Acta Haematologica Polonica 2024
Number 2, Volume 55, pages 126–128
DOI: 10.5603/ahp.98334
ISSN 0001–5814
e-ISSN 2300–7117

VIA MEDICA

Multidrug rescue for pediatric refractory ITP complicated by intracranial bleeding

Bartosz Urbański[1*], Olga Wegner[1], Ewelina Subocz[1], Monika Zjawiona[1], Magdalena Wojdalska[1], Dobromiła Barańska[2], Wojciech Młynarski[1], Szymon Janczar[1]

[1]Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Łódź, Poland
[2]Department of Pediatric Radiology, Medical University of Lodz, Łódź, Poland

Introduction

Immune thrombocytopenia, formerly known as idiopathic thrombocytopenic purpura (ITP), is the most common cause of low platelet count in children. As the previous name suggests, an ITP diagnosis follows the exclusion of other identifiable diseases and confirmation via successful therapy [1]. It is estimated that c.95% of children with ITP experience spontaneous remission or a positive response to initial treatments, while the majority of the remaining non-responders eventually achieve platelet normalization with second-line therapies [2, 3]. Newly diagnosed refractory ITP is rare among pediatric patients. Although there is no consensus definition for this condition in childhood, it is generally considered after a failure to achieve a response to two standard first-line treatments, i.e. intravenous immunoglobulin (IVIG) and steroids [2, 4]. It is becoming accepted that newly diagnosed refractory ITP requires intensive diagnostics and a rapid transition to second-line treatments [2, 5].

Case report

A 3-month-old male infant with no significant medical history was admitted to hospital due to a petechial rash and severe isolated thrombocytopenia. There was no family history of bleeding disorders or hematological diseases. A 5-day course of IVIG, with a total dose of 2 g/kg, was immediately started because of pronounced cutaneous bleeding signs and a positive test for occult fecal blood. On the second day of treatment, the intestinal bleeding became clinically overt, resulting in anemia and the need for packed red blood cell transfusions. The patient was also transfused multiple times with platelet concentrates without elevating the thrombocyte levels. Consequently, methylprednisolone at a dose of 2 mg/kg daily was added to the initial IVIG regimen. On the fourth day of treatment, romiplostim was initiated at a weekly dose of 10 μg/kg and steroid therapy was escalated to 4 mg/kg daily. The next day, the patient exhibited signs of neurological impairment, and a computed tomography (CT) scan revealed intracranial bleeding (see Figure 1).

Following transfer to the pediatric intensive care unit (PICU), the patient was put into deep sedation and administered emergency vincristine at a dose of 0.05 mg/kg. Additionally, he developed severe hypertension requiring treatment with a continuous urapidil infusion. The day after, eltrombopag was introduced to the therapy with a daily dose of 25 mg, and the methylprednisolone dose was increased to 10 mg/kg daily. On the eighth day, his thrombocyte level remained zero, even after receiving a platelet concentrate transfusion. Therefore, a first dose of rituximab was administered, and two days later a second course of IVIG was started.

In the meantime, significant diagnostic data was obtained, including negative results of genetic testing for Epstein–Barr virus (EBV) and cytomegalovirus (CMV), normal ADAMTS13 activity, and positive findings for antiplatelet antibodies of undetermined specificity at that stage. Bone marrow cytology was non-contributory. The patient's mother tested negative for antiplatelet antibodies, ruling out fetal and neonatal alloimmune thrombocytopenia [6]. A follow-up CT scan revealed minimal progression of the initial hemorrhagic lesion (see Figure 1).

*Address for correspondence: Bartosz Urbański, Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Łódź, Poland.
e-mail: bartosz.urbanski@umed.lodz.pl

