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Romiplostim Administration to a Preterm Neonate with Severe Prolonged Acquired Thrombocytopenia

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Abstract

Platelet transfusions can be lifesaving for neonates with thrombocytopenic hemorrhage. However, multiple transfusions themselves convey risks and hazards. We cared for a preterm neonate with severe/prolonged acquired thrombocytopenia who received 61 platelet transfusions. Her platelet counts stabilized, and further transfusions were not needed, following three escalating doses of romiplostim.

Abbreviations

Tpo: thrombopoietin

DOL: day of life

NEC: necrotizing enterocolitis

SQ: subcutaneously

IPF: immature platelet fraction

Keywords: thrombopoietin; immature platelet fraction; platelet transfusion

Established Facts

- Thrombocytopenia is a common problem and may affect up to 70% of extremely low birth weight neonates
- Platelet transfusion is the current treatment option for neonates with severe symptomatic thrombocytopenia
- Mortality and risk for sepsis is increased in those requiring multiple platelet transfusions so other options need to be explored

Novel Insights

- Thrombopoietic stimulators like romiplostim may reduce the need for multiple platelet transfusions in neonates with symptomatic and persistent thrombocytopenia.

Introduction

The purpose of this report is to describe a case in which an extremely premature, low birth weight neonate, developed a prolonged course of thrombocytopenia requiring multiple platelet transfusions but subsequently stopped requiring platelet transfusions following a short course of the Tpo-mimetic, romiplostim.

In 1994 the principal physiological regulator of thrombopoiesis, thrombopoietin (Tpo), was cloned (1). Two recombinant forms were created: a full-length Tpo and a pegylated form containing only the receptor-binding domain. In early clinical trials, a few subjects receiving these molecules developed cross-reactive neutralizing antibodies against their endogenous Tpo, resulting in severe hypo-regenerative thrombocytopenia and aplastic anemia (2).

Second-generation Tpo-mimetics were developed, which do not share any sequence homology with endogenous Tpo, but stimulate thrombopoiesis by binding and activating the Tpo receptor (3). In 2018, the FDA approved romiplostim for use in children >1 year of age with immune thrombocytopenic purpura of > 6 months (3). Although romiplostim has been used in cases of refractory thrombocytopenia in children, published use in neonates is limited (4). We would like to describe our experience of using romiplostim in a neonate with protracted thrombocytopenia.

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Case Report

A 540 gram, 23-week female was admitted to the neonatal intensive care unit with an initial platelet count of 201 x 10^3/μL. The mother had been visiting Seattle from the East Coast when she delivered. Her prenatal laboratory values included non-reactive rapid plasma regain and human immunodeficiency virus titer, immune Rubella titer, normal cell-free DNA screen. Her platelet count was 151 x 10^3/μL

On day of life (DOL) 10, the infant's abdomen became dusky and distended. No pneumatosis or free air was detected on her abdominal radiographs. Fluconazole was started after Candida albicans grew from a blood culture. Platelets were transfused four days later for a platelet count of 91 x 10^3/μL; because she was a septic 23-week infant with a germinal matrix hemorrhage, we

were trying to prevent further extension.

On DOL 30, her abdomen became distended and firm. Despite serial abdominal radiographs without pneumatosis or free air, necrotizing enterocolitis (NEC) was suspected. She was severely ill, requiring platelets and fresh frozen plasma transfusions for disseminated intravascular coagulation. Due to pancytopenia and extreme instability, exploratory surgery was deferred. During this time, she required 1-2 platelet transfusions daily to keep her platelet count > 100 x 10^3/μL. Post transfusion platelet counts were rarely > 100 x 10^3/μL (Figure); therefore, starting on DOL 47, all aliquots were plasma reduced. Subsequent, immediate post-transfusion platelet counts were frequently > 200 x 10^3/μL but by 48 hours would invariably fall to < 100 x 10^3/μL, as low as 9 x 10^3/μL.

