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Diffuse Alveolar Hemorrhage After Allogeneic Hematopoietic Stem-Cell Transplantation: Treatment With Recombinant Factor VIIa

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A M E R I C A N C O L L E G E O F
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patients with primary pulmonary angiosarcoma. Paclitaxel, which exerts antiangiogenic and apoptotic effects, has been shown¹⁶ to possess substantial activity against angiosarcoma as a single agent, even in patients who have been treated previously with radiotherapy or chemotherapy. Further investigations are warranted to define optimal multimodality strategies, including radiotherapy, immunotherapy, and chemotherapy, to combat this challenging disease.

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Diffuse Alveolar Hemorrhage After Allogeneic Hematopoietic Stem-Cell Transplantation*

Treatment With Recombinant Factor VIIa

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Diffuse alveolar hemorrhage (DAH) is a serious pulmonary complication that occurs in patients undergoing hematopoietic stem-cell transplantation (HSCT). Current management strategies are limited to corticosteroids, platelet transfusions, and mechanical ventilator support to treat acute respiratory failure. Recombinant factor VIIa (rFVIIa) is an approved agent for the treatment of bleeding in patients with hemophilia A or B and the presence of inhibitors. We report a case of DAH after allogeneic HSCT that failed standard therapy and was then successfully treated with rFVIIa.

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Key words: allogeneic hematopoietic stem-cell transplantation; diffuse alveolar hemorrhage; recombinant factor VIIa

Abbreviations: DAH = diffuse alveolar hemorrhage; HSCT = hematopoietic stem-cell transplantation; rFVIIa = recombinant factor VIIa; TF = tissue factor

Diffuse alveolar hemorrhage (DAH) is an infrequent but serious pulmonary complication that occurs in < 20% of patients after autologous or allogeneic hematopoietic stem-cell transplantation (HSCT). Mortality rates range from 64 to 100% in those who require mechanical ventilator support.^{1–4} The etiology and pathogenesis of DAH in HSCT recipients are unknown. Risk factors are thought to include pretransplant high-dose chemotherapy, total-body irradiation, thoracic irradiation, old age, renal insufficiency, and the period of WBC engraftment.³ Injury to alveolar capillary endothelium and alveolar inflammation resulting in the release of inflammatory cytokines have been implicated in the pathogenesis of DAH.³

Recombinant human factor VIIa (rFVIIa) [Novo Seven; Novo Nordisk Pharmaceuticals; Princeton, NJ] is an ap-

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proved agent for the treatment of bleeding episodes in patients with hemophilia A or B when inhibitors to factor VIII or factor IX are present. We report a case of DAH after allogeneic HSCT that was treated with rFVIIa in addition to standard therapy.

CASE REPORT

A 48-year-old man who underwent HSCT for treatment of non-Hodgkin lymphoma was admitted to the ICU with massive hemoptysis associated with hypoxemic respiratory failure requiring intubation and mechanical ventilator support. Copious amounts of bright red blood were suctioned from the endotracheal tube.

Non-Hodgkin lymphoma was diagnosed in October 1999, and was treated with six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and intrathecal methotrexate for CNS prophylaxis. The disease recurred 6 months after chemotherapy, and the patient was retreated with three cycles of rituximab and ICE (ifosfamide, carboplatin, and etoposide). He then underwent allogeneic T-cell–depleted HSCT from his human leukocyte antigen-identical sister in January 2001 after a conditioning regimen of cyclophosphamide, thiopeta, and hyperfractionated total body irradiation. His posttransplant course was complicated by relapse of the underlying disease, graft-vs-host disease of the skin and GI tract, hypothyroidism, autoimmune idiopathic thrombocytopenic purpura, penicillin-resistant *Streptococcus pneumoniae*, and atrial fibrillation treated with rate control and warfarin. One month prior to the current ICU admission, he was also admitted to the ICU with mild hemoptysis, dyspnea, and pulmonary edema. Echocardiography at that time revealed moderate mitral regurgitation and overall preserved left ventricular function. The warfarin was discontinued, and he was treated with IV antibiotics and diuretics with resolution of pulmonary symptoms. He remained on corticosteroids and sirolimus for treatment of the graft-vs-host disease. He went home and returned to the hospital 12 days later with recurrence of hemoptysis.

