

Recombinant activated factor VII in patients with cancer and hemorrhagic disseminated intravascular coagulation

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Hemorrhagic disseminated intravascular coagulation (DIC) associated with the presence of underlying advanced or metastatic tumors are often difficult to control by conventional methods. We report the use of recombinant activated factor VII (rFVIIa) in patients with cancer and bleeding secondary to DIC. A total of 18 patients with cancer met pre-defined criteria for DIC. All patients had failed to respond to transfusion with blood products and treatment of the underlying malignancy prior to the introduction of rFVIIa. The median laboratory data at the time of treatment with rFVIIa were as follows: hemoglobin, 7.7 g/dl; platelets, $54 \times 10^9/l$; prothrombin time, 21 s; activated partial thromboplastin time, 41 s fibrinogen, 83 mg/dl; D-dimer, 17 $\mu\text{g/ml}$; and antithrombin, 32%. The dose of rFVIIa was 90 $\mu\text{g/kg}$ and the median number of doses administered was 5 (range, 3–10). Serial measurements of coagulation parameters were obtained at frequent intervals during treatment with rFVIIa. Of the 18 patients, 15 responded with cessation of bleeding and improvement in coagulation data. The prothrombin time and activated partial thromboplastin time normalized in all responding patients within 24 h of treatment. The median fibrinogen was 214 mg/dl while the median D-dimer was

6 $\mu\text{g/dl}$ at 48 h following the administration of rFVIIa. No thromboembolic complications were observed following rFVIIa. Our data provide evidence that rFVIIa can be used successfully to control the hemorrhagic episodes associated with DIC. Although this type of treatment appears to be safe, close monitoring of the patients is warranted. *Blood Coagul Fibrinolysis* 15:577–582 © 2004 Lippincott Williams & Wilkins.

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Introduction

Malignancy is a common cause for disseminated intravascular coagulation (DIC). The majority of patients with cancer and DIC present with hemorrhagic episodes that often do not respond to conventional measures [1]. Because DIC is a secondary phenomenon, no specific therapy can be applicable to any individual patient. In general, the usual approach to patients with cancer and DIC is based on two principles: replacement with blood products and treatment of the underlying tumor. Because a considerable proportion of these patients have advanced or metastatic malignancies, chemotherapy may not have favorable impact on the course of disease and, therefore, the trigger for DIC is not significantly altered [2].

Recombinant activated factor VII (rFVIIa) (NovoSeven[®]; Novo Nordisk A/S, Bagsvaerd, Denmark) is a novel hemostatic agent that has been used effectively in patients with hemophilia and inhibitors [3]. Because of the unique mechanism of action of rFVIIa that is dependent on forming a complex with tissue factor (TF) and generating sufficient thrombin at the site of injury, the drug has been also used in

bleeding disorders not caused by factor deficiency or inhibitor development [4–6]. Successful treatment with rFVIIa has been reported in patients with platelet disorders, post-surgical bleeding and in critically injured patients, as well as in bleeding episodes in patients with underlying malignancy [7–16]. We herewith report on the use of rFVIIa in patients with hemorrhagic DIC and underlying malignancy.

Patients and methods

Criteria for DIC

The diagnosis of DIC in patients with cancer was established using criteria from a recent report [1]. The definition was based on the clinical presentation with bleeding episode in combination with at least three of the following laboratory data: fibrinogen < 200 mg/dl, D-dimer > 0.5 $\mu\text{g/ml}$, platelets < $150 \times 10^9/l$, prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (aPTT), and antithrombin (AT) III < 80%.

Transfusion protocol

The criteria for transfusion with packed red blood cells (PRBC), platelets, cryoprecipitate, fresh frozen plasma

(FFP) and AT III concentrates are presented in Table 1. It should be emphasized that the administration of rFVIIa was based on the physician's discretion in terms of the timing following the support with blood products. During treatment with rFVIIa, the platelet count was maintained $\geq 50 \times 10^9/l$ by platelet transfusion and cryoprecipitate was administered to keep fibrinogen ≥ 100 mg/dl. Treatment for the underlying malignancy with chemotherapy was administered based on the extent of disease, prior chemotherapeutic regimens and the bone marrow reserve of the patients.