Three weeks later, she was stable enough to go to surgery for a bowel obstruction. No intra-abdominal abscess, candidiasis, or necrotic bowel was identified. Her bowel was matted and friable. Handling the bowel trying to find the area of obstruction left her with multiple enterotomies. A diversion was not possible, so the abdomen was left open, and the baby was brought back to the NICU with the peritoneum open and the bowel exteriorized. She continued to require platelet transfusions, assumed to be consumptive related to her abdomen. The previous work-up for other possible causes for thrombocytopenia were negative, including urine polymerase chain reaction testing for cytomegalovirus and heparin-induced antibody testing (done due to the prolonged presence of a central line infusing heparinized solution). Laboratory values for liver failure, including coagulation factors, liver function tests, urine organic acids, and serum amino acid screen, were normal. Mother had a normal platelet count. The infant's platelet count was > 104 x 10^3/μL for the 10 first days of life, making alloimmune or autoimmune thrombocytopenia less likely. Her platelet count did not fall until she became septic.

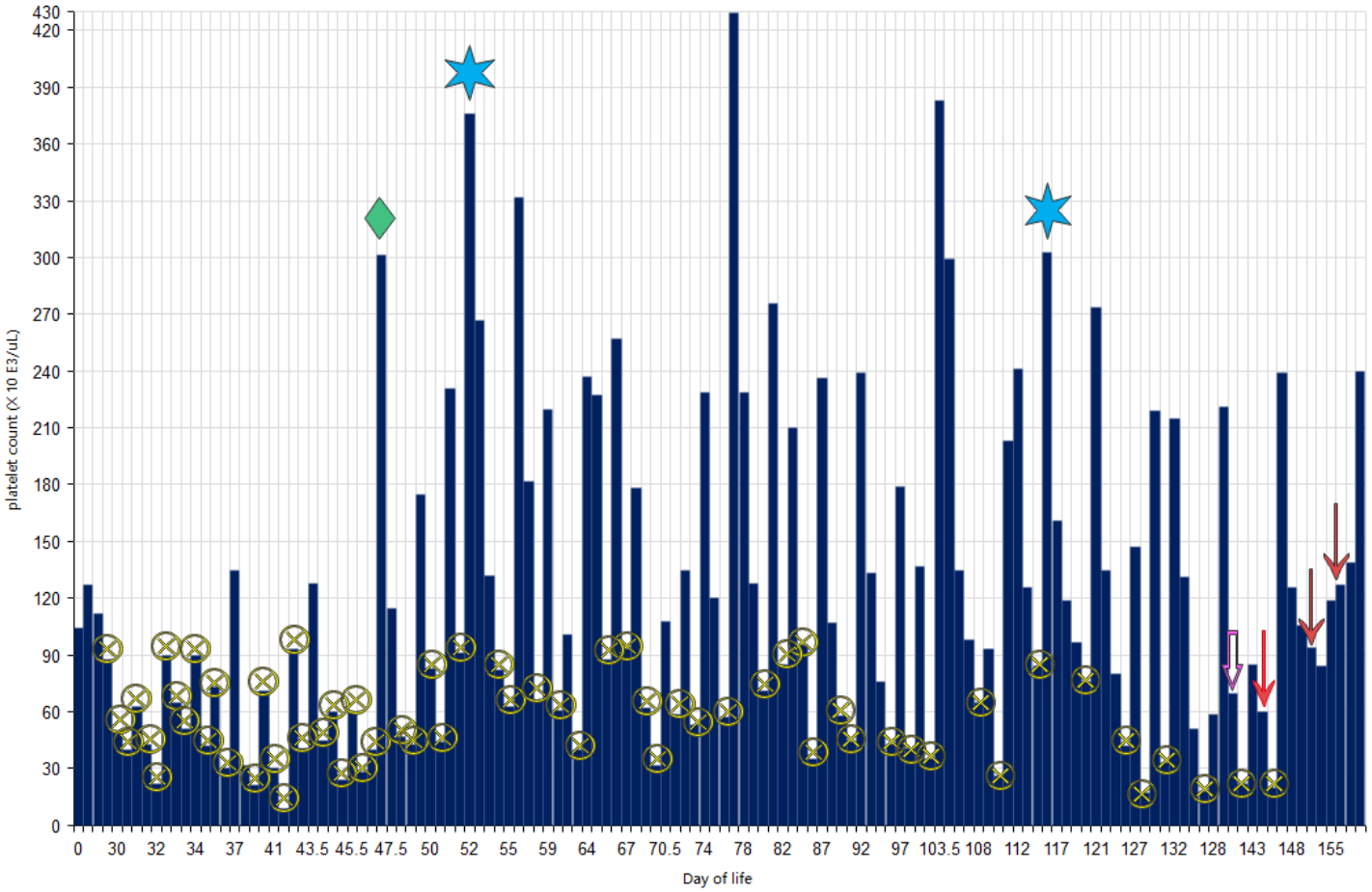
Her clinical condition improved following her surgery, such that by DOL 87, she was transfused only for platelet counts < 50 x 10^3/μL. She returned to surgery eight weeks later, where a primary end-to-end anastomosis was performed. The bowel, but not the liver, could be reduced into the peritoneal cavity. The closure was accomplished with a vicryl mesh.

