction test for Epstein-Barr virus–DNA was admitted to our transplant ward. His treatment scheme had to be modified at the last moment because of a donor disqualification due to a positive polymerase chain reaction result for severe acute respiratory syndrome coronavirus 2 just before the apheresis. We decided to perform salvage haploidentical bone marrow transplant from the patient's mother because it was the only possible option. Now, in a 5-month observation period after the hematopoietic stem cell transplantation, our patient is in good general condition. His case convinced us to redirect our approach to transplant procedure preparation. Following the European Group of Blood and Marrow Transplantation recommendations, we use cryopreserved apheresis materials to ensure the availability of stem cell products before the start of a conditioning regimen.

**T**HE worldwide outbreak of the coronavirus disease 2019 (COVID-19) pandemic forced us to face new challenges in the field as we managed patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and dealt with other medical problems in the new COVID 2019 reality. We had to redirect our approach to treatment in many branches of medicine and adjust our standards.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening systemic, hyperinflammatory syndrome. Its clinical manifestations include acute unremitting fever, lymphadenopathy, hepatosplenomegaly, and multiorgan failure. Because of a massive cytokine release, it is recognized as a cytokine storm syndrome, which requires aggressive immunosuppressive treatment. Even though we increasingly know more about its pathogenesis, diagnosis, and management, there is still plenty to discover.

HLH can be classified as primary when it is caused by some gene defects (*PRF1*, *UNC13D*, *STXBP2*, *STX11*, *RAB27A*, *LYST*, *AP3B1*, *SH2D1A*, and *XIAP/BIRC4*) or secondary when it is acquired and triggered by factors such as infection, malignancy, autoimmune disease, or postallogeic hematopoietic stem cell transplantation (HSCT) [1].

X-linked lymphoproliferative disorder is especially challenging for physicians because of its complex medical manifestation. It is considered a primary immune deficiency syndrome with clinical presentation of HLH and special vulnerability to Epstein-Barr virus (EBV) infection. An impaired immune

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system and insufficient number of CD27 memory B cells make it difficult to generate an effective response to EBV, so the infection may be chronic and lead to severe complications such as bone marrow failure, irreversible hepatitis, or lymphoma. Although the exact connection between EBV and X-linked lymphoproliferative disorder is not yet well established. It is possible that EBV infection triggers HLH in secondary forms of the syndrome and also in its familial types. To distinguish the kind of disorder presenting with the same clinical manifestation, it is vital to obtain a molecular diagnosis. It is recommended to aim at allogeneic HSCT in genetically verified or familial types of disease (Fig 1) [2].

## CASE REPORT

Herein we present a prevalent problem in the COVID-19 pandemic era, namely how to rescue a patient when the matched unrelated donor tested positive for SARS-CoV-2 on the day of stem cell collection and the patient had almost finished his conditioning regimen.

A 2-year-old boy was diagnosed with X-linked lymphoproliferative disease type 2 (OMIM 300635) on April 30, 2020. The disorder is characterized by the sex-linked recessive inheritance.

A molecular genetic test using targeted next-generation sequencing analysis was performed, revealing 2 nucleotides deletion in XIAP gene (HIAPNM\_001204401.1:c.[393\_394del];[0], NP\_001191330.1:p.Arg131SerfsTer3).

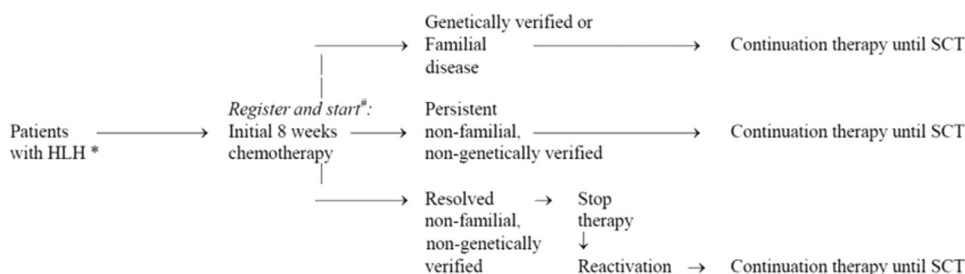
The primary manifestation of X-linked lymphoproliferative disease type 2 in our patient was HLH, which was treated with dexamethasone monotherapy according to the national coordinator's recommendations. Because the patient had a positive polymerase chain reaction (PCR) test for EBV-DNA, we hypothesized that EBV infection was a trigger in his case. Nevertheless, according to HLH-2004, he fulfilled criteria and was scheduled for HSCT after achievement of controllable disease [2]. HLA typing including class I and II antigens was performed on June 3, 2020. No matched family donor was selected, but many potential non-related donors were recognized in the Polish bone marrow donor registry. The patient was admitted to the Department of Paediatric Bone Marrow Transplantation, Oncology, and Haematology in Wrocław on October 15, 2020 in good clinical condition and remission of HLH. It was decided to include rituximab (MabThera, Roche, Grenzach-Wyhlen, Germany) in treatment at a dose of 375 mg/m<sup>2</sup> body surface area (BSA) as EBV-induced

