

# Successful Non-Standard Approaches to Massive Hemoptysis in Invasive Pulmonary Aspergillosis

Mirjana Mitrović<sup>1</sup>, Ivo Elezović<sup>1,2</sup>, Nada Suvajdžić-Vuković<sup>1,2</sup>, Darko Antić<sup>1,2</sup>

<sup>1</sup>Clinic of Hematology, Clinical Center of Serbia, Belgrade, Serbia;

<sup>2</sup>School of Medicine, University of Belgrade, Belgrade, Serbia

## SUMMARY

**Introduction** Invasive pulmonary aspergillosis (IA) is the most frequent invasive fungal infection in patients with hematological malignancies. Massive hemoptysis (MH) with blood loss more than 300-600 ml in 24 hours is a rare (5-10% of IA patients) but frequently fatal complication. Standard treatment of MH, such as oxygenation, a semi-sitting position with the bleeding site down, bronchoscopical suctioning, antifungal therapy, transfusion support and surgical resection might be either ineffective or not feasible in some cases.

**Outline of Cases** We report two patients with life threatening, non-controlled, massive hemoptysis who were successfully managed by non-standard measures. A 61-year-old male with acute myeloid leukemia developed pulmonary IA and massive hemoptysis after consolidation cure by chemotherapy. The bleeding site was localized in the VI lung segment by bronchoscopy. Local application of fibrinogen-thrombin concentrate (fibrin glue) stopped the bleeding. A 22-year-old female patient with the diagnosis of severe aplastic anemia developed IA and massive hemoptysis early after application of immunosuppressive therapy (antilymphocyte globulin, cyclosporine and corticosteroids). Conventional transfusion therapy, desmopresine and antifibrinolytics were ineffective. This urgent condition was successfully treated with human activated recombinant factor VII (rFVIIa, NovoSeven®).

**Conclusion** Our experience together with data from the available literature suggests a potential benefit of fibrinogen-thrombin concentrate and rFVIIa in the treatment of refractory critical bleeding in hematological patients.

**Keywords:** invasive pulmonary aspergillosis; massive hemoptysis; rFVIIa; fibrinogen-thrombin concentrate

## INTRODUCTION

Invasive pulmonary aspergillosis (IA) is increasingly reported in patients with hematological malignancies [1]. Hemoptysis is a frequent complication, occurring in 50-83% of patients with IA [1]. Massive hemoptysis (MH), defined as a blood loss of more than 300-600 ml coughed up within 24 hours; it occurs in 5-10% of patients and, as a medical emergency requires immediate treatment [2]. Standard treatment measures include: supplemental oxygen, positioning the patient with the bleeding site down, bronchoscopical suctioning, antifungal therapy, transfusion support and emergency surgical resection in combination with antifungal treatment [2, 3].

Hemoptysis, usually moderate, was registered in a considerable number of our patients with IA. Antifungal therapy, alone or accompanied with other standard measures, stopped the bleeding in the majority of patients. We report two patients with MH who were treated in a non-standard way.

## CASE REPORT 1

A 61-year-old male with acute myeloid leukemia (AML) M2, normal karyotype, intermediate risk group, Eastern cooperative oncology

group performance status 2, had been treated with the „MRC 10” protocol, induction chemotherapy „ADE 3+5+10” (cytosine arabinoside, daunorubicin and etoposide) with subsequent achievement of complete remission. After a consolidation cycle „ADE 3+5+8” he experienced febrile neutropenia lasting for 15 days. All the time he had been receiving Fluconazole as antifungal prophylaxis. On the 32nd day the patient was febrile with a complete blood count (CBC): hemoglobin (Hb) 98 g/L, white blood count (WBC)  $2.0 \times 10^9/L$  with 43% neutrophils, platelet count  $80 \times 10^9/L$ . A chest X-ray showed focal bronchopneumonia of the left lung (at the junction of the VII and IV ribs). Neither high-resolution computer tomography (CT) nor the galactomannan tests were available. The culture from the central venous catheter was positive for *Aspergillus niger* and the blood culture for *Staphylococcus aureus*. Risk factors for invasive fungal infection (IFI) were prolonged neutropenia (lasting 15 days), a central vein catheter (CVC), advanced age, AML and persistent fever for 72 hrs refractory to broad-spectrum antibiotic treatment. The antibiotic therapy was modified (Vancomycin) and antimycotic therapy (Amphotericin B 1 mg/kg) was initiated. Two days later MH developed. There was no evidence of a hemostatic defect as the platelet count was  $100 \times 10^9/L$ , fibrinogen 3.54 g/L, prothrombin time (PT)

