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RECOMBINANT ACTIVATED FACTOR VII CONTROLS CHEMOTHERAPY-RELATED HEMORRHAGE IN PATIENTS WITH SOLID INTRA-ABDOMINAL TUMORS: A REPORT OF THREE PEDIATRIC CASES

Ernest Bilić[1], Ljubica Rajić[1], Ranka Femenić[1], Josip Konja[1], Katarina Vučić[1], Milivoj Novak[2], Miran Cvitković[2], Slobodan Galić[2] and Nikola Krmek[3]

[1]Department of Pediatric Hematology and Oncology, [2]Pediatric Intensive Care Unit, University Department of Pediatrics, Zagreb University Hospital Center; [3]University Department of Pediatrics, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) is used predominantly for the treatment of bleeding in patients with hemophilia and inhibitors, and in patients with traumatic injury. There are also literature reports of its use in chemotherapy-related bleeding in leukemia patients and intra- or postoperative bleeding in patients with solid tumors. We describe three pediatric patients where rFVIIa was successfully used to manage bleeding following the failure of conventional hemostatic treatments during chemotherapy for intra-abdominal tumors (hepatoblastoma, rhabdomyosarcoma and non-classified malignant sarcoma). Recombinant FVIIa proved effective and maintained hemostasis in two of three cases, with no evidence for toxic or adverse events in any of the treated patients.

Key words: *Blood loss – surgical; Blood loss – prevention and control; Factor VII – adverse effects; Abdominal neoplasms – complications; Abdominal neoplasms – chemotherapy; Abdominal neoplasms – surgery; Child*

Introduction

Massive hemorrhage and its consequences remain a significant cause of morbidity and mortality in critically ill patients with liver failure or tumors that affect hepatic function. Conventional treatment of such bleeds usually involves transfusion of red blood cells (RBCs), fresh frozen plasma (FFP), cryoprecipitate, and platelets in an attempt to replace deficient blood components. However, these treatments often fail to provide effective hemostasis[1]. Furthermore, replacement therapy has been associated with an increased risk of complications, including volume overload and transmission of infectious blood-borne agents[2].

Octreotide and desmopressin have recently been used for the management of hemorrhage in pediatric patients. Octreotide reduces splanchnic blood flow and is currently used for the treatment of acute variceal hemorrhage in children, but there are few reports of its use in pediatric patients with liver disease[3]. Desmopressin shortens a prolonged bleeding time in cirrhotic patients; however, we have been unable to find data supporting its efficacy in children with intra-tumor bleeding. In addition, the antidiuretic effect of this agent has been associated with a risk of water intoxication and secondary seizures when used in infants and small children[4].

Alternative hemostatic treatments are needed for the management of tumor- and chemotherapy related bleeding in pediatric patients. One such alternative may be

Correspondence to: *Ernest Bilić, MD, PhD*, Department of Pediatric Hematology and Oncology, University Department of Pediatrics, Zagreb University Hospital Center, Šalata 4, HR-10000 Zagreb, Croatia
E-mail: ernest.bilic@zg.t-com.hr

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provided by recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark). Developed for the treatment of bleeding episodes in patients with hemophilia and inhibitors[5], rFVIIa has also been used successfully in patients with life-threatening hemorrhage associated with massive trauma, surgery, Glanzmann's thrombasthenia, congenital FVII deficiency, liver failure, and other situations in which conventional therapeutic interventions often fail to achieve hemostasis[6-11]. Here, we report on its use in three pediatric patients with intra-abdominal tumors, coagulopathy, and chemotherapy-related hemorrhage. In all three cases, conventional hemostatic treatments proved ineffective, and the compassionate use of rFVIIa represented the last resort in attempting to achieve bleeding control. Written consent was obtained in all three cases.

Case Reports

Case 1

A full-term male infant weighing 4.2 kg was noted to have significant abdominal distension on the first day of life. The distension was caused by extreme hepatomegaly, with the liver extending to the pelvic entrance. Following histopathologic analysis of a liver biopsy, the diagnosis of hepatoblastoma was made. Initial hematologic studies are shown in Table 1. During chemotherapy with the PLADO protocol (cisplatin and doxorubicin), and despite supportive therapy with FFP, 20% albumin, and cryoprecipitate, the patient's clinical and laboratory status worsened. Repeat coagulation screen provided values shown in Table 1. The infant's abdomen diameter increased from 44 to 48 cm, and computed tomography (CT) revealed intraperitoneal hemorrhage. Hemoglobin (Hb) level dropped to 74 g/L and platelets to $30x10^9$/L despite continued supportive therapy with RBCs, platelets, albumin and FFP. The persistent bleeding produced a life-threatening condition, and the patient began to show signs of edema and tachycardia. Maximum oxygen saturation of the blood was 90%, and cardiorespiratory insufficiency was deemed imminent.