Statistical consideration

Unless otherwise indicated, all values are reported as the median and range. Box-plot analysis was used to report the time course of hemoglobin, PT, aPTT, fibrinogen, and D-dimer before and at 12, 24 and 48 h following the first dose of rFVIIa. Although coagulation parameters were assessed at frequent intervals in the majority of patients, and since patients received a variable number of doses of rFVIIa, these time points were chosen to assure homogeneity of reporting. Therefore, time 0 represents mean values just prior to the administration of the first dose of rFVIIa. The course of D-dimer is also reported at 72 h.

Results

Characteristics of patients

A total of 18 patients with cancer met the criteria for a diagnosis of hemorrhagic DIC. The median age for these 15 men and three women was 58 years (range, 48–68 years). The type of underlying malignancy was as follows: prostate cancer (three patients), lung cancer (three patients), breast cancer (two patients), gastric cancer (two patients), pancreatic cancer (two patients), soft tissue sarcoma (two patients), colon cancer (one patient), renal cell carcinoma (one patient), unknown primary (one patient), and acute myelomonocytic leukemia (one patient). Of the 18 patients, 15 had metastatic cancer and two had stage III disease. Table 2 presents the type of hemorrhagic events and laboratory data before the administration of rFVIIa. The bleeding episodes followed resection of a tumor or a metastatic lesion in five patients and biopsy of bone marrow in one patient. Hemorrhage

Table 2. Type of bleeding episodes, laboratory data and blood products administered to 18 patients with disseminated intravascular coagulation

Parameter	Value
Type of bleeding (n)	
Post-operative	6
Soft tissue	5
Hematuria	4
Gastrointestinal	3
Ecchymoses	3
Abdominal	2
Bone marrow	1
Laboratory data [median (range)]	
Hemoglobin (g/dl)	7.7 (6.8–8.5)
Platelets ($\times 10^9/l$)	54 (33–74)
Prothrombin time (s)	21 (15.5–35)
Activated partial thromboplastin time (s)	49 (37–73)
Fibrinogen (mg/dl)	83 (38–110)
D-dimer ($\mu g/ml$)	17 (9–36)
Antithrombin (%)	32 (22–68)
Blood products [median (range)]	
Packed red blood cells (U)	6 (4–12)
Platelets (U)	18 (12–36)
Cryoprecipitate (U)	30 (20–50)
Fresh frozen plasma (U)	8 (6–14)
Antithrombin (bags)	2 (2–4)

and DIC was triggered after bladder catheterization in two patients and venous access placement in one patient. The median number of doses of rFVIIa administered was 5 (range, 3–10 doses). Chemotherapy for the underlying cancer was administered to three patients.

