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Rescue rFVIIa Treatment for Gestational Leukemia with Severe Bleeding Combined with Ineffective Platelet Transfusion: A Case Report and Literature Review

*Wenyi G[1], Shuli G[1], Li Bo[1], Junli S[2], Zhihong Z[3] and Huirui W[1]**

[1]Department of Hematology, Luoyang Central Hospital, Zhengzhou University, China

[2]ICU, Luoyang Central Hospital, Zhengzhou University, China

[3]Department of Blood transfusion, Luoyang Central Hospital, Zhengzhou University, China

Abstract

Background: Severe bleeding is a leading cause of death among acute leukemia patients. For those patients with non-acute promyelocytic leukemia, Platelet Transfusion Refractoriness (PTR) often coincides with thrombocytopenia during the bone marrow suppression phase after chemotherapy, as this period is characterized by a high risk of bleeding in patients. Recombinant activated Factor VII (rFVIIa) has shown good therapeutic efficacy in diseases including hemophilia and thrombocytopenia, but it has not been widely used in patients with malignant hematological diseases.

Methods: Here, we describe the case of a patient with gestational leukemia who developed PTR, but whose bleeding systems failed to improve after multiple treatments. This patient subsequently underwent treatment with rFVIIa.

Results: Following the administration of rFVIIa, the patient's bleeding stopped and they did not experience any adverse events.

Conclusion: This case demonstrates that rFVIIa holds promise as a potential rescue treatment for use in patients with malignant hematological diseases experiencing severe bleeding accompanied by PTR.

Keywords: rFVIIa; Malignant hematological diseases; PTR; Bone marrow suppression; Severe bleeding

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Correspondence:
Huirui Wang, Department of Hematology, Luoyang Central Hospital, Zhengzhou University, Luoyang, Henan 471009, China, Tel: +86-15538887399

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Introduction

Severe bleeding is an extremely serious complication that can arise in patients with malignant hematological diseases, necessitating urgent interventions. However, these patients often experience a lack of platelet transfusion efficacy for a variety of factors, and the use of immunoglobulin and HLA-matched platelets to manage these patients is often associated with poor efficacy. rFVIIa is a coagulation factor that is primarily employed for the treatment of patients with hemophilia, whereas there have been few reports focused on its application in patients suffering from Platelet Transfusion Refractoriness (PTR).

Here, we describe a case in which rFVIIa was successfully administered as a rescue treatment in a case of gestational leukemia. Following chemotherapeutic treatment, this patient experienced PTR during the bone marrow suppression phase that was accompanied by severe, life-threatening bleeding that failed to respond to multiple rounds of treatment. The patient finally underwent treatment with rFVIIa, which successfully stopped the bleeding. This case is presented along with an overview of the relevant literature pertaining to the hemostatic mechanisms whereby rFVIIa functions, thereby offering a reference for future research efforts.

Case Presentation

A 30-year-old female who was 26+1 weeks pregnant presented to the Intensive Care Unit (ICU) of our hospital due to fatigue and thrombocytopenia. She had undergone routine prenatal examinations during pregnancy, and was normal. Examination on admission revealed clear consciousness, a weak mental state, an anemic appearance, and scattered purpura visible in both

lower limbs. Bone marrow puncture, genetic, and chromosomal analyses confirmed a diagnosis of Acute Myeloid Leukemia (AML1/ETO positive, low-risk). Routine blood counts on admission revealed a WBC count of 25×10^9/L, hemoglobin levels of 56 g/L, and a platelet count of 4×10^9/L. She was administered an infusion of RBCs, which led to some apparent improvement in her symptoms of anemia. The patient's platelet HLA antibody results were ++++, and she was administered a platelet transfusion and human immunoglobulin. However, re-examination did not reveal any increase in platelet count. The fetal condition remained stable. Owing to the patient's extremely low platelet count and lack of obstetric indications, induced abortion surgery was not an option. The patient was therefore transferred to the hematology department for standard (Daunorubicin and Ara-C [DA]) induction chemotherapy.