Supportive therapy provided only temporary improvement of the laboratory status, and the bleeding continued; therefore, a decision was made to administer two doses of rFVIIa 110 μg/kg, separated by a 3-h interval. Hematologic and liver profile immediately prior to rFVIIa administration is shown in Table 1. Following rFVIIa treatment, the hemorrhage slowed considerably and the patient's condition showed slight improvement. However, the same dosage was repeated the next day, upon which hemorrhage stopped completely and the patient's clinical status improved significantly. Labora-

Table 1. Case 1: rFVIIa administration during first cycle of chemotherapy in life-threatning persistant bleeding

Disease	Hematologic and liver profile upon diagnosis	Repeat hematologic and liver profile after chemotherapy	Hematologic and liver profile before rFVIIa administration	Hematologic profile after second day of rFVIIa treatment administration
Hepatoblastoma	Hb 113 g/L Htc 0.33 WBC $14.0x10^9$/L Plt $283x10^9$/L PT 0.48 aPTT 58.4 s TT 28.2 s Fibr 1.4 g/L D-dimer <0.3 mg/L AST 77 U/L ALT 15 U/L γGT 142 U/L ALP 284 U/L Bilirubin 223 μmol/L	Hb 86 g/L Htc 0.26 Plt $219x10^9$/L PT 0.30 αPTT 74.3 s TT 35.2 s Fibr 1.7 g/L AST 133 U/L ALT 17 U/L AGT 161 U/L ALP 231 U/L Bilirubin 131 μmol/L	Hb 95 g/L Htc 0.28 WBC $4.4x10^9$/L Plt $93x10^9$/L PT 0.30 αPTT 44 s Fibr 1.6 g/L AST 192 U/L ALT 57 U/L γGT 208 U/L Bilirubin 280 μmol/L	Hb 88 g/L Htc 0.26 WBC $4.2x10^9$/L Plt $96x10^9$/L PT 0.55 αPTT 36 s Fibr 1.73 AST 153 U/L ALT 44 U/L γGT 202 U/L Bilirubin 193 μmol/L

rFVIIa = recombinant activated factor VII; Hb = hemoglobin; Htc = hematocrit; WBC = white blood cell count; Plt = platelet count; PT = prothrombin time; αPTT = activated partial thromboplastin time; Fibr = fibrinogen; AST = aspartate transaminase; ALT = alanine transaminase; γGT = gamma glutamyl transpeptidase; ALP = alkaline phosphatase

tory measurements taken after the second day of rFVIIa treatment are shown in Table 1. The diameter of the abdomen also decreased to 47 cm. No further treatment with blood products was required. Following the last cycle of chemotherapy, CT showed regression of the tumor mass, and the patient was transferred to surgical department for further treatment. The child made full recovery and, three years later is alive and well.

Case 2

An 8-year-old boy was admitted with a 3-week history of abdominal pain and vomiting. γCT scan revealed a massive tumor in the upper abdomen (the origin of the tumor was in the liver) and the diagnosis of embryonic rhabdomyosarcoma was established upon histopathologic analysis of biopsy material. Initial hematologic studies are shown in Table 2. Following the first cycle of chemotherapy (IVA: iphosphamide, vincristine, actinomycin D), the patient demonstrated severe bone marrow aplasia, sepsis, bilateral pneumonia, pulmonary edema, multi-organ dysfunction syndrome, and severe intra-abdominal bleeding. He received platelets, RBCs, FFP, and cryoprecipitate, but hemorrhage continued. On the third day after the first cycle of chemotherapy, evidence of persistent gastrointestinal bleeding, melena, and hematemesis was observed. An ultrasound scan conducted at this time highlighted the accumulation of free fluid within the abdominal cavity.