Received: 27.11.2023 Accepted: 20.12.2023 Early publication: 05.03.2024

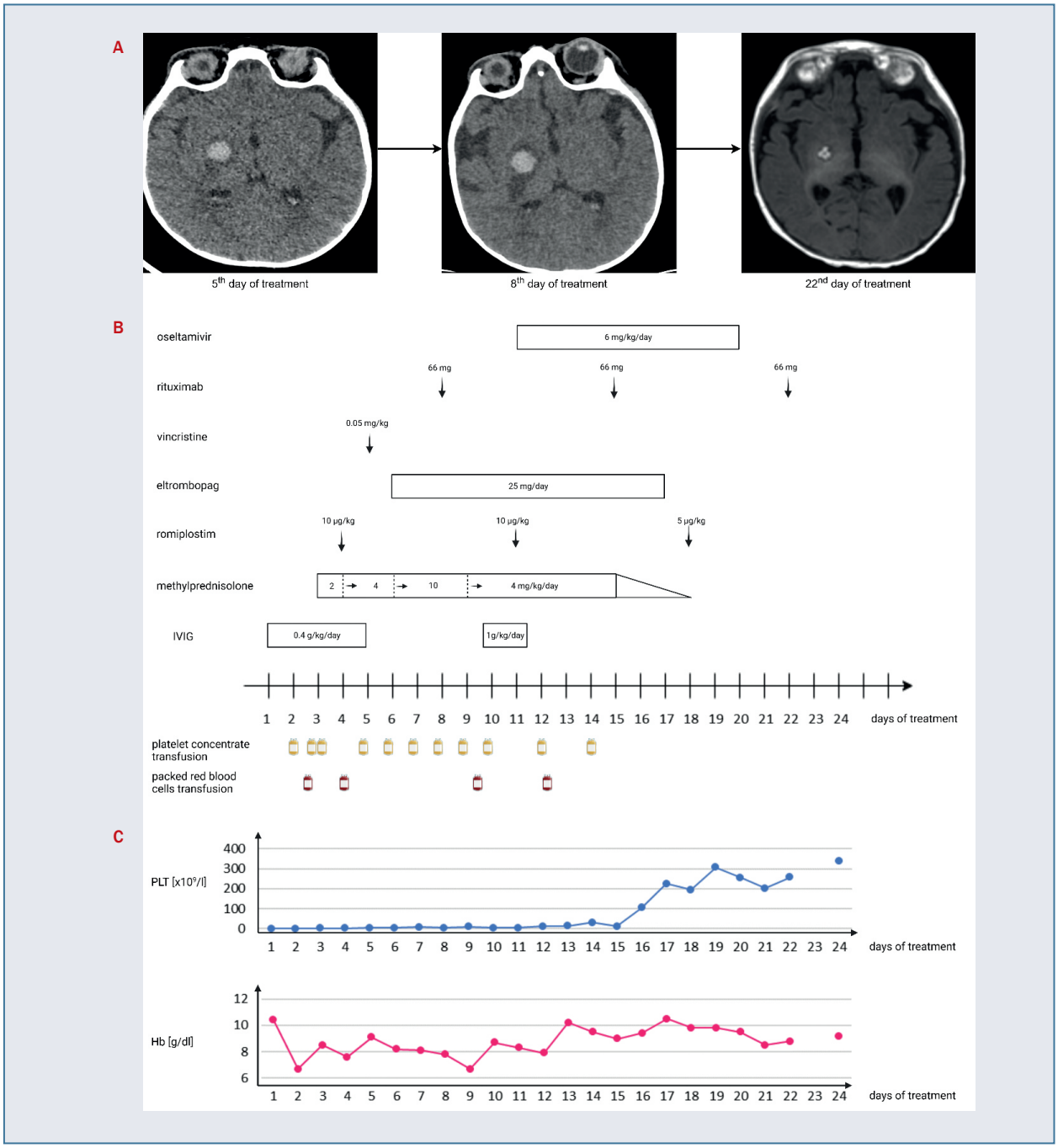

Figure 1A. Evolution of intracerebral hemorrhage on computed tomography and magnetic resonance neuroimaging; **B.** Therapeutic interventions with drug doses presented on time axis; **C.** Graphs depicting platelet levels (PLT) and hemoglobin concentration (Hb) during hospitalization; IVIG — intravenous immunoglobulin

On the 12th day of treatment, oseltamivir was added to the therapy due to persistently low platelet counts and the determination of anti-GPIIb/IIIa specificity in the previously detected antiplatelet antibodies. Some studies have suggested that anti-GPIIb/IIIa antibodies may induce desialylation, contributing to platelet death, which can be alleviated by neuraminidase inhibitors [7–9].

On the 14th day of treatment, the first significant increase in platelet levels was noted, and two days later the patient's thrombocyte count exceeded 100,000/µl. The therapies were gradually discontinued, as shown in Figure 1.