Response and coagulation parameters

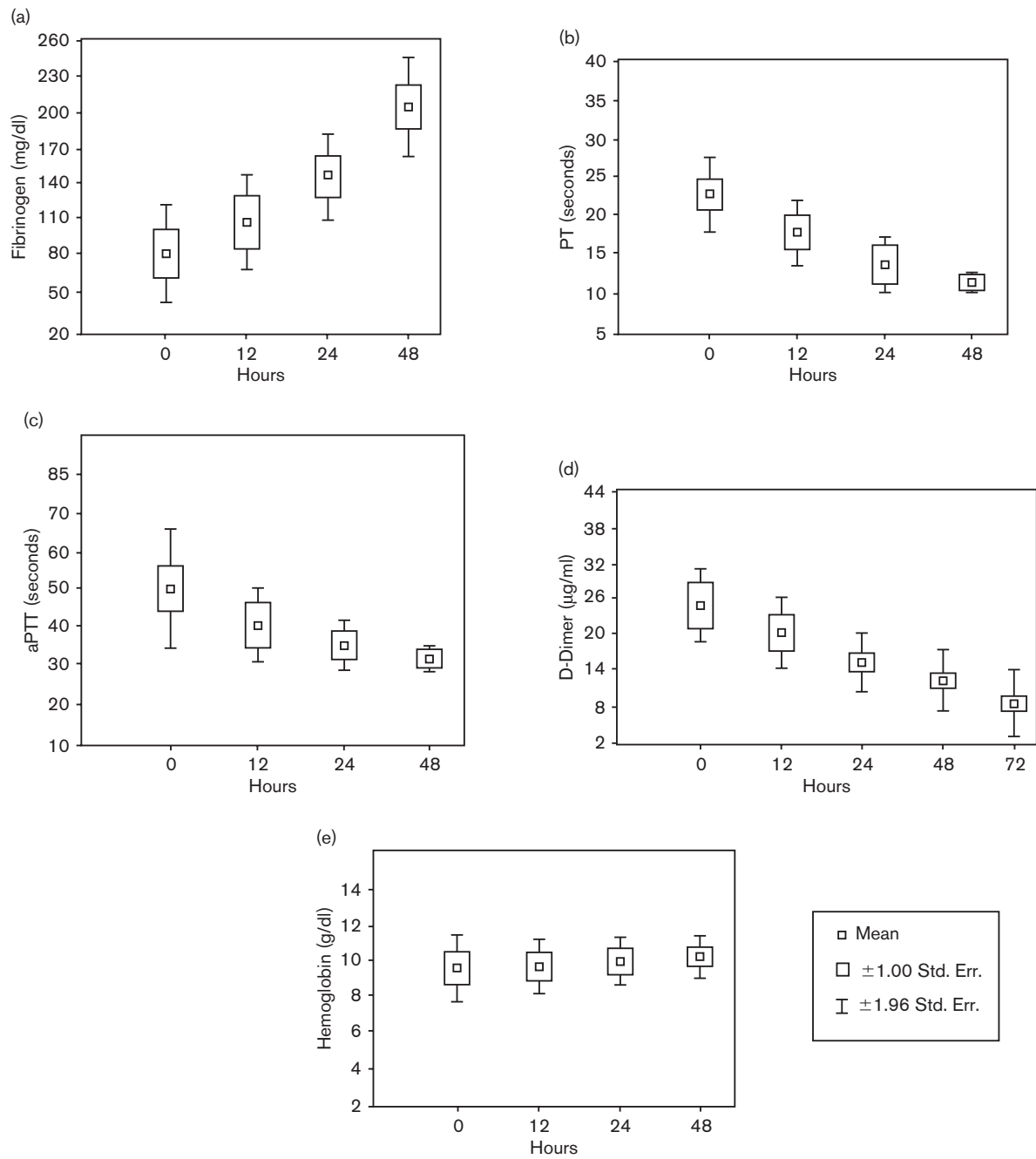
Of the 18 patients treated with rFVIIa, 15 achieved complete cessation of hemorrhage and resolution of DIC. The median time to achieve hemostatic control following the administration of rFVIIa was 28 h (range, 8–48 h). The time course for hemoglobin, PT, aPTT, fibrinogen and D-dimer in all 18 patients is shown in Figure 1a–c. In the responding patients, the PT, aPTT, and fibrinogen normalized within 48 h after rFVIIa. The decline in plasma levels of D-dimer lagged behind fibrinogen, but normalized in the responding patients after a median of 24 h after the last dose of rFVIIa.

No major toxicity related to rFVIIa administration was

Table 1 Transfusion protocol for patients with hemorrhagic disseminated intravascular coagulation

Transfuse with packed red blood cells if patient is hemodynamically compromised and/or hemoglobin < 8.0 g/dl
Obtain coagulation data prior to transfusion with plasma derivatives. The threshold for these products was: fibrinogen < 150 mg/dl, administer 10 bags cryoprecipitate; prolonged prothrombin time (PT)/activated partial thromboplastin time (aPTT), administer 2 U fresh frozen plasma. Transfuse with antithrombin concentrates for antithrombin III < 80%. Repeat tests after transfusion
Administer platelets if platelet count < $70 \times 10^9/l$ or as clinically indicated, and request count after transfusion
If hemostatic control of the episode is not achieved, repeat above measures and reassess coagulation values
Administer recombinant activated factor VII (rFVIIa) at 90 $\mu g/kg$ if cessation of bleeding has not been achieved by transfusion. Repeat rFVIIa depending on the physician's discretion and as dictated by the patient's status
Repeat fibrinogen, D-dimer, PT/aPTT and platelet measurements at frequent intervals during the administration and at 24 and 48 h after the last dose of rFVIIa. Obtain antithrombin III level on daily basis

Fig. 1



Box-plot of the time course of (a) fibrinogen, (b) prothrombin time (PT), (c) activated partial thromboplastin time (aPTT), (d) D-dimer, and (e) hemoglobin. The average values of these variables are depicted before (0 h) and following the administration of the first dose of recombinant activated factor VII. Std. Err., standard error.

observed. Minor adverse events included nausea in two patients and back pain in one patient. All three non-responding patients died. The causes of death were, hypovolemic shock, acute renal failure and acute respiratory distress syndrome.

