NOWOTWORY Journal of Oncology • 2002 • volume 52
Number 4 • 309–311

Successful use of activated recombinant factor FVIIa in the management of intra abdominal haemorrhage after cytoreductive surgery for advanced carcinoma of the ovary – a case report

Grzegorz Panek, Paweł Derlatka, Mariusz Bidziński
Elżbieta Stachurska[1], Ryszard Krynicki

Cytoreductive surgery plays a major role in the treatment of advanced carcinoma of the ovary. The procedure is frequently associated with a significant perioperative blood loss and tissue damage which, in some cases, might lead to initiation of life threatening pathologic clotting and fibrinolysis reactions. The authors describe a case of successful treatment of massive intra-abdominal haemorrhage complicating debulking surgery for advanced ovarian cancer with activated recombinant factor VIIa (NovoSeven, Novo Nordisk). After administration of NovoSeven in two doses of 20 μg/kg the patient fully recovered with no further blood loss and complete restoration of hemostasis. In conclusion, we suggest that activated recombinant factor VIIa is an effective haemostatic agent which can be used for the treatment of severe intra-abdominal haemorrhage which has failed to respond to conventional therapy.

Zastosowanie rekombinowanego czynnika krzepnięcia FVIIa w leczeniu ciężkiego krwotoku dootrzewnowego u chorej po rozległej operacji cytoredukcyjnej z powodu zaawansowanego raka jajnika – opis przypadku

Chirurgia cytoredukcyjna stanowi podstawę leczenia zaawansowanego raka jajnika. Towarzysząca tego typu operacjom utrata krwi oraz rozległe uszkodzenia tkanek mogą wyzwolić patologiczne procesy wykrzepiania i fibrynolizy, które w niektórych sytuacjach mogą stanowić bezpośrednie zagrożenie życia chorej.
Przedstawiono szczegółowy opis przypadku skutecznego zastosowania rekombinowanego czynnika VIIa u chorej z ciężkim krwawieniem dootrzewnowym, po operacji cytoredukcyjnej, wykonywanej z powodu zaawansowanego raka jajnika. U chorej bez pierwotnych zaburzeń układu krzepnięcia krwi zastosowano dwukrotnie preparat NovoSeven w dawce 20 μg/kg, uzyskując zatrzymanie krwawienia zagrażającego życiu. Korzystny efekt działania tego preparatu wskazuje na możliwość rozważenia jego użycia w przypadku ciężkich krwawień, niemożliwych do opanowania klasycznymi metodami.

Key words: recombinant factor VIIa, intra-abdominal haemorrhage, ovarian cancer, DIC
Słowa kluczowe: rekombinowany czynnik krzepnięcia krwi VIIa, krwotok dootrzewnowy, rak jajnika, DIC

Introduction

Despite significant progress in the understanding of complex mechanisms of malignant tumour pathogenesis and treatment improvements ovarian cancer remains the leading cause of death of women with tumours of the genital tract [1]. The high fatality ratio associated with ovarian cancer is linked to the lack of recognisable pattern of symptoms in the early stage. About 60-70% of women with ovarian cancer are diagnosed as advanced stage disease [2]. Both surgery and chemotherapy play major roles in the treatment of ovarian cancer. The aim of primary surgery is to stage the disease and to remove, optimally, all tumour mass. Although this is possible in early cancer of the ovary, it becomes less achievable as the tumour spreads throughout the abdominal cavity. Over the past 20 years, maximum cytoreductive surgery has been advocated on the premise that women with minimal residual disease have a better prognosis than those with bulky disease [2]. Cytoreductive surgery is commonly associated with tissue and vascular damage with the release of blood clotting activators [3]. From a wide spectrum of coagulation abnormalities associated with solid tumours including ovarian cancer, disseminated intravascular coagulation (DIC) is diagnosed in about 20-70% of patients

Department of Gynaecologic Oncology
[1] Department of Clinical Biochemistry
The Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Warsaw, Poland

[3]. In most cases DIC presents as a chronic sub-clinical disorder detected by laboratory tests. Overt DIC, with consumption of platelets and clotting factors and resultant acute bleeding, is a life-threatening condition which requires immediate transfusion of blood or blood products like fresh frozen plasma, cryoprecipitate or platelet concentrates.