She received 61 platelet transfusions from DOL 14 to 145. The last three weeks of her hospital stay showing the platelet count in relation to platelet transfusions, dexamethasone start, and romiplostim are seen in the table. Dexamethasone was started for worsening bronchopulmonary dysplasia. Her last transfusion for a platelet count of 20 x 10^3/μL was the day after the initial romiplostim. Before her first dose of romiplostim (2 mcg/kg/dose) subcutaneously (SQ), her immature platelet fraction (IPF) was 3.2% (NL 1.1-7.1%). The platelet count continued to decrease, so a second dose (4 mcg/kg/dose) SQ was given after one week. The platelet count nadir was two days later. The first rise in the platelet count was four days after the second dose. After receiving her 3rd dose, her IPF was 11.6%. The mean platelet volume was 10.2 fL with a platelet count of 70 x 10^3/μL One day after her third dose, she was transferred across the country to a NICU closer to her mother's home. A follow-up call to the hospital caring for this infant reported the platelet count was 240 x 10^3/μL on DOL 200, and she had not received any platelet transfusions follow her transfer. No complications that we could attribute to romiplostim occurred prior to her transfer, and we did not have access to follow-up data to evaluate for complications after the transfer.

Discussion

This was an unusual case of chronic thrombocytopenia associated with a platelet count as low as 22 x 10^3/μL from DOL32 to as

DOL	Platelet (x 10^3/μL)	transfusion	medication	Dose (mcg/kg)
136	18	yes		
140	70			
141			dexamethasone	
142	22	yes		
143	85			
144	60		Romiplostim	2.4
145	20	yes		
146	239			
148	126			
150	106			
151			Romiplostim	4
152	94			
153	84			
155	119			
156	127			
158			Romiplostim	4
159	139			
200	240			



FIGURE

Shows platelet count in response to platelet transfusion and romiplostim

Romiplostim; ⊗ platelet transfusion; plasma reduced platelets; surgery dexamethasone

late as DOL 145. Following three doses of romiplostim, the baby never received another platelet transfusion.

"In a survey of United States and Canadian neonatologists, Josephson found 30% - 45% of the neonatologists would transfuse platelets in a sick preterm infants with platelet counts of > 50 x 103/μL (5), a threshold of < 20 x 103/μL was selected by < 5%; and 50% selected 50 x 103/μL as the "transfusion" trigger for extremely low-birthweight neonates despite the absence of apparent bleeding (5)."

We have no unit standard when to transfuse platelets, and nationally, there are no universally accepted guidelines for platelet transfusion in neonates. In a survey of United States and Canadian neonatologists, Josephson found 30% - 45% of the neonatologists would transfuse platelets in a sick preterm infants with platelet counts of > 50 x 10^3/μL (5), a threshold of < 20 x 10^3/μL was selected by < 5%; and 50% selected 50 x 10^3/μL as the "transfusion" trigger for extremely low-birthweight neonates despite the absence of apparent bleeding (5). More recently, Curley showed a platelet count threshold of 50 x 10^3/μL had a significantly higher rate of death or major bleeding than those transfused at a platelet count threshold of 25 x 10^3/μL (6). Their study included infants who were older, up to 34 weeks and did not include in their analysis any infants born at 23 weeks and no mention of how many were included who underwent major surgery as in our this case. The platelet count was < 50 x 10^3/μL 24 times and < 25 x 10^3/μL 6 times as late as DOL 145. There were days when there as a rapid decrease in the platelet count to 26-50 x 10^3/μL. We suspect by waiting, the platelet count would have eventually decreased to < 25 x 10^3/μL, and the baby would have needed to be transfused. The number of transfusions may have been reduced if the lower threshold of 25 x 10^3/μL was followed, but in this sick, extremely premature infant, we were concerned the risk for significant bleed-

ing complications would be too great using such a low threshold.