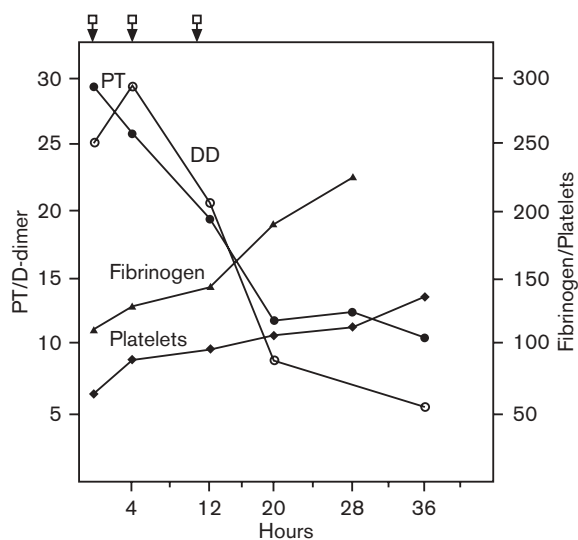
To illustrate the clinical course and the laboratory data

during and after treatment with rFVIIa, the following three patients are presented.

Acute myeloid leukemia

A 49-year-old man with liver cirrhosis was admitted to our institution for evaluation of acute leukemia (Fig. 2). Two days prior to transfer, a liver biopsy to assess for

Fig 2



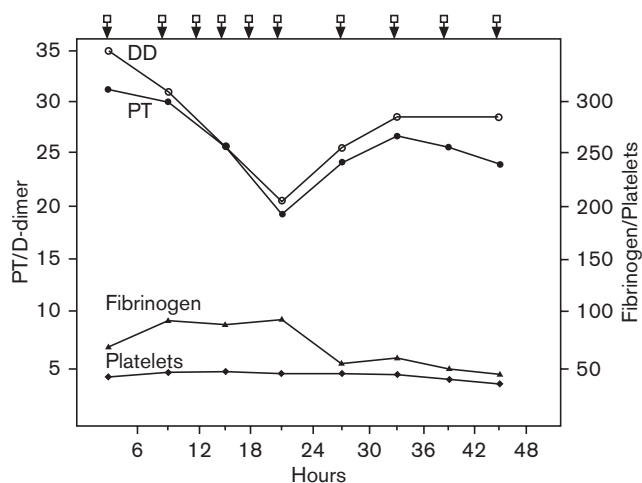
The time course of coagulation tests in the patient with acute myeloid leukemia.

possible liver transplantation was performed and showed chloasma. Upon transfer, the patient's medications included fragmin for portal vein thrombosis. Complete blood counts showed white blood cells of 11200 , hemoglobin of 11.2 g/dl and platelets of $81 \times 10^9/l$. The PT/aPTT and fibrinogen were not reported. A bone marrow aspiration and biopsy was performed and a diagnosis of acute myelomonocytic leukemia was made. Approximately 30 min after the procedure, the nurse noticed bleeding from the puncture site that did not respond to local measures. Oozing was also reported from a venous access site. Laboratory data showed a hemoglobin of 9.1 g/dl, platelets of $72 \times 10^9/l$, fibrinogen of 110 mg/dl, PT of 28 s and D-dimer was 25 µg/ml. Ten units of cryoprecipitate, 2 U FFP and 2 U PRBC were administered. On repeat coagulation tests, fibrinogen was 107 mg/dl, D-dimer was 25 µg/ml, PT was 25 s and AT III was 34% . Increased bleeding from the bone marrow puncture site, venous access and liver biopsy sites was observed. At this time rFVIIa (\downarrow) at a dose of 90 µg/kg was administered, and was repeated at 4 and 10 h. Correction of the PT and an increase in fibrinogen and platelet counts was observed after the third dose of rFVIIa.