On this hospital admission, his platelet count was 23,000/ μ L. Diagnostic evaluation of the hemoptysis included a chest radiograph that demonstrated clear lung fields and no pleural effusions. CT of the chest revealed interval progression of patchy alveolar opacities in both lungs, mild bronchiectasis in the right middle lobe, new bilateral small pleural effusions and a small pericardial effusion. Fiberoptic bronchoscopy revealed old blood in the airways but no evidence of endobronchial lesions or active bleeding; Gram stain and culture results of bronchial washings for bacteria, acid-fast bacilli, and fungi were negative, and there were no malignant cells noted. The patient was treated with corticosteroids, broad-spectrum antibiotics, and platelet transfusions to keep the platelet count $> 50,000/\mu$ L. Culture results of the urine and blood were negative. His condition worsened, and he was again admitted to the ICU with gross hemoptysis.

On admission to the ICU, he was sedated and placed on mechanical ventilation with a BP of 137/90 mm Hg, heart rate of 97 beats/min, respiratory rate of 16 breaths/min, and temperature of 37.1°C; central venous pressure was 2 mm Hg. The physical examination was remarkable for bilateral coarse breath sounds and rales in the middle and lower lung fields. Initial laboratory data revealed a WBC count of 6,200 cells/ μ L with a differential count showing 82% neutrophils; a hemoglobin level of 8.7 g/dL, and a platelet count of 153,000/ μ L after receiving 12 U of platelets. Prothrombin time was 13.4 s with an international normalized ratio of 0.96, and activated partial thromboplastin time was 22 s. BUN was 28 mg/dL with a serum creatinine of 1.5 mg/dL. Serum transaminase and alkaline phosphatase levels were mildly elevated, and the total bilirubin was 1.7 mg/dL. An ECG showed sinus rhythm at a rate of 100 beats/min with no

ischemia. An arterial blood gas obtained on 100% fraction of inspired oxygen showed a pH of 7.42, PaCO₂ of 39 mm Hg, PaO₂ of 94 mm Hg, and HCO₃ of 26 mmol/L. The chest radiograph obtained after intubation showed markedly increased bilateral patchy alveolar opacities (Fig 1). A repeat chest CT confirmed the bilateral alveolar infiltrates along with interval increase in the bilateral pleural effusions (Fig 2).

In the ICU, he was treated with corticosteroids and platelet transfusions to keep the platelet count $> 100,000/\mu$ L. Antimicrobial coverage was broadened to include piperacillin/tazobactam, amikacin, vancomycin, liposomal amphotericin, caspofungin, and acyclovir.

The clinical impression was that of a patient with DAH based on the large amounts of bright red blood suctioned from the endotracheal tube coupled with the rapid progression of bilateral airspace disease. There was no evidence of coagulopathy, infection, or cardiogenic pulmonary edema. As the patient continued to have massive hemoptysis 6 h into the ICU admission, the decision was made to administer rFVIIa using the approved bolus dose of 90 μ g/kg IV q2h. The hemoptysis rapidly subsided after two doses of rFVIIa, and no further doses of rFVIIa were administered. No adverse effects due to rFVIIa were observed. Fiberoptic bronchoscopy 24 h after ICU admission showed old blood clots overlying the main carina and extending into both major bronchi with no active bleeding observed. Culture results of the blood and sputum were negative.

On ICU day 6, the patient was successfully extubated. The chest radiograph at this time showed significant resolution of the bilateral alveolar infiltrates. The patient remained clinically stable and was transferred out of the ICU to the transplant ward on ICU day 8. He eventually went home 3 weeks after ICU discharge. The patient has continued to do well with no recurrence of pulmonary hemorrhage approximately 3 months since his discharge from the ICU.

DISCUSSION

Due to the high morbidity and mortality rates of HSCT patients with DAH¹⁻⁴ treated with standard therapy and supportive care, novel therapeutic approaches should be considered for this high-risk patient population. Recent advances in our understanding of hemostasis and devel-



FIGURE 1. A portable chest radiograph obtained after intubation showing bilateral patchy alveolar opacities.