On day two after chemotherapy during the bone marrow suppression phase, the patient's platelet count was 2×10^9/L, and she exhibited significant increases in systemic purpura, gingival bleeding, and hematuria, with a urine red blood cell count of 25,684 red blood cells per uL. Her bleeding symptoms failed to improve following platelet transfusion. The patient did not exhibit DIC, and she had a bleeding score of 3 points [1]. As platelet transfusion was ineffective, the patient was administered intravenous immunoglobulin and HLA-matched platelets. However, her bleeding symptoms continued to worsen and her hemoglobin levels declined to 58 g/L. On day 5 after chemotherapy, 1.2 mg of rFVIIa was urgently administered, collecting platelets before use. At 3 h after treatment, her gum bleeding stopped and the color of her blood and urine became noticeably lighter. rFVIIa was again administered after 24 h, and her urine color returned to normal with no evidence of microscopic hematuria, no new bleeding on the skin, and stable hemoglobin levels such that bleeding was found to have stopped, consistent with pronounced therapeutic efficacy. After chemotherapy treatment for 13 days, her bone marrow had recovered and passed the critical period, and the pregnancy was terminated in obstetrics. The patient did not experience any thrombotic events during this period.

Discussion

The hemostatic mechanisms of FVIIa

FVIIa is a 406 amino acid glycoprotein, and it is a coagulation factor that is dependent on vitamin K for its activity. While it has been used in clinical settings for more than three decades, the hemostatic mechanisms through which FVIIa functions remain incompletely understood. The traditional mechanism of action is one in which FVII combined with Tissue Factor (TF) to form a complex that subsequently activates FIX and FX, triggering the conversion of prothrombin into thrombin and thereby activating platelets in the damaged region such that they bind to FVIIIa and FV, converting fibrinogen into fibrin and thereby forming a thrombus to achieve hemostasis.

Despite this well-documented evidence, there is also evidence from clinical practice that rFVIIa can function through TF-independent mechanisms. For example, a study published in 1990 demonstrated the ability of purified FVIIa to activate FX even when tissue factors including phospholipids, apolipoprotein, and Ca2+ were absent [2]. In another study, rFVIIa was found to be capable of binding the surfaces of activated platelets and promoting the production of thrombin in the absence of TF [3]. This TF-independent mode of action is dependent on a coagulant and a Phosphatidylserine (PS)-containing cell membrane. In a separate mouse model study, a mouse model was established wherein FVIIa was found to directly induce the release of extracellular vesicles containing PS from endothelial cells, thereby producing the necessary surface for this activity [4]. These authors further determined that rFVIIa was capable of mediating the formation of a procoagulant surface in endothelial cells and promoting FXa and thrombin activation, thus confirming that it functions as more than merely a FXa agonist.

In 2007, Ghosh et al. [5] confirmed the ability of Endothelial Cell Protein C Receptor (EPCR) to serve as a site for FVIIa binding on cells, and several studies utilizing mouse models of hemophilia confirmed the ability of rFVIIa to bind to EPCR [6-9]. Through the downregulation of the protein C anticoagulant pathway, this factor is capable of inducting anti-inflammatory signaling activity and promoting vascular barrier integrity. Fager et al. [10] additionally found that EPCR is expressed by human platelets and that the hemostatic effects of FVIIa can be enhanced through the regulation of EPCR binding. *In vitro* analyses conducted by Kjalke et al. further revealed that in patients with a reduced platelet count, high-dose rFVIIa administration has the potential to accelerate the activation of these platelets and to achieve hemostatic efficacy through increases in initial thrombin production [11].

Analysis of the causes of PTR

The incidence of PTR among patients with hematological diseases has been reported to be as high as 43% [12], and this condition is often associated with immunological factors including antiplatelet antibodies. As the treatment of these patients' advances and the number of platelet transfusions rises, this can easily result in isoimmune reactions. Accordingly, as antiplatelet antibody positivity rates rise, so too does the incidence of PTR.

Allogeneic hematopoietic stem cell transplantation is an effective approach to treating malignant hematological diseases. In addition to needing multiple platelet transfusions in the context of transplantation, resulting in higher rates of antibody production that can result in PTR, patients suffering from post-transplantation graft-versus-host disease face a greater risk of dysregulated self- and non-self immune responses, further contributing the antiplatelet autoantibody production. These antibodies can also impact hematopoietic cell implantation, increasing the odds of early implantation failure and leading to a poor prognosis [13].

Pregnancy is closely associated with the maternal generation of antiplatelet antibodies, with some studies having reported significantly higher anti-HLA antibody positivity rates among pregnant women as compared to non-pregnant women, with these rates increasing with the number of pregnancies. From weeks 16 to 28 of pregnancy, platelet antibody positivity rates gradually rise. The patient in the present case was in the middle stages of pregnancy and tested strongly positive for platelet antibodies, potentially accounting for the incidence of PTR.