Gastric cancer

A 71-year-old man underwent resection for gastric cancer. Excessive intraoperative bleeding from the surgical site prompted massive blood transfusion (Fig. 3). A hemoglobin of 2.7 g/dl, a PT of 34 s, platelets of $34 \times 10^9/l$, fibrinogen of 51 mg/dl and D-dimer at 37

Fig 3



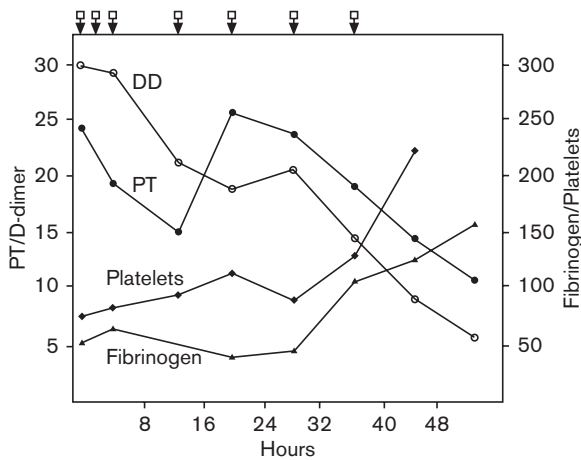
The time course of coagulation tests in the patient with gastric cancer.

µg/ml were recorded prior to PRBC transfusion. A total of 10 U cryoprecipitate, 4 U FFP and 6 U platelets were administered without correction of bleeding. rFVIIa (\downarrow) at a dose of 90 µg/kg was administered. The surgical team identified a laceration in the mesenteric vessels that prompted the closure of the surgical wound and placement of two drainage tubes. Subsequently, the patient was transferred to the surgical intensive care. There was continuous bleeding from the drainage tubes. Repeat labs showed hemoglobin of 5.3 g/dl, platelets of $42 \times 10^9/l$, fibrinogen of 91 mg/dl, D-dimer of 32 µg/ml, PT of 28 s and AT III of 8% . Further blood products and AT III concentrates were administered. A total of five more doses of rFVIIa at 90 µg/kg were administered with transient clinical improvement. Approximately 26 h after surgery, a new episode of bleeding from the surgical wound and access sites was noted. Repeat data demonstrated a severe drop in hemoglobin and worsening of DIC. The patient died from severe hypovolemia and organ failure. A total of 10 doses of rFVIIa were administered during the 48 h of surgery until the death of the patient.

Soft tissue sarcoma

A 56-year-old man was admitted to the surgical service for resection of a malignant sarcoma of the abdominal wall. The pre-operative history, the PT/aPTT and the platelet count were normal. Excessive blood loss from the surgical wound and oozing from access sites were noticed intraoperatively (Fig. 4). Hemodynamic compromise of the patient and a hemoglobin of 7.2 g/dl prompted PRBC transfusion. The coagulation service was notified after a total of 9 U PRBC had been transfused. Laboratory data at this point showed fibrinogen of 44 mg/dl, D-dimer of 30 µg/ml, prolonged PT/

Fig 4



The time course of coagulation tests in the patient with soft tissue sarcoma.

aPTT and platelets at $87 \times 10^9/l$. Ten units of cryoprecipitate and 2 U FFP were administered. Repeat fibrinogen was 53 mg/dl, D-dimer was $> 30 \mu\text{g/dl}$ and the platelet count was $72 \times 10^9/l$. Ten further units of cryoprecipitate, 2 U FFP and 2 U PRBCs were administered. Persistent bleeding from the surgical incision prompted the infusion of rFVIIa (\downarrow) at a dose of 90 $\mu\text{g/kg}$, which was repeated at 2 and 4 h. Upon transfer to the surgical care unit, repeat laboratory showed a hemoglobin of 9.8 g/dl, D-dimer of 28 $\mu\text{g/ml}$, fibrinogen of 65 mg/dl, PT of 19 s and platelets of $79 \times 10^9/l$. Because of continuous oozing, rFVIIa (\downarrow) was administered on four more occasions within 24 h after transfer. The patient was extubated within 36 h from surgery with platelets $> 200 \times 10^9/l$, fibrinogen of 162 mg/dl and normal PT. The D-dimer level normalized 48 h after surgery.