Faced with severe gastrointestinal, intra-tumor, and intraperitoneal hemorrhage, a decision was made to administer two daily doses of rFVIIa 85 μg/kg, separated by a 3-h interval. Investigations immediately prior to rFVIIa therapy are shown in Table 2. The same tests repeated after rFVIIa administration indicated changes that are also shown in Table 2. Hemorrhage was temporarily stopped. Importantly, although rFVIIa was administered during the early stages of septic shock, there was no evidence of thrombotic complications.

The patient was transferred to the Intensive Care Unit (ICU), where he received additional four doses of rFVIIa over two days (two doses of 85 μg/kg at 3-h intervals *per* day). Metabolic acidosis (pH, 7.24) was observed and corrected on the first day at ICU. Bleeding stopped completely after the second day of rFVIIa treatment at ICU; the patient's hematologic status at that time is presented in Table 2. The patient was then treated for iatrogenic bone marrow aplasia, sepsis, and bilateral pneumonia.

Three weeks after admission to ICU, stabilization was obtained and chemotherapy was continued (six cycles of IVA, VAI [vincristine, actinomycin D, iphosphamide] and IVA – protocol CWS-96). Surgery was performed following reduction of the tumor mass (the rest of the tumor mass was removed together with the left hepatic lobe and caudate lobe). Then the patient received three more cycles of chemotherapy, following

Table 2. Case 2: rFVIIa administration during first cycle of chemotherapy in life-threatening persistent bleeding

Disease	Hematologic and liver profile at diagnosis	Hematologic and liver profile prior to rFVIIa administration	Hematologic and liver profile after rFVIIa administration	Day 3 of rFVIIa administration
Embryonal rhabdomyosarcoma	Hb 118 g/L Htc 0.33 (L) WBC 6.8x10^9/L Plt 313x10^9/L PT 0.24 αPTT 65.8 s Fibr 5.8 g/L D-dimer <0.3 mg/L AST 93 U/L ALT 80 U/L γGT 358 U/L ALP 431 U/L Bilirubin 139 μmol/L	Hb 94 g/L Htc 0.28 WBC 0.9x10^9/L Plt 46x10^9/L PT 0.36 αPTT 46.9 s Fibr 7.5 g/L D-dimer <0.3 mg/L AST 54 U/L ALT 26 U/L γGT 191 U/L ALP 169 U/L Bilirubin 63.7 μmol/L	Hb 90 g/L Htc 0.26 Plt 46x10^9/L PT 0.50 αPTT 42 s Fibr 7.2 g/L AST 67 U/L ALT 27 U/L γGT 191 U/L Bilirubin 47 μmol/L	Hb 85 g/L Htc 0.24 WBC 0.3x10^9/L Plt 28x10^9/L PT 0.68 αPTT 43 s Fibr 6.1 g/L AST 41 U/L ALT 22 U/L γGT 102 U/L Bilirubin 32 μmol/L

rFVIIa = recombinant activated factor VII; Hb = hemoglobin; Htc = hematocrit; WBC = white blood cell count; Plt = platelet count; PT = prothrombin time; αPTT = activated partial thromboplastin time; Fibr = fibrinogen; AST = aspartate transaminase; ALT = alanine transaminase; γGT = gamma glutamyl transpeptidase; ALP = alkaline phospatase

which no sign of tumor could be detected. Radiotherapy completed the patient's treatment, and he made full recovery.

Case 3

A 15-month-old male infant was admitted with a 2-week history of anemia, which was detected during treatment of pyelonephritis and bilateral otitis media. The child was lethargic, with a tumor mass of approximately 6 cm in diameter in the epigastric region. Ultrasonography and CT scans revealed a tumor of the left hepatic lobe. Initial investigations provided the measurements shown in Table 3. Doppler ultrasonography, angiography with embolization of the left hepatic artery, and tumor biopsy were performed. Histopathologic analysis of biopsy material showed large cells with no signs of differentiation, and the diagnosis of non-classified malignant sarcoma with undifferentiated rhabdoid components was established. Evidence of bleeding necessitated exploratory laparotomy, which revealed necrotic and diffusely bleeding tumor tissue. The neoplasm was found to be inoperable, with metastases distributed throughout all organs of the upper abdomen. At this time, laboratory parameters had values shown in Table 3.