## Correspondence to:

Mirjana MITROVIĆ  
Clinic of Hematology  
Clinical Center of Serbia  
Dr Koste Todorovića 2  
11000 Belgrade  
Serbia  
mmg@beotel.net

94% and activated partial thromboplastin time (aPTT) 25.4 s. The bleeding site was localized via bronchoscopy in the VI lung segment and abated after local application of fibrinogen-thrombin concentrate (fibrin glue, Beriplast®, Aventis). After 30 days of antifungals (Voriconazole 10 days and Amphotericin B 20 days) the lesion completely resolved.

## CASE REPORT 2

A 22-year-old female patient with severe aplastic anemia (initial CBC: Hb 82 g/L, WBC  $0.4 \times 10^9/L$ , absolute neutrophil count  $0.03 \times 10^9/L$ , platelets  $10 \times 10^9/L$ ) had been treated with antilymphocyte globulin (ATG-Fresenius® 400 mg on day 1, 300 mg on days 2 and 4 and 200 mg on days 3 and 5), Cyclosporine A, methyl-prednisolone, G-CSF and antifungal prophylaxis (Itraconazole  $2 \times 200$  mg). Seven days after therapy initiation the patient developed high fever with a non-productive cough. The chest X-ray showed multiple bilateral pulmonary infiltrates. Culture results of blood and sputum were both negative. Risk factors or IFI were prolonged neutropenia (lasting 30 days) and CVC. Treatment with Meropenem, Vankomycin and Amphotericin B (1 mg/kg) was initiated. Three days later MH developed with CBC as follows: Hb – 39 g/L and platelet count –  $7 \times 10^9/L$ . Coagulation studies were normal (fibrinogen 8.4 g/L, PT 83%, PTT 31.2 s, D-dimer 193 µg/L). Intensive transfusion therapy (packed red blood cells 1446 ml, platelets 772 ml and fresh frozen plasma 550 ml) increased the Hb level to 70 g/L and platelet count to  $51 \times 10^9/L$ , but with no significant effect on MH intensity. Tranexamic acid (Ciclokapron®) and desmopressine (Emosint®) were also ineffective. Bronchoscopy with infusion of fibrinogen-thrombin was unmanageable due to the diffuse pattern of bleeding. Faced with this life threatening situation human activated recombinant factor VII (rFVIIa, NovoSeven®, NovoNordisk) at a bolus dose of 90 µg/kg (total dose 4.8 mg) was administered, followed by complete cessation of hemoptysis. Despite this hemostatic effect hypoxemia progressively worsened (pO<sub>2</sub> 46–62 kPa) and the patient was placed on mechanical ventilation. Unfortunately, multiple organ failure developed followed by death 30 hours after the onset of bleeding and 6 hours after Novo Seven initiation.

## DISCUSSION

MH is a well described and frequent fatal complication of IA [1, 2, 4]. Standard treatment might be ineffective and surgical resection may be unfeasible due to difficulty

in identifying the bleeding site and time delay to surgery [2, 3, 4].

IA is the second most common fungal infection in acute leukemia, occurring in 5–25% of patients [1, 4]. Minor hemoptysis has been reported in up to 58% of patients with IA and AML. On the other hand, massive fatal hemoptysis is rare and usually happens during bone marrow recovery [2, 3, 4]. In our first AML patient, localized bleeding in the sixth lung segment was successfully managed by the local application of fibrinogen-thrombin concentrate via bronchoscopy. According to our experience and data in the literature, local infusion of fibrinogen-thrombin is established as a simple and effective therapy for localized hemoptysis [5, 6].

rFVIIa is a hemostatic agent originally developed for the treatment of hemorrhage hemophiliacs with inhibitors [7, 8]. The supraphysiological level of FVIIa resulting from an injection of 90 µg/kg (approximately 25 times normal), combined with abundant tissue factor exposed to subendothelial cells of the damaged vessels, was necessary to generate sufficient thrombin for a stable clot formation [7, 8]. In the last few years rFVIIa has been employed with success in many „off label” bleeding conditions unresponsive to standard therapy [9, 10, 11]. A systematic literature review from 2007 recorded 162 hemato-oncological patients with bleeding (49 non-transplanted/ 113 transplanted), who were treated with rFVIIa. Cessation or significant reduction in either blood loss or need for blood transfusion was obtained in 93.9% of the non-transplanted and in 61.1% of the transplanted patients [10].