Discussion

The process of DIC is characterized by an uncontrolled activation of the clotting and fibrinolytic pathways resulting in excessive release of thrombin and fibrin [1,2]. The end result of this activation is the consumption of coagulation factors and platelets and diffuse deposition of fibrin in different organs. This manifests clinically as bleeding, clotting and organ failure. It is unclear how malignancy can trigger DIC; the process, however, may be related to expression of TF on cancer cells or the release of proteases that directly activate factor X and subsequently activate coagulation [2]. The frequent presentation with bleeding as opposed to thrombosis in patients with cancer and DIC may be indicative of a dominant activation of fibrinolysis [1]. Management of these patients is confounded by the

use of chemotherapy and the functional status of the patients.

It is important to emphasize that the criteria used for the diagnosis of DIC in the current series are based on a previous study [1] and differ from the scoring systems of DIC defined by the Scientific Subcommittee on DIC of the International Society on Thrombosis and Haemostasis [17]. For example, a higher cut-off for fibrinogen level was chosen because patients with malignancy often have higher plasma fibrinogen levels than other risk groups for DIC. Also, both D-dimer and AT III plasma levels were incorporated in our definition to enhance the validity of diagnosis and to be used as surrogate markers of response to treatment. The need for immediate management of bleeding in our patients required a comprehensive robust approach rather than a scoring system.

The hemostatic effect of rFVIIa appears to be related principally to two factors. First, rFVIIa binds to TF and the complex TF/rFVIIa activates coagulation by activating factor X and factor IX [5]. Second, rFVIIa binds to the surface of activated platelets, causing activation of factor X and generation of thrombin [4–6]. Since TF is expressed and activated platelets are present in areas of tissue injury, hemostasis achieved using rFVIIa remains localized to the site of vascular compromise. This probably accounts for the relatively rare thromboembolic events reported with the use of rFVIIa [18]. Also, this unique mechanism of action has prompted the administration of rFVIIa in a variety of bleeding disorders including those related to DIC and trauma [10–16].

In the current report, 18 patients with cancer and DIC were treated with rFVIIa after failure of conventional measures, including support with blood and plasma products. Of the 18 patients, 15 achieved complete response in terms of cessation of bleeding and normalization of the coagulation parameters. One may argue that this successful outcome is confounded by the use of plasma and blood products that may obscure the interpretation of data. It is clear, however, that these standard measures failed to control the hemorrhagic episodes in our patients. This is corroborated by the recent data that only approximately one-third of patients with cancer and DIC achieve hemostatic response with conventional replacement and chemotherapy [1]. Only three patients in this series were deemed to be good candidates to receive chemotherapy for the underlying tumor.

An additional observation emerged from our study that merits some consideration. Throughout the course of treatment with rFVIIa, plasma D-dimer levels remained elevated in all patients despite improvement in

fibrinogen level and shortening of PT and aPTT in the 15 responding patients. Although we do not have a clear explanation for this phenomenon, it is possible that administration of rFVIIa in patients with over-activity of the fibrinolytic pathway, such as the patients in this series, may cause an increase in the formation of fibrin extravascularly. Excessive lysis in the extravascular compartment and back diffusion of the dimers might have led to persistent elevation in the D-dimer. This remains a hypothesis that needs to be confirmed by further investigation.

During the course of treatment in our group of patients, we attempted to maintain a fibrinogen level > 100 mg/dl and a platelet count $> 50 \times 10^9/l$ by transfusion with blood products. It is not known whether an ideal level of these parameters is required to obtain more effective results in patients with DIC undergoing treatment with rFVIIa.

Despite the impressive results obtained in our group of patients, which was heavily pretreated with chemotherapy, caution should be exercised before the generalization of the application of this type of treatment. It should be emphasized that the therapeutic approach followed in the current series remains experimental and it is imperative that a full understanding of the underlying disorder and ensuing DIC process exists before using rFVIIa. Also, pending data from prospective studies, the most appropriate dose and the frequency of administration of rFVIIa in DIC remain to be defined. Nevertheless, our results are encouraging and provide an important therapeutic option in the treatment of hemorrhagic DIC in patients failing conventional management.

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