The introduction of activated recombinant factor VII (rVIIa) (NovoSeven; Novo Nordisk) has been a significant advancement in the management of patients with congenital factor VII deficiency, haemophilia A and B with acquired coagulation inhibitors, thrombocytopenia and platelet function disorders [4].

Recently published reports confirm its efficacy in controlling severe haemorrhage after gynaecologic, urologic, gastrointestinal and brain surgery in patients without pre existing coagulation disorders [4].

We report the successful use of rVIIa in the treatment of severe intra-abdominal haemorrhage complicating cytoreductive surgery for advanced ovarian cancer.

Case report

A 40-year old woman presented to a regional hospital in January 2001 because of ascites and pelvic mass. The patient underwent explorative laparotomy with biopsies obtained from the ovarian tumours and omentum. After microscopic examination the diagnosis of stage IIIc moderately differentiated serous adenocarcinoma of the ovary was established. The patient was referred to the Department of Gynecologic Oncology of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, where she received six cycles of chemotherapy consisting of paclitaxel 170 mg/m^2 and cisplatin 70 mg/m^2. A partial response (PR) was achieved after completion of adjuvant treatment. After detailed clinical evaluation supported by imaging techniques the patient was qualified for second laparotomy. All preoperative results of haematologic and coagulation tests were normal. Total hysterectomy with bilateral salpingo-oophorectomy, omentectomy and anterior resection of the rectum with a low recto-sigmoid anastomosis was carried out.

The operation was completed with an adequate haemostasis with an intraoperative blood loss of about 1000 ml. Two units of packed red blood cells were administered at the final stage of the operation. Eighteen hours later the patient became hemodynamically unstable. Postoperative blood loss in the abdominal drain reached the level of 600 ml/h. This was initially managed conservatively with the infusion of 8 units of packed red blood cells and 4 units of fresh frozen plasma (FFP). As the patient did not stabilise interventional surgery was performed. About 2000 ml of blood were evacuated from the peritoneal cavity, while no specific bleeding site was found. A profuse oozing from the naked pelvic side walls and floor was evident. In order to diminish the blood supply to the pelvis a bilateral ligature of the internal iliac artery was performed, with subsequent improvement of vital hemodynamic parameters. Additional supplementation of 8 units of packed red blood cells, 4 units of FFP and 2 units of platelets was given. Despite blood volume supplementation and administration of desmopressin (0.4 μg/kg) blood loss in the abdominal drain was 200 ml/h with simultaneous deterioration of the patient's general condition. She received the first dose of NovoSeven of 20 μg/kg. PT value fell from 30.2 to 21.3 s and APTT from 85.4 to 48.8 s and drain blood loss to 35-40 ml/h. The second dose of NovoSeven of 20 μg/kg was administered 12 h later. A cessation of bleeding was observed with further improvement of PT to12.3 s and APTT to 34.3 s. The results of principal blood coagulation tests before and after administration of NovoSeven are presented in Table I.

Table I. Evolution of principal coagulation parameters after administration of rVIIa

	PLT 1000/ml	PT s	INR	APTT s	D-dimer ng/ml
before primary surgery	111	11.5	0.99	28.6	–
before I dose of rVIIa	27	30.2	2.41	85.4	437
after I dose of rVIIa	59	21.3	1.09	48.8	438
after II dose of rVIIa (48h)	101	12.3	1.43	34.3	205

The subsequent postoperative recovery was uneventful and the patient was discharged from the hospital on the 11th postoperative day. Five weeks after surgery she received her next cycle of CAP chemotherapy.

Discussion

Surgery plays a principal role in the diagnosis, staging and treatment of ovarian cancer. The aim of cytoreductive surgery is to remove both the primary lesions of the ovary and other intra-peritoneal implants. In advanced ovarian cancer removal of bulky tumour masses may improve patient's comfort, reduce the adverse metabolic consequences of the tumour, increase the ability to tolerate intensive chemotherapy and, above all else, improve survival.

Despite surgical technique improvements cytoreductive operations lead inevitably to tissue damage with liberation of clot-promoting agents into the circulatory system, initiating pathologic coagulation. Endothelial damage at the site of bleeding is associated with an increased tissue factor (TF) expression, which binds to the circulating factor VII, resulting in its activation and the formation of TF-FVIIa complexes. They, in turn, activate the coagulation cascade.