The patient's condition improved over time, leading to his transfer from the PICU to the hematology department

and eventual discharge after 26 days of hospitalization. The boy continued rituximab, receiving four doses in total, and four months after the onset of the disease remains in remission without further treatment. During that time, he has displayed notable advances in psychomotor development while under the care of a medical team comprising a pediatric hematologist, a neurologist, and a rehabilitation specialist. Nevertheless, further observation is necessary to monitor for potential long-term neurological sequelae.

Discussion

Although we cannot identify which specific treatment component had the most significant impact on the patient's remission, this case report supports the opinion that prompt initiation of second-line treatments in refractory ITP cases is justified [2, 4, 5]. It is highly probable that a combination of medications, which exhibit a cumulative effect, played a crucial role.

Recent research has suggested that combining steroids with rituximab or thrombopoietin receptor agonists may determine synergistic results, rather than just the sum of each drug's action [10]. Further studies are needed to assess the potential effect of oseltamivir in this context. It is noteworthy that most of the drugs used in this case were administered off-label. Despite the aggressive treatment approach and the rapid introduction of multiple agents with partially overlapping activities, no complications explicitly attributed to any drug used were observed.

We conclude that in the setting of primary refractory ITP, the potential benefits of early aggressive multimodal treatment far outweigh the possible adverse effects.

Article information and declarations

Acknowledgments
Not applicable.

Authors contributions
BU — conceptualization, writing of manuscript; OW, ES, MZ, MW — clinical data; DB — radiological imaging data; WM — supervision; SJ — conceptualization, writing and critical review of manuscript, supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interests
The authors declare no conflict of interests.

Ethics statement
Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

Funding
This study was conducted with the support of a scholarship program financed by the Saving Kids with Cancer Foundation.

Supplementary material
None.

References:

1. Miltiadous O, Hou M, Bussel JB. Identifying and treating refractory ITP: difficulty in diagnosis and role of combination treatment. Blood. 2020; 135(7): 472–490, doi: 10.1182/blood.2019003599, indexed in Pubmed: 31756253.
2. Neunert C, Heitink-Polle KMJ, Lambert MP. A proposal for new definition (s) and management approach to paediatric refractory ITP: Reflections from the Intercontinental ITP Study Group. Br J Haematol. 2023; 203(1): 17–22, doi: 10.1111/bjh.19072, indexed in Pubmed: 37641973.
3. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019; 3(23): 3829–3866, doi: 10.1182/bloodadvances.2019000966, indexed in Pubmed: 31794604.
4. Ibrahim L, Dong SX, O'Hearn K, et al. Pediatric refractory immune thrombocytopenia: a systematic review. Pediatr Blood Cancer. 2023; 70(3): e30173, doi: 10.1002/pbc.30173, indexed in Pubmed: 36579787.
5. Vianelli N, Auteri G, Buccisano F, et al. Refractory primary immune thrombocytopenia (ITP): current clinical challenges and therapeutic perspectives. Ann Hematol. 2022; 101(5): 963–978, doi: 10.1007/s00277-022-04786-y, indexed in Pubmed: 35201417.
6. Kjeldsen-Kragh J, Fergusson DA, Kjaer M, et al. Fetal/neonatal alloimmune thrombocytopenia: a systematic review of impact of HLA-DRB3*01:01 on fetal/neonatal outcome. Blood Adv. 2020; 4(14): 3368–3377, doi: 10.1182/bloodadvances.2020002137, indexed in Pubmed: 32717028.
7. Zheng SS, Ahmadi Z, Leung HH, et al. Antiplatelet antibody predicts platelet desialylation and apoptosis in immune thrombocytopenia. Haematologica. 2022; 107(9): 2195–2205, doi: 10.3324/haematol.2021.279751, indexed in Pubmed: 35199503.
8. Marini I, Zlamal J, Faul C, et al. Autoantibody-mediated desialylation impairs human thrombopoiesis and platelet lifespan. Haematologica. 2021; 106(1): 196–207, doi: 10.3324/haematol.2019.236117, indexed in Pubmed: 31857361.
9. Zheng SS, Perdomo JS, Leung HH, et al. Acquired Glanzmann thrombasthenia associated with platelet desialylation. J Thromb Haemost. 2020; 18(3): 714–721, doi: 10.1111/jth.14722, indexed in Pubmed: 31869497.
10. Kochhar M, Neunert C. Immune thrombocytopenia: a review of upfront treatment strategies. Blood Rev. 2021; 49: 100822, doi: 10.1016/j.blre.2021.100822, indexed in Pubmed: 33736875.