We don't have a clear understanding of why the platelet count would continue to fall to < 25 10^3/µL at five months of age. We assumed the chronic thrombocytopenia resulted from prolonged gut inflammation resulting from infection or NEC. Thrombocytopenia can be categorized kinetically as hyporegenerative, consumptive, or a mixed mechanism. The great majority of neonates who receive >20 platelet transfusions have a consumptive or mixed mechanism (7). The mortality rate has been reported to be 50% for infants receiving ≥ 20 platelet transfusions. Though some of this correlation may be related to the degree of illness, platelet transfusions themselves may also be responsible for the increased mortality rate. The risk of sepsis from platelet bacterial contamination increases in those receiving >10 transfusions (8), so other treatment options need to be explored.

In certain thrombocytopenic conditions, corticosteroids can increase platelet counts. Bourchier and Weston reported that dexamethasone increased platelet counts, which was speculated to be on the basis of reduced inflammation and diminished platelet consumption (9). In contrast, Peng did not find dexamethasone increased platelet counts (10). Dexamethasone may have contributed to the increase in the platelet count in our case. However, the IPF was low at the time dexamethasone was started, suggesting the thrombocytopenia might have a hypoproliferative component. The platelet count continued to fall for 12 days, and she still required two platelet transfusions after starting dexamethasone.

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In certain problematic cases, thrombopoietic stimulators like romiplostim might be considered to reduce or eliminate platelet transfusions (3). Early in her hospital course, the rapid decrease in the platelet count suggested a consumptive process. Following sepsis and possible NEC, thrombocytopenia normally resolves in 1-2 weeks, but in some, thrombocytopenia may persist for several weeks. Before initiating romiplostim, the lower IPF indicated impaired capacity to increase platelet production, suggesting hyporegenerative thrombocytopenia (11). Sepsis or NEC can result in an insufficient compensatory increase in thrombopoiesis (12), which may explain why she responded to romiplostim. We also cannot know what effect the increased number of transfusions had on bone marrow hyporegeneration linked to transfusion inhibition of endogenous thrombopoietin as in this case. However, the platelet count rise and the IPF following romiplostim may suggest a possible boost from the exogenous thrombopoietin agonist.

The starting dose in neonates is unknown. Data from the ITP Consortium of North America ICON2 found the median starting dose was 2 mcg/kg with a maximum 10 mg/kg/dose (2). The only study in a neonate started with 1 mcg/kg/dose and increased up to 3 mcg/kg/dose. Four doses were given over a 35 day period. (4). After discussion with our hematology, co-author consultant, we elected to start with 2 mcg/kg SQ and increase the dose weekly until we had a sustained result. We doubled the dose to 4 mcg/kg after the first dose since the platelet count continued to fall. After the second dose, the platelet count began to increase four days later.

Possible complications following romiplostim have been reported to be rebound thrombocytopenia, bone marrow fibrosis, and thrombocytosis (13). Non-hematopoietic effects of romiplostim have not yet been well characterized, but recent data suggests that Tpo may result in proapoptotic and differentiating–blocking effects on neuronal cells (14), so the effects on subsequent neonatal neurodevelopment are unknown. In the first pediatric studies, the most frequent non-bleeding adverse events were headache, upper respiratory tract infections, vomiting, and oropharyngeal pain (15). No thrombotic or embolic events were noted in this baby prior to transfer, and her records were not available for review after her transfer.

This anecdotal use does not constitute a cause-and-effect relationship, nor does it establish the success of this treatment. It may have been a coincidence that the platelet count increased after the romiplostim. We would consider the cautious use of romiplostim in cases of severe and persistent thrombocytopenia in an attempt to reduce the number of platelet transfusions needed to control bleeding. We hope this case may encourage the study of romiplostim in neonates to define which platelet disorders would make this an appropriate drug for use.

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