Clinical applications of rFVIIa in non-hemophilic patients with bleeding

In 1988, Hedner [14] was the first to deploy rFVIIa as a successful approach to treating two patients with severe type A hemophilia exhibiting with high valent inhibitors, prompting further clinical evaluation of the utility of rFVIIa in the clinic. Currently, rFVIIa has received approval for the treatment of congenital hemophilia, acquired hemophilia, congenital FVII deficiency, and thrombocytopenia with positive coagulation Factor VIII (FVIII) or FIX inhibitor. The positive

effects of rFVIIa in patients with inhibitor-positive hemophilia have prompted clinicians to explore its off-label use for other severe bleeding events. Among patients who do not have hemophilia, rFVIIa has been explored for its ability to control major post-traumatic bleeding and for use in contexts such as liver transplantation, cardiac surgery, and intracranial hemorrhage [15-18].

Hematological malignancies are often characterized by coagulatory dysfunction and thrombocytopenia, with patients often experiencing ineffective platelet transfusion such that bleeding can be difficult to control. Hoffman [19] described a patient with relapsed AML following autologous transplantation who underwent anti-CD33 treatment and experienced thrombocytopenia resulting in gastric bleeding. Following treatment with proton pump inhibitors, the patient experienced uncontrollable bleeding and was administered FVII (90 μg/kg). After 20 min, follow-up gastroscopy revealed significantly reduced gastric bleeding and blood clotting. Abdulkareem [20] was able to successfully treat a case of recurrent ALL complicated by pulmonary hemorrhage through the administration of nebulized rFVIIa. Amir [21] reported the case of a patient with multiple extramedullary plasma cell tumors complicated with intracranial hemorrhage that was treated with a 90 μg/kg q2h dosage of rFVIIa three total times, followed by q4h five total times. While post-infusion platelet counts in this patient remained extremely low, their intracranial hemorrhaging stabilized.

In patients with malignant tumors experiencing bleeding events, no optimal rFVIIa dose has been established, and the frequency of dosing remains similarly uncertain. Some reports have suggested that, for cancer patients experiencing life-threatening bleeding, the respective frequencies and dosages for treatment range from 1 to 17 times and 40 μg/kg to 120 μg/kg [22]. In clinical practice, the utilization of rFVIIa should be based on the specific bleeding situation of a given patient, with the supplemental administration of platelets and the correction of any underlying coagulation abnormalities prior to treatment. When a single dose is ineffective or partially effective, continued re-administration is indicated. The patient in the present case experienced severe urinary tract and skin mucosal bleeding during the post-chemotherapy bone marrow suppression period. Such circumstances pose a major risk to the lives of both pregnant women and fetuses. Owing to economic considerations for this patient, the frequency and dosages of rFVIIa used were lower than those in other reports. Platelets were transfused before both applications of rFVIIa, and following the cessation of bleeding the patient successfully emerged from the bone marrow suppression period.

The safety of rFVIIa treatment

The use of rFVIIa can result in the activation of systemic coagulatory activity, such that the potential for drug-related thromboembolic events is a potential complication of concern [23-25]. In one recent report, FVIIa increased the incidence of arterial thromboembolism when used to prevent or treat bleeding in non-hemophilic patients. A large comprehensive cohort study focused on rFVIIa revealed an association between the risk of arterial thrombosis and high-dose rFVIIa (≥ 80 ug/kg) treatment, particularly among elderly patients [26]. The reduction of the risk of allogeneic transfusion and related transfusion and bleeding events may, however, be conducive to more rapid improvements in clinical symptoms of bleeding, thereby having life-saving benefits [27]. One single-center retrospective analysis of 21 heart transplant recipients who received rFVIIa did not observe any differences in overall thromboembolic event incidence or the incidence of any other negative outcomes [28]. Similarly, no thromboembolic events were reported in a study in which 12 surgical patients were treated with rFVIIa [29]. Thrombotic events associated with rFVIIa administration are thus more likely to arise in patients with underlying risk factors, occurring so in a dose-dependent fashion [30,31]. The patient in the present case was a pregnant individual with a hematological malignancy in a hypercoagulable state, but she did not experience any thrombotic events, potentially owing to the low dose of rFVIIa that was administered. Even so, these concerns underscore the need to carefully monitor the coagulation status of patients and to be aware of the family history of thrombosis for all patients so that the risks of bleeding and thrombosis can be carefully weighed to guide therapeutic decision-making.

Conclusion

While current clinical guidelines do not recommend that rFVIIa be routinely used to treat bleeding events in patients with hematological disorders for whom platelet transfusion I ineffective, the present case highlights the safety and feasibility of low-dose rFVIIa treatment in patients with AML experiencing life-threatening bleeding for whom platelet transfusion is ineffective. At present, the optimal dosages and dosing regimens for rFVIIa remain unclear such that further research focused on this treatment approach is necessary.

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