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CASE REPORT

Romiplostim – an emergency treatment of intracranial haemorrhage in the course of severe primary immune thrombocytopaenia

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ABSTRACT

We present a case of a 16-year-old girl with newly diagnosed/persistent immune thrombocytopaenia (ITP) with a complication of intracranial haemorrhage. She did not respond adequately to first-line treatment, i.e. intravenous immunoglobulin infusions, glucocorticosteroids, and transfusion of platelets, and developed numerous bleeding complications. During the treatment she developed bleeding into the central nervous system, which is a rare and devastating complication of ITP. In such cases, the available data in the literature suggest a potential role of the thrombopoietin receptor agonist as a life-saving emergency treatment for severe, newly diagnosed immune thrombocytopaenia. The prognosis of our patient's survival and neurological status was completely dependent on this treatment. After obtaining consent from the appropriate bioethics committee, romiplostim was administered to the patient, with a good response and without side effects.

KEY WORDS:

platelet count, ITP, intracranial haemorrhage, romiplostim.

INTRODUCTION

Immune thrombocytopaenia (ITP) is the most common cause of significant acute thrombocytopaenia in children. In most cases it has a mild course, and life-threatening bleeding is rare [1, 2].

Depending on the duration of symptoms, we can divide thrombocytopaenia into 3 categories: newly diagnosed – within 3 months of diagnosis, persistent – duration 3–12 months, and chronic – continuing beyond one year [1, 3]. The first-line treatment includes intravenous immunoglobulin infusions, glucocorticosteroids, and platelet transfusions, although they are not always effective [1, 4].

Intracranial bleeding is a rare but devastating complication with an incidence rate of 0–1% [3, 5]. According to the literature, 25% of cases of intracranial haemorrhages are fatal, and another 25% leave children with permanent consequences such as neurological and psychiatric disorders [3, 6]. Therefore, this complication requires aggressive, multi-specialist treatment and the maintenance of a stable and safe platelet count [1, 6].

CASE REPORT

A 16-year-old girl was admitted, due to severe immune thrombocytopaenia, to the Department and Clinic of Oncology, Paediatric Haematology, Clinical Transplan-

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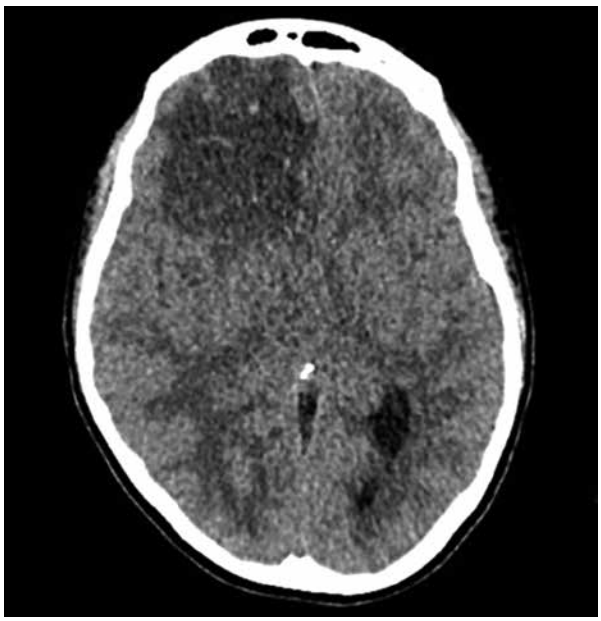

FIGURE 1. First computed tomography imaging after stroke, 2021 October 10th. Extensive area of intracerebral haemorrhage in the right frontal lobe accompanied by oedema of the surrounding brain tissue

tology and Paediatrics of the University Paediatric Hospital in Warsaw, on 17 September 2021.

Her past medical history revealed that she had received intensive chemotherapy and had an autologous haemopoietic cell transplant as a part of treatment for Hodgkin's lymphoma. The oncological treatment was successfully completed in 2017.