posttransplantation lymphoproliferative disorder prophylaxis [3]. In the course of the conditioning regimen, the patient was planned to receive treosulfan (36g/m<sup>2</sup> BSA), fludarabine (5 × 30mg/m<sup>2</sup> BSA), thiotepa (2 × 5 mg/kg body weight [b.w.]), and antithymocyte globulin (ATG) at a dose of 45 mg/kg body weight, but only 7.5 mg/kg body weight of ATG was administered owing to extensive allergic reactions on day 3. Unexpectedly, the patient's transplantation treatment scheme had to be modified at the very last moment because the donor was disqualified because of a positive PCR result for SARS-CoV-2 just before the apheresis. A solution had to be found immediately and the only possible option was to perform salvage haploidentical bone marrow transplant with post-transplant cyclophosphamide (PTCY) as a method of graft-versus-host disease (GvHD) prophylaxis. The patient's 6 of 10 HLA allele-matched mother was chosen immediately as a donor and was cleared for donation. Our solution was discussed and approved by Prof. M. Albert (Munich, Germany), who has had extensive and excellent experience on haploidentical HSCT (with PTCY) in patients with primary immune deficiency disorders [4].

Finally, our patient was given the following rescue conditioning regimen: treosulfan (36g/m<sup>2</sup> BSA), fludarabine (5 × 30mg/m<sup>2</sup> BSA), thiotepa (1 × 5 mg/kg body weight) and PTCY. Bone marrow transplantation was performed on October 29, 2020. A total of 3.30 × 10<sup>6</sup> CD34+ cells/kg of recipient's body weight were infused. There were 8.04 × 10<sup>7</sup> lymphocytes CD3+/kg body weight contained in the material. Cyclophosphamide at a dose of 2 × 50 mg/kg b.w. was administered on days 3 and 4, cyclosporine A (1.5 mg/kg body weight) and mycophenolate mofetil (20 mg/kg body weight) were included in treatment from day +5 as in the original study by Shlomchik [5,6].

Granulocyte recovery (absolute neutrophil count > 0.5 G/L) was reached on day 18, satisfied platelet level (platelet count test > 20 G/L) was reached on day 32, and platelet count above 50 G/L was achieved 10 days later.

In the post-HSCT observation time the patient developed multisystem GvHD disease grade III. First symptoms were observed on day 44 posttransplant, when generalized maculopapular skin rash appeared, affecting over 50% of the patient's total body surface. Diarrhea occurred one week after the appearance of initial symptoms. Our patient required treatment with methylprednisolone 2mg/kg body weight, etanercept (Enbrel, Pfizer Manufacturing, Puurs, Belgium) at a dose of 10 mg once a week (6 doses overall and the last dose on December 14, 2020; day 47), and basiliximab (Simulect, Novartis, Dublin, Ireland) at a dose of 10 mg once a week (4 doses overall and the



**Fig 1.** Flowsheet for children with hemophagocytic lymphohistiocytosis (HLH) in HLH-2004. SCT, stem cell transplantation.

last dose on December 7, 2020). Nevertheless, no improvement was reached and the escalation of symptoms ensued. The patient presented with fever and elevated inflammatory parameters. Finally, it was decided to administer an ATG (Grafalon, Neovii Biotech GmbH, Grafelfing, Germany) at an overall dose of 20 mg/kg body weight (5 mg/kg b.w. each for 4 consecutive days) as salvage therapy (Fig 2). The patient recovered gradually and on day 56 his clinical condition enabled us to discharge him from the hospital.

We regularly saw the patient in our outpatient clinic during the 5-month observation period after the HSCT, and he has been in good general condition and with full donor chimerism in peripheral blood. The only concern was associated with the development of cytomegalovirus reactivation in February 2021, which was successfully treated with valganciclovir per os. Shortly before then, in January 2021, our patient developed a catheter-related bloodstream infection and *Proteus mirabilis* was grown in culture. The boy recovered quickly after central line removal and antibiotics implementation.

## DISCUSSION

Although our patient went home in a good medical state, the results of clinical trials on haploidentical HSCT in HLH patients encourage us to withhold excessive optimism. A study of 86 children treated with HLH-94 protocol followed by HSCT presented similar long term disease-free survival rates (70% at 3 years) with matched unrelated donor transplants and with matched sibling transplants. On the other hand, survival with family haploidentical donor transplants or mismatched unrelated transplants showed less favorable results with a long term disease-free survival of 50% [7]. Other clinical reports suggest that haploidentical HSCT with PTCY is a reasonable option for children with HLH lacking a matched sibling donor [8]. Although the conclusions mentioned above are drawn on the basis of 2 patients only, alternative donor transplants (including

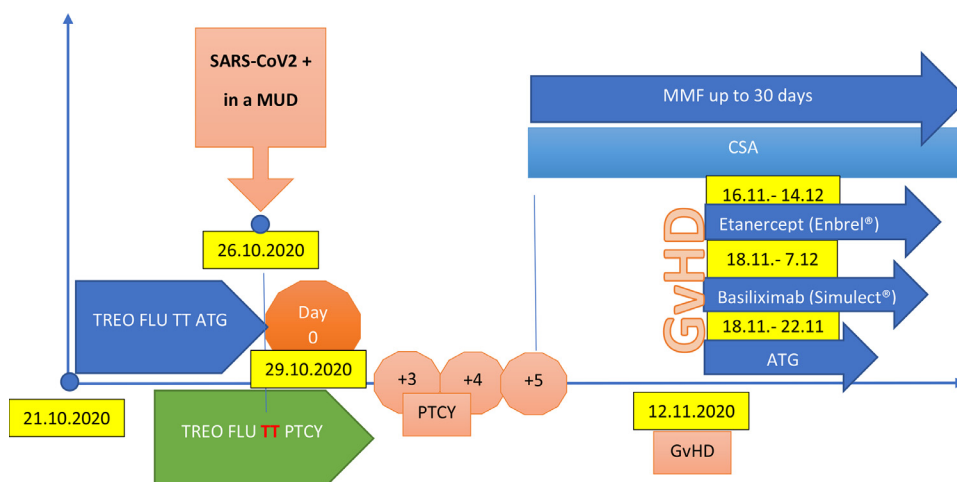
transplants from haploidentical donors) remain a promising option in HLH and also in other indications for HSCT.

In 2018, Duléry et al [9] reported interesting conclusions from their studies on sequential conditioning with thiotepa in T cell-replete HSCT for the treatment of refractory hematologic malignancies. They compared matched related, haplo-mismatched, and unrelated donors. The group of patients who underwent haplo-HSCT had a lower incidence of acute GvHD and a higher GvHD-free and relapse-free survival than the group with matched unrelated donors. Moreover, the overall survival was not lower in haploidentical transplantations. Interestingly, this study did not support the preference for matched unrelated donor when a haploidentical donor is easily available [9]. As the list of indications for HSCT increases at a quick pace, donor availability is the limiting factor that needs to be broadened. New GvHD prophylactic treatment options, such as PTCY and other supportive methods in HSCT regimens, should be intensively investigated to improve the availability of donor sources [10].

Because there is an increased risk of graft rejection in patients with HLH, we decided to use full marrow with PTCY and not in vitro T-cell depleted peripheral blood stem cells. The use of ATG during conditioning regimen in patients undergoing HSCT with PTCY might increase the risk of GvHD, which was observed in our case. The same ATG proved to be a curative option in steroid- and multidrug-refractory GvHD, which occurred in our patient. With extended anti-GvHD armamentarium at our disposal, we feel safer even in life-threatening salvage procedures during the COVID-19 pandemic.

## CONCLUSIONS

Bearing in mind the patient's medical history and the circumstances in which we were placed, the HSCT treatment with haploidentical donor was not optimal for this boy, but it was salvage and the only possible option.



**Fig 2.** Treatment scheme. ATG, antithymocyte globulin; CSA, cyclosporine A; FLU, fludarabine; GvHD, graft-versus-host disease; MMF, mycophenolate mofetil; MUD, matched unrelated donor; PTCY, posttransplant cyclophosphamide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TREO, treosulfan; TT, thiotepa.

The European Society on Blood and Marrow Transplantation recommendations on secured stem cell product access have recently been changed because the COVID-19 pandemic situation has altered since the summer of 2020. Freezing products is no longer the advised procedure because there were several reports of cryopreserved products that were never infused. On the other hand, the emergence of new SARS-CoV-2 strains in the United Kingdom and in the Republic of South Africa, along with consecutive new travel restrictions, threatens donor availability and again increases the need for cryopreservation [11].

This case has convinced us to change our policy on donor procurement and collection logistics. Since the transplant described in this article, we have used only cryopreserved apheresis materials from matched unrelated donors to ensure the availability of stem cell products before the start of a conditioning regimen.

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