Chemotherapy was initiated with the IVA cycle chemotherapy (CWS-96 protocol). On the next day, intraperitoneal hemorrhage occurred, with evidence of worsening hematologic parameters (Table 3). A total of 2300 mL of bloody fluid was found in the drain. The patient was treated at ICU for abdominal hemorrhage, hemorrhagic shock, restrictive respiratory insufficiency, and acute pulmonary edema with lung hemorrhage. Upon stabilization, chemotherapy was resumed. Next day, the patient's abdomen became distended as the result of progressive intraperitoneal bleeding, and his clinical state worsened. Recombinant FVIIa was administered on 11 consecutive days (two daily doses of 100 μg/kg at 3-h intervals), producing temporary hemostasis of approximately 3-h duration each time (chemotherapy was not administered for these 11 days). The patient also received concomitant RBCs, FFP, and cryoprecipitate. During treatment with rFVIIa, hematologic tests revealed mostly normal coagulation parameters. This therapy led to slow recovery of the patient and improvement of his general state over a period of three weeks. There were no signs of further bleeding. Following this apparent improvement, the chemotherapy regimen was continued (VAI). During the next chemotherapy cycle, hemorrhage recurred and was again partially controlled by the administration of FVIIa. Eventually, the patient died from multiple organ failure.

Table 3. Case 3: rFVIIa administration during chemotherapy in life-threatening persistent bleeding

Disease	Hematologic and liver profile at diagnosis	Hematologic and liver profile at the time of exploratory laparotomy	Day 1 of chemotherapy initiated
Non-classified malignant sarcoma with undifferentiated rhabdoid components	Hb 90 g/L Htc 0.27 WBC 12.2x10^9/L Plt 393x10^9/L PT 0.8 αPTT 26.5 s Fibr 1.7 g/L D-dimer <0.3 mg/L AST 81 U/L ALT 13 U/L γGT 31 U/L ALP 86 U/L Bilirubin 8 μmol/L	Hb 105 g/L Htc 0.32 WBC 19.4x10^9/L Plt 262x10^9/L PT 1.05 αPTT 26 s Fibr 1.6 g/L AST 71 U/L ALT 18 U/L γGT 48 U/L ALP 84 U/L Bilirubin 7 μmol/L	Hb 87 g/L Htc 0.25 WBC 10.2x10^9/L Plt 714x10^9/L PT 0.98 αPTT 33 s Fibr 1.7 g/L AST 65 U/L ALT 20 U/L γGT 45 U/L ALP 87 U/L Bilirubin 7 μmol/L

rFVIIa = recombinant activated factor VII; Hb = hemoglobin; Htc = hematocrit; WBC = white blood cell count; Plt = platelet count; PT = prothrombin time; αPTT = activated partial thromboplastin time; Fibr = fibrinogen; AST = aspartate transaminase; ALT = alanine transaminase; γGT = gamma glutamyl transpeptidase; ALP = alkaline phosphatase

Discussion

Multiple mechanisms predispose to bleeding in patients undergoing chemotherapy. Some of the cytostatic agents used in these regimens induce hepatotoxic effects, leading to decreased production of coagulation factors II, VII, IX, X, and fibrinogen. The production of proteins C and S may also be reduced; as these proteins inhibit coagulation, the treatment with cytostatics may thus increase the risk not only of hemorrhage, but also of thrombosis. Cytostatics also cause myelosuppression, resulting in anemia, thrombocytopenia, and leukocytopenia. Recent studies conducted in trauma victims have shown that anemia and hemodilution can, in turn, exert negative effects on the hemostatic process[7]; anemia causes prolongation of the bleeding time, whereas hemodilution reduces hematocrit and thus inhibits platelet adhesion and aggregation. A hematocrit of 20%, for example, restricts platelet aggregation to a degree similar to that observed when the platelet count drops below $20x10^9$/L. The severity of such dilutional coagulopathy is determined by both the volume and type of fluids infused; subsequently, the choice of fluid used to improve hydration is an important consideration in chemotherapy regimens[12]. Another negative effect of cytostatics can be found in their interference with the rebuilding of gastrointestinal epithelium. Finally, the blood vessels found in tumors are much more fragile than normal vessels, increasing the risk of hemorrhage. Several different stages of the coagulation pathway are thus affected in patients receiving chemotherapy, and bleeding often becomes severe and difficult to treat.