In July 2021, she was admitted to The Children's Memorial Health Institute in Warsaw due to an appearance of petechial and mucosal bleeding. Blood tests revealed severe thrombocytopaenia with a platelet count of 2×10^9/l, with normal haemoglobin and leukocyte levels, which led to the diagnosis of primary immune thrombocytopaenia. She received an infusion of immunoglobulins (2 g per kg of body weight). Due to coexisting mucosal bleeding, it was also necessary to transfuse the platelet concentrate. This resulted in an increase in the platelet count but to only to 33×10^9/l. Clinical remission lasted until 12 September 2021, when the platelet count was 2×10^9/l, and she was admitted to the paediatric ward of the district hospital in her place of residence. Between 12 and 16 September she again received a full dose of intravenous immunoglobulin (2 g/kg); however, no effect was achieved. Due to the lack of treatment success, the patient was transferred to the University Clinical Centre of the Medical University of Warsaw, initially to the Nephrology Clinic and then to the Department and Clinic of Oncology, Paediatric Haematology, Clinical Transplantology and Paediatrics.

Initially it was necessary to exclude proliferative disease; therefore, bone marrow biopsy and trepanobiopsy were performed. The results of the procedures led to a diagnosis of ITP, and glucocorticoids were included in her treatment. She also received pulses of high doses of IV methylprednisolone. After 7 days of methylprednisolone therapy, she received oral prednisone, but despite this the platelet count ranged $0–3 \times 10^9$/l.

Clinically petechiae and mucosal bleeding (especially from the area of a damaged tooth) were observed, then later haematuria and tarry stools. Because of anaemia and hypofibrinogenaemia, as a result of gastrointestinal bleeding and persistent haematuria, the patient required transfusions of red blood cells, platelet cell concentrate, and cryoprecipitate. Due to the gastrointestinal bleeding, the route of steroid administration was changed back to intravenous. Although the platelet cell concentrate was transfused twice, there was no correction of platelet count in complete blood count.

On 10 October 2021, at around 12 o'clock, the patient lost consciousness following an episode of vomiting and headache. Due to breathing difficulties cardiopulmonary resuscitation was performed successfully. She was transferred to the Intensive Care Unit, where the suspicion of intracranial bleeding was confirmed. The computed tomography imaging of the head revealed an extensive haematoma in the frontal lobe with a mass effect (Figure 1). As interventions she received transfusions of red blood cells, platelet cell concentrate, and cryoprecipitate and correction of mineral ion deficiencies. According to the haematologist's consultation, an infusion of immunoglobulin (1 g/kg) and intravenous administration of eptacog alfa (activated) were also used. After this procedure the platelet count increased to 109×10^9/l, which allowed for a safe neurosurgery intervention. This was successfully performed during the night; she was stable following neurosurgery but required mechanical ventilation. On 15 October 2021, the platelet count dropped, so intravenous pulses of methylprednisolone were restarted.

At the same time, the Bioethics Committee was asked for the possibility of the use of romiplostim as a life-saving treatment. After the positive decision of the Bioethics Committee and the consent of patient's parents, on 20 October 2021, 5 mcg/kg romiplostim was administered subcutaneously; the platelet count then was 69×10^9/l. From 21 October an increase in platelet count to 450×10^9/l was observed.

The girl was extubated on 22 October 2021. She was in a stable state but with persistent left hemiplegia and central facial palsy on the left side. She was able to follow simple commands and open her eyes spontaneously. On 27 October she was transferred to the Neurology Department to continue treatment and rehabilitation.

Unfortunately, the effects of a single dose of romiplostim were not sustained, and the platelet count came down to less than 100×10^9/l again.

On 8 November, 19 days after first administration, romiplostim was re-injected, at a dose of 3 mcg/kg. Because the expected effect was not achieved and the platelet count dropped to around 70×10^9/l, the patient again required a course of intravenous immunoglobulin.

On 12 November, the platelet count was 88 × 10⁹/l; thus, it was again decided to administer romiplostim at a dose of 5 mcg/kg subcutaneously. We observed a rapid response to the treatment (the next day) with a platelet count of 152 × 10⁹/l, and in the next 10 days the platelet count gradually increased to 682 × 10⁹/l.