From a spectrum of coagulation abnormalities associated with solid tumours DIC is the most frequently diagnosed coagulopathy. Overt DIC with rapid consumption of platelets and clotting factors and acute bleeding is an emergency, which requires immediate transfusion of

blood, plasma, cryoprecipitate or platelet concentrates. This traditional method of management of DIC is not always effective while the infusion of a large volume of blood products carries the risk of transmitting infectious diseases. The introduction of recombinant activated factor VII (NovoSeven) has offered a significant advancement in the management of patients with congenital and acquired coagulation disorders. Although the principal indication for rVIIa administration is a deficiency of factor VII or the inhibitors to factor VIII or IX, there are numerous reports indicating a high effectiveness of NovoSeven in patients without the primary defects of coagulation [6-8]. The unique feature of thrombin generation at the site of vascular injury after rVIIa administration has been successfully utilized for the treatment of acute bleeding complicating cardiovascular, urologic and brain surgery [6]. There are also a few reports on the successful treatment of acute bleeding from locally advanced endometrial and vaginal cancer [8]. The presented case is the first description on the effective use of NovoSeven in the treatment of acute intra-abdominal bleeding with DIC complicating surgery for advanced ovarian cancer. The satisfactory clinical effect had been achieved after two doses of rVIIa of 20 μg/kg each. The optimal dosage of NovoSeven is a subject of intensive clinical investigation. Doses between 20 and 90 μg/kg are recommended for emergencies [4]. There are some controversies regarding the optimal mode of administration of NovoSeven. A single or repeated bolus injection seems to be as effective as continuous infusion, and more cost-effective [7]. Prophylaxis of excessive blood loss during radical surgery is another potential application of NovoSeven.

Preliminary results of a randomized trial comparing an intra- and postoperative blood loss of patients undergoing radical prostatectomy showed a significant reduction of blood loss in patients who had received a prophylactic dose of NovoSeven [9].

This trial will be continued to include more patients before the final conclusions are made.

To summarise – we believe that recombinant FVIIa may be an effective treatment of severe intra-abdominal haemorrhage of patients without inherited coagulation disorders when classic methods of treatment are ineffective.

Grzegorz Panek M.D., Ph.D.
Department of Gynaecologic Oncology
The Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Warsaw, Poland
W. K. Roentgena 5, 02-781 Warsaw, Poland

References

1. Zatoński W, Tyczyński J. *Nowotwory złośliwe w Polsce w 1996 r.* Warszawa: Centrum Onkologii; 1999, 21-2.
2. Pecorelli S. Annual report on the results of treatment of gynecological cancer. *J of Epid Stat* 2001; 6: 112-6.
3. Derlatka P, Gawrychowski K. Powikłania zakrzepowo-zatorowe u chorych na nowotwory narządów płciowych kobiecych. *Terapia* 1999; 79: 36-42.
4. Negrier C, Lienhart A. Overall experience with NovoSeven. *Blood Coagul Fibrinolysis* 2000; 11: 19-24.
5. Hedner U. Recombinant activated factor VII as a universal haemostatic agent. *Blood Coagul Fibrinolysis* 1998; 9: 147-52.
6. White B, McHale I, Ravi N et al. Successful use of recombinant FVIIa (NovoSeven) in the management of intractable post-surgical intra-abdominal haemorrhage. *Br J Haematol* 1999; 107: 677-8.
7. Vlot AJ, Ton E, Mackaay AJ et al. Treatment of a severely bleeding patient without preexisting coagulopathy with activated recombinant factor VII. *Am J Med* 2000; 108: 421-2.
8. Sajdak S, Moszyński R, Opala T et al. Kliniczne efekty zastosowania rekombinowanego czynnika krzepnięcia VIIa w przypadkach krwawienia u kobiet z nowotworem złośliwym endometrium i pochwy – opis dwóch przypadków klinicznych. *Ginekologia Praktyczna* 2001; 4: 1-4.
9. Friederich PW, Geerdink MG, Spataro M et al. The effect of the administration of recombinant activated factor VII (NovoSeven) on perioperative blood loss in patients undergoing transabdominal retropubic prostatectomy: the PROSE study. *Blood Coagul Fibrinolysis* 2000; 11: 129-32.

Paper received: 13 February 2002
Accepted: 10 June 2002