To the best of our knowledge, this is the first report of rFVIIa use in bleeding associated with solid tumor chemotherapy. There are case reports of rFVIIa use in patients with solid tumors[13-16], but without chemotherapy. All three pediatric patients suffered hemorrhage that remained refractory to conventional hemostatic treatments, and all were deemed to be at an imminent risk of death. Each patient received two daily doses of rFVIIa (85-110 μg/kg) at 3-hour intervals in an attempt to manage the bleeding. Following rFVIIa treatment, all three children showed improvements in coagulopathy.

Interestingly, the first and second cases initially presented with coagulopathy, as evidenced by shortened prothrombin time (PT), prolonged activated partial thromboplastin time (aPTT), and low (case 1) or high (case 2) fibrinogen levels. Both patients had neoplasms that affected the liver, and so the presence of coagulopathy may have been related to the decreased production of these coagulation factors synthesized by this organ. One of the patients (case 2) also had metabolic acidosis (pH, 7.24); as even a slight decrease in pH can compromise the function of coagulation enzymes and platelets[17], this may have contributed to the coagulopathy witnessed in this patient. However, in both cases, laboratory measures of coagulation, aPTT in particular, tended to improve following rFVIIa administration. The profound bleeding also stopped after two doses of rFVIIa; however, in view of the severity of the patients' clinical conditions, additional two (case 1) or four (case 2) doses were administered. The use of rFVIIa helped meet protocol requirements for treating individual neoplasm; at the time of writing, both patients are alive and well.

In the third case, a large hepatic tumor with a necrotic surface bled into the peritoneal cavity. Hemorrhage worsened within 1-3 days of administration of cytostatic agents (iphosphamide, vincristine, actinomycin D). As the patient's D-dimers were elevated (4 mg/L compared with normal values of <0.3 mg/L), it is possible that the high levels of tissue plasminogen activator had a negative effect on coagulation. In this patient, rFVIIa only temporarily halted the bleeding, and the child died at ICU during the next chemotherapy cycle. In this case, the benefits of rFVIIa were found mainly in the reduced need for blood product transfusion. A failure of rFVIIa to achieve hemostasis has been reported in cases of extensive bleeding from large surface areas, particularly when coupled with profound hemostatic compromise[18].

In conclusion, patients undergoing chemotherapy for solid tumors often present with an increased hemorrhagic tendency caused by hemodilution, insufficient hepatic production of coagulation factors, and the development of anemia and thrombocytopenia. As a result, they are often resistant to conventional hemostatic interventions, including replacement therapy with blood products. Recombinant FVIIa proved effective and maintained hemostasis in two of the three cases reported herewith, and no evidence of toxic or adverse events was noted in any of the treated patients. However, the cost of treatment was high, and it is very important that rational guidelines are developed for rFVIIa use in this indication. However, we believe that further research is warranted to confirm and extend our promising findings.

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Sažetak

REKOMBINIRANI AKTIVIRANI FAKTOR VII KONTROLIRA KRVARENJE POVEZANO S KEMOTERAPIJOM U BOLESNIKA SA SOLIDNIM INTRA-ABDOMINALNIM TUMORIMA: TRI PEDIJATRIJSKA PRIKAZA SLUČAJA

E. Bilić, Lj. Rajić, R. Femenić, J. Konja, K. Vučić, M. Novak, M. Cvitković, S. Galić i *N. Krmek*

Rekombinirani aktivirani faktor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) rabi se za liječenje krvarenja kod bolesnika s hemofilijom i inhibitorima, kao i u bolesnika s traumatskim ozljedama. U literaturi se nalaze prikazi slučajeva njegove primjene kod krvarenja u bolesnika tijekom kemoterapije leukemije, kao i kod intra- ili poslijeoperacijskih krvarenja u bolesnika sa solidnim tumorima. Prikazujemo tri pedijatrijska bolesnika kod kojih je rFVIIa uspješno primijenjen nakon što su zakazali uobičajeni terapijski postupci zaustavljanja krvarenja tijekom kemoterapije intra-abdominalnih tumora (hepatoblastom, rabdomiosarkom i nediferencirani sarkom). Rekombinirani FVIIa pokazao se posve učinkovitim u dvoje od troje opisanih bolesnika, a da pritom nisu zabilježene nuspojave u liječene djece.

Ključne riječi: *Gubitak krvi – kirurški; Gubitak krvi – prevencija i kontrola; Faktor VII – štetni učinci; Abdominalne novotvorine – komplikacije; Abdominalne novotvorine – kemoterapija; Abdominalne novotvorine – kirurgija; Dijete*