On 23 November, the girl started intensive physiotherapy at the Rehabilitation Department of The Children's Memorial Health Institute in Warsaw. At the time of transfer the patient had discrete features of left-sided paresis with reduced muscle tone. The girl was able to sit, eat, drink, and mobilize in a wheelchair independently. She still required support when standing and trying to walk.

On 1 December she returned to the Department and Clinic of Oncology, Paediatric Haematology, Clinical Transplantology and Paediatrics due to a decrease in platelet count to 100 × 10⁹/l. That was the last administration of romiplostim at a dose of 5 mcg/kg. Over the following days, the patient developed symptoms of a mild upper respiratory tract infection (SARS-CoV-2 test was negative). Due to lack of effect and platelet count remaining below 100 × 10⁹/l, 1 g/kg of immunoglobulins was administered intravenously on 4 December. On subsequent monitoring a gradual increase in the platelet count was observed. Since then, the platelet count has remained safe and stable at over 150 × 10⁹/l.

During her last visit in February 2022, the platelet count was 240 × 10⁹/l. On the last MRI further evolution of haemorrhagic and post-ischaemic changes were observed (Figure 2).

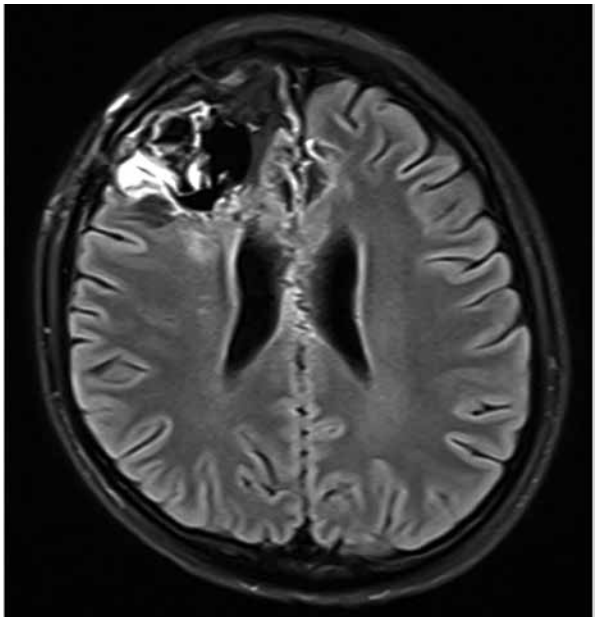

FIGURE 2. Follow-up magnetic resonance imaging, 2022 January 4th further evolution of haemorrhagic and post-ischemic changes. In the right and left frontal lobe as well as in the corpus callosum, areas of malathion, laminar necrosis and hemosiderin – slightly smaller than in the previous study

Figure 3 shows the treatment schedule and platelet counts.