Local intrapulmonary administration of rFVII is a new, attractive treatment option for critical pulmonary bleeding. Symptomatic therapy of diffuse alveolar hemorrhage with intrapulmonary administration of rFVIIa in six patients, in a lower dose (50 µg/kg vs. 90 µg/kg), was found to have a hemostatic effect in all patients without adverse events [12]. In our patient with severe aplastic anemia and MH, the context of conventional therapy for IA was ineffective. This urgent condition was successfully treated with rFVIIa.

Our experience showed that standard therapy measures for MH in IA could be ineffective or not feasible and suggests benefit from a non-standard therapy approach, like rFVIIa therapy or local application of fibrinogen-thrombin concentrate via bronchoscopy. However, most currently available literature data concerning non-standard therapy are derived from uncontrolled studies including single cases or small series of patients [9–12]. Thus, future trials with a larger number of patients are needed to establish indications for both local fibrinogen-thrombin concentrate and rFVIIa therapy, as well as to assess the most appropriate mode of application, timing, optimal dosage of rFVIIa and its efficacy and safety in this setting.

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## Успешни нестандартни приступи лечењу масивне хемоптизије код болесника с инвазивном аспергилозом плућа

Мирјана Митровић<sup>1</sup>, Иво Елезовић<sup>1,2</sup>, Нада Сувајџић-Вуковић<sup>1,2</sup>, Дарко Антић<sup>1,2</sup>

<sup>1</sup>Клиника за хематологију, Клинички центар Србије, Београд, Србија;

<sup>2</sup>Медицински факултет, Универзитет у Београду, Београд, Србија

### КРАТАК САДРЖАЈ

**Увод** Инвазивна аспергилоза (ИА) плућа је најчешћа инвазивна гљивична инфекција код болесника с хематолошким малигнитетима. Масивна хемоптизија (МХ), са губитком крви већим од 300-600 ml за 24 сата, јесте ретка (5-10% болесника са ИА), али често смртоносна компликација. Стандардни приступ лечењу МХ, који подразумева постављање болесника у полуседећи положај, оксигенацију, бронхоскопску сукцију, антигљивичну терапију, трансфузиону потпору и хируршку ресекцију, често је неефикасан или недоступан за хематолошке болеснике с поремећајима хемостазе.

**Прикази болесника** Приказујемо два болесника с масивном, по живот опасном и неконтролисаним хемоптизијом који су успешно лечени нестандартним приступом. Код болесника старог 61 годину са дијагнозом акутне мијелоидне левкемије ИА плућа праћена МХ се развила по примени консолидационе кура хемиотерапије. Место крварења је бронхоскопски локализовано у шестом плућном сегменту. Током

бронхоскопије локално је примењен концентрат фибриногена и тромбина (фибрински лепак), чиме је крварење заустављено. Код болеснице узраста од 22 године са дијагнозом апластичне анемије тешког степена ИА плућа и МХ су се развиле непосредно након примене имunosупресивне терапије (антилимфоцитни глобулин, циклоспорин и кортикостероиди). Конвенционална трансфузиона терапија, дезмопресин и антифибринолитици нису значајно смањили крварење. Ово хитно стање је успешно збринуто применом активираним рекомбинантног фактора VII (*rFVIIa*, *NovoSeven*<sup>®</sup>). **Закључак** Наше искуство уз податке из литературе указује на потенцијално значајну улогу концентрата фибриногена и тромбина и *rFVIIa* у лечењу рефрактерних, животно угрожавајућих крварења код хематоонколошких болесника са ИА плућа и МХ.

**Кључне речи:** инвазивна аспергилоза плућа; масивна хемоптизија; *rFVIIa*; концентрат фибриногена и тромбина

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