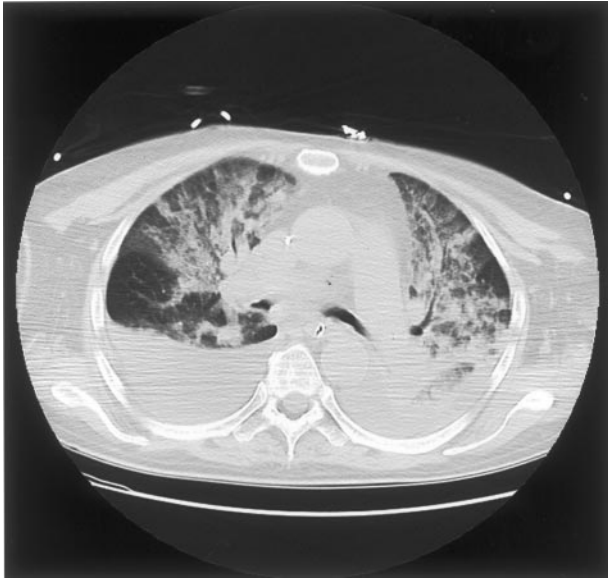


FIGURE 2. Chest CT scan demonstrating the bilateral alveolar infiltrates and small-to-moderate pleural effusions.

opment of novel hemostatic agents have resulted in the safe and successful application of these agents in clinical practice (Fig 3).^{5,6} In particular, rFVIIa has been shown to be safe and effective for life-threatening bleeding and perioperatively for patients with hemophilia, as well as in patients with disease states characterized by impaired thrombin generation such as congenital or acquired thrombocytopenias.⁶⁻⁹ It has been proposed that the rFVIIa promotes hemostasis primarily by enhancing thrombin generation on activated platelets independently of tissue factor (TF).^{5,6} The agent should be used with caution in patients with an increased risk for thrombotic events, including those with active coronary artery disease, disseminated intravascular coagulation, hepatic veno-occlusive disease, and thrombotic microangiopathy.^{6,7}

Based on anecdotal reports and retrospective studies,^{3,4,10} the recommended treatment regimen for DAH in HSCT recipients includes the early use of high-dose corticosteroids, platelet transfusions, and mechanical ventilator support for acute respiratory failure. Treatment with high-dose corticosteroids is typically initiated with methylprednisolone, 500 mg to 2 g IV daily, in divided doses for the first 4 to 5 days, followed by a gradual taper over the next 2 to 4 weeks. The increased risk for the development of opportunistic infections remains a serious complication of prolonged corticosteroid use especially in transplant recipients. Platelet transfusions are associated with several risks including blood-borne infections and transfusion reactions. In our case, rFVIIa was used because conventional treatment with corticosteroids and multiple platelet transfusions failed to control the massive pulmonary hemorrhage. The administration of only two doses of rFVIIa resulted in prompt cessation of bleeding and improvement of the patient's clinical status and radiographic findings.

In a prior description of rFVIIa for DAH in an HSCT recipient, the patient also had rapid resolution of bleeding

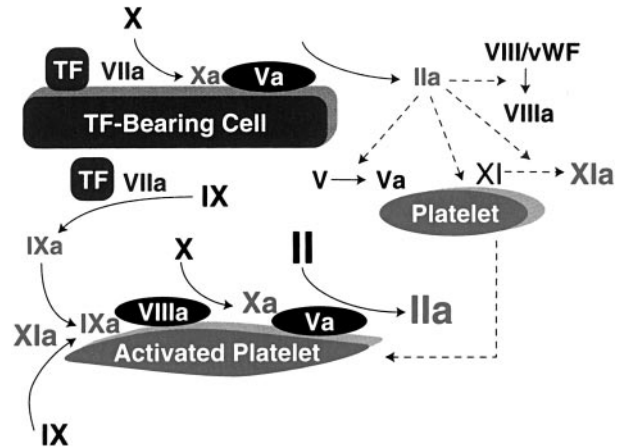


FIGURE 3. The classical model of the coagulation cascade is being replaced by a new, cell-based coagulation model that incorporates the key roles of endothelial cells and platelets. In this model, there are three distinct hemostatic steps: initