VIA MEDICA

CLINICAL VIGNETTE

Acta Haematologica Polonica 2023
Number 5, Volume 54, pages 335–337
DOI: 10.5603/ahp.97103
ISSN 0001–5814
e-ISSN 2300–7117

Successful triple line stimulation after peripheral blood stem cell transplantation in pediatric hepatitis-associated aplastic anemia

Melissa Prodisteanu[1], Hanna Markowska[2], Adrianna Kaczmarek[2], Magdalena Drozd[2], Natalia Far[2], Monika Richert-Przygońska[3], Robert Dębski[3], Katarzyna Pawelec[4], Krzysztof Czyżewski[3*]

[1]*Université de Montréal*, Montreal, Quebec, Canada

[2]Student Scientific Society, *Collegium Medicum*, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland

[3]Department of Pediatric Hematology and Oncology, *Collegium Medicum*, Nicolaus Copernicus University in Toruń, Jurasz University Hospital 1, Bydgoszcz, Poland

[4]Department of Pediatric Hematology and Oncology, Clinical Transplantology and Pediatrics, Medical University of Warsaw, Warsaw, Poland

Severe aplastic anemia (SAA) is a rare, life-threatening bone marrow disorder characterized by pancytopenia in the peripheral blood secondary to aregenerative hematopoietic failure.

In 1–5% of cases, SAA is associated with pre-existing hepatitis, which precedes the onset of anemic symptoms by up to 6 months [1]. The standard primary therapy for SAA in 2023 for children is allogeneic hematopoietic cell transplantation (allo-HCT) from a matched family donor (MFD) [2]. When an MFD is unavailable, immunosuppressive treatment (IST) using rabbit globulin, cyclosporine and steroids is used. If immunoablation fails, allo-HCT from a matched unrelated donor (MUD) is recommended.

Over the years, significant advances have been made in treatments for SAA involving three key medications: eltrombopag, darbepoetin alpha, and filgrastim, which each play a role in stimulating blood cell production [3–6]. Eltrombopag is an orally administered thrombopoetin receptor agonist (TPO-RA). By stimulating the thrombopoietin receptor, platelet production increases. Studies have demonstrated the efficacy of eltrombopag as a first-line treatment or combined with IST to treat SAA [5, 7]. Darbepoetin alpha is a synthetic erythropoietin-stimulating agent regulating red blood cell production, while filgrastim is a recombinant form of human granulocyte colony-stimulating factor (G-CSF) which stimulates the production of white blood cells, particularly neutrophils.

The aim of this report was to present a case of successful triple line stimulation therapy in a pediatric patient following allo-HCT.

A 14-year-old boy with autoimmune hepatitis was diagnosed in July 2021 *via* a hepatic biopsy. Two months later, the patient was hospitalized in another hospital, where a diagnosis of hepatic associated severe aplastic anemia (HA-SAA) was confirmed after ruling out Fanconi anemia and nocturnal paroxysmal hemoglobinuria. In December 2021, IST consisting of rabbit thymoglobulin, cyclosporine and steroids was implemented. Due to the lack of response to IST, a search for a MUD was initiated. On admission to the transplant unit, physical examination revealed features of Cushing syndrome, jaundice and inflammatory anal lesions. Laboratory investigations demonstrated pancytopenia, hyperbilirubinemia (predominantly direct hyperbilirubinemia) and elevated inflammatory markers. In February 2022, after conditioning with fludarabine (30 mg/m^2/day; days –6 to –3), cyclophosphamide (750 mg/m^2/day; days –6 to –3) and anti-thymocyte globulin (ATG) (2.5 mg/kg/day; days –6 to –3) peripheral blood hematopoietic stem cells (PBHSC) (NC = 7.26 × 10^8 cells/kg, CD34+ = 4.52 × × 10^6 cells/kg) were transplanted. Cyclosporine and a short

*Address for correspondence: Krzysztof Czyżewski, Department of Pediatric Hematology and Oncology, *Collegium Medicum*, Jurasz University Hospital 1, Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, phone +48 52 585 48 03, e-mail: k.czyzewski@cm.umk.pl

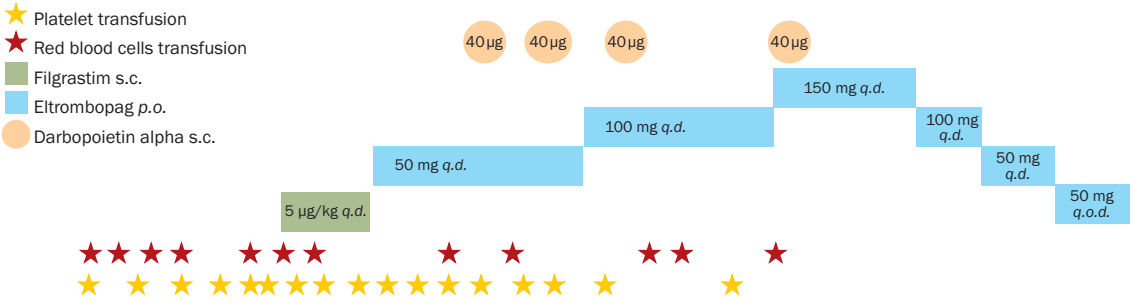
Received: 25.08.2023 Accepted: 30.08.2023 Early publication date: 11.10.2023

Copyright © 2023

The Polish Society of Haematologists and Transfusiologists, Insitute of Haematology and Transfusion Medicine.

All rights reserved.

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.



Days since transplantation	–3	–16	–4	+3	+120	+16	+26	+32	+38	+45	+53	+67	+91	+98	+117	+128	+186	+215	+266	+308	+348	+389	+432	+475	+515
WBC [10^3/µL]	0.16	0.14	0.03	0	0	0.82	1.71	1.90	1.40	2.08	1.44	1.67	2.02	4.11	2.10	2.30	1.48	2.83	3.74	5.16	3.72	4.72	5.65	5.66	5.02
ANC [10^3/µL]	–	–	–	–	–	–	1.25	1.36	1.04	1.75	0.9	1.12	1.12	2.3	1.58	0.98	0.6	1.41	1.85	2.81	1.92	2.6	2.27	3.14	3.2
Hb [g/dL]	7.3	9.1	8.1	8.2	11.3	8.9	10.6	9.2	7.9	9	10.3	8.2	7.9	11.6	11	7.3	9.5	9.4	11.7	13.7	12.3	13.6	14.2	14.9	14.9
PLT [10^3/µL]	5	18	5	8	30	12	26	10	7	11	5	45	36	42	17	25	71	130	132	178	183	199	169	154	175

Figure 1. Hematological results and applied therapy; s.c. — subcutaneous; *p.o.* (Latin *per os*) — oral administration; *q.d.* (Latin *quaque die*) — once daily; *q.o.d.* (Latin *quaque altera die*) — every other day; WBC — white blood cells; ANC — absolute neutrophil cells; Hb — hemoglobin; PLT — platelets

course of methotrexate were used for graft-versus-host disease (GvHD) prophylaxis. For prevention of Epstein-Bárr virus (EBV) reactivation, rituximab was administered on day +5 post-transplantation, and prophylaxis with letermovir was administered against cytomegalovirus (CMV) reactivation. The post-transplantation period was complicated by bloodstream infection by *Staphylococcus haemolyticus* and virus BK (BKV)-cystitis.

Due to a lack of hematopoietic recovery, filgrastim [5 µg/kg subcutaneous (s.c.)] was used from days +10 to +25. Granulocyte engraftment was observed on day +26. The same day, a myelogram revealed a poorly cellular marrow, with representation of all cell lines. From day +31 onwards, the patient repeatedly required supplementary transfusions of red blood cells and platelets due to anemia and symptomatic thrombocytopenia. Consequently, on day +40, it was decided to include erythropoietin (EPO) and thrombopoietin receptor agonist eltrombopag. The patient received a total of four doses of darbepoetin alpha (40 µg s.c.), with progressively longer intervals between the doses. For eltrombopag, initially a dose of 50 mg *per os* (*p.o.*)/day was used, followed by 100 mg *p.o.*/day, up to a maximum dose of 150 mg *p.o.*/day, and then back down to 50 mg *p.o.*/day followed by 50 mg every other day.

This triple line stimulation therapy resulted in a gradual normalization of hematological parameters (Figure 1). No adverse effects were observed, apart from a transient increase in transaminases.

Triple therapy with eltrombopag, darbepoetin alpha, and filgrastim contributed to the achievement of remission and sustained hematological reconstruction, despite bone marrow hypoplasia after transplantation. This treatment proved effective, safe, and fairly well tolerated.

In conclusion, the enhancement of allo-HCT with the supportive use of triple stimulation comprising eltrombopag, darbepoetin alpha, and filgrastim, improved pancytopenia and prevented other complications. By understanding these drugs, treatment plans can be made to improve the outcomes and prognosis for patients with HA-SAA.

Acknowledgments

The authors would like to thank Professor Jan Styczyński for valuable suggestions during the preparation of this manuscript.

Authors' contributions

KC, MRP — design of study. MP, HM, AK, MD, NF, MRP, RD, KP, KC — provision of clinical data. MP, KC — analysis of clinical data. MP, KC — literature search and analysis of data. MP, KC — writing manuscript. All authors — critical revision and final approval.

Conflict of interest

The authors declare no conflict of interest.

Financial support

None.

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; uniform requirements for manuscripts submitted to biomedical journals.

References

1. Alshaibani A, Dufour C, Risitano A, et al. Hepatitis-associated aplastic anemia. Hematol Oncol Stem Cell Ther. 2022; 15(2): 8–12, doi: 10.1016/j.hemonc.2020.10.001, indexed in Pubmed: 33197413.
2. de Latour RP, Risitano A, Dufour C. Severe aplastic anemia and PNH. The EBMT Handbook. 2018: 579–585, doi: 10.1007/978-3-030-02278-5_77.
3. Styczyński J. Inspiration from Annual Meeting of European Society for Blood and Marrow Transplantation. Acta Haematol Pol. 2023; 54(2): 51–52, doi: 10.5603/ahp.a2023.0021.
4. Styczyński J. Inspiration from American Society of Hematology Annual Meeting. Acta Haematol Pol. 2023, doi: 10.5603/ahp.a2023.0009.
5. Scheinberg P. Novel therapeutic choices in immune aplastic anemia. F1000Res. 2020; 9, doi: 10.12688/f1000research.22214.1, indexed in Pubmed: 32953089.
6. Snowden JA, Sánchez-Ortega I, Corbacioglu S, et al. European Society for Blood and Marrow Transplantation (EBMT). Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant. 2022; 57(8): 1217–1239, doi: 10.1038/s41409-022-01691-w, indexed in Pubmed: 35589997.
7. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med. 2017; 376(16): 1540–1550, doi: 10.1056/NEJMoa1613878, indexed in Pubmed: 28423296.