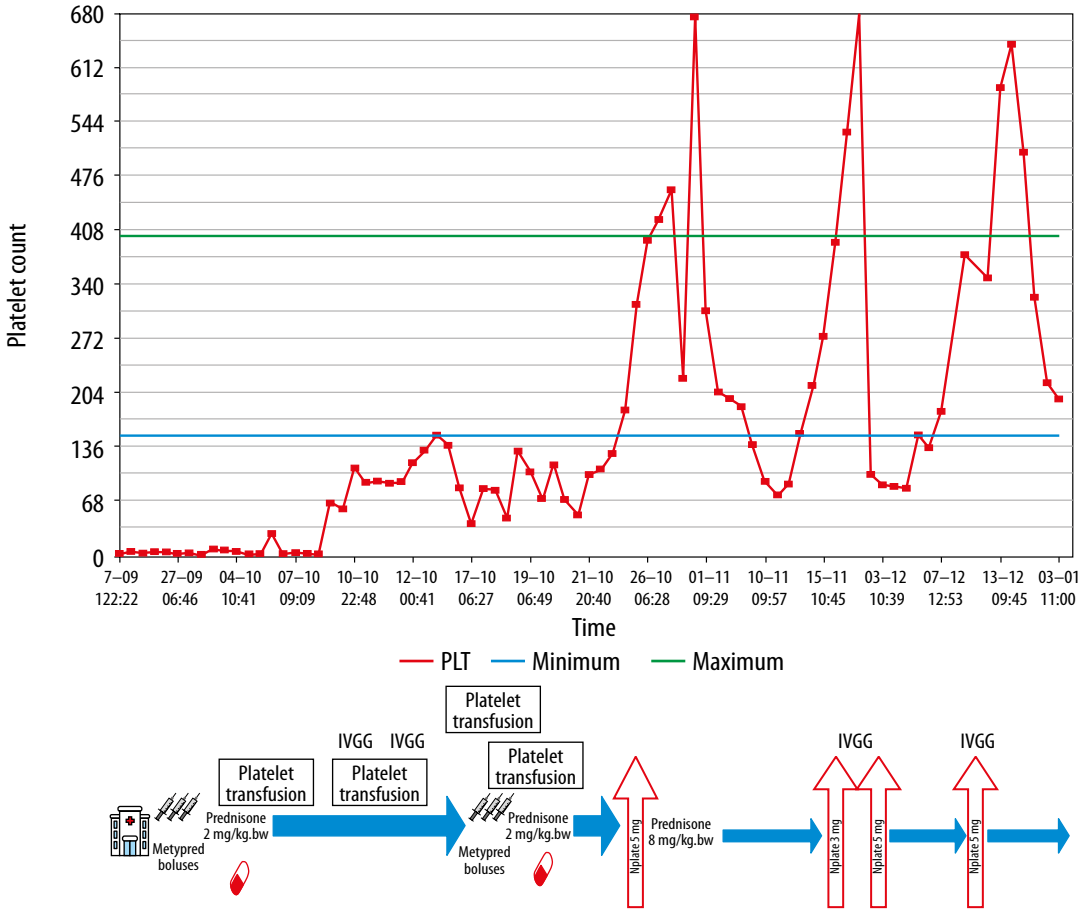

FIGURE 3. Course of treatment and platelet count

At the time of writing this article, she remains under observation, and is being rehabilitated. There is still a need for regular blood counts, with a particular emphasis on the platelet count. The next administration of romiplostim is recommended with a decrease in platelets to 120×10^9/l. During the entire treatment, the girl received 4 doses of romiplostim (3 times at a dose 5 mg/kg and once at 3 mg/kg), and no side effects of the therapy were observed.

It is unknown whether with the use of romiplostim our patient achieved a complete ITP remission and what kind of long-term consequences from the intracranial haemorrhage will persist. But undoubtedly the drug has fulfilled its role as a life-saving emergency treatment, which is why we present this case.

DISCUSSION

Romiplostim – one of the thrombopoietin receptor agonists – is currently available and commonly used in paediatric patients with chronic ITP [1, 2]. It has been proven to be effective and has a good safety profile in this group of patients [1, 4]. In the latest literature reports we can find descriptions of good results of using romiplostim in the treatment of patients with acute haemorrhagic complications of ITP [1–3]. Intracranial bleeding during ITP is a rare but devastating complication, which is fatal in 25% of cases and in another 25% of children causes permanent consequences such as neurological and psychiatric disorders [3, 5, 6]. Therefore, this complication requires aggressive and multi-specialist treatment and the maintenance of a stable and safe platelet count [1].

That is why, when the patient had no remission of ITP after conventional therapy, we decided to start the emergency management of severe ITP with life-threatening haemorrhage with romiplostim. The therapy was effective and safe, as we described above.

According to available data, in most of the previously described cases, the average dose of 5 mcg/kg romiplostim was used [2, 3]. Therefore, that exact dosing was initially used in our patient. Good initial response to the drug administration gives hope for long-term remission later in the patient's follow up [2].

CONCLUSIONS

Currently there are no well-established guidelines for the emergency management of severe ITP with life-threatening haemorrhage; thus, we hope that the above case will become a voice in the discussion on how to proceed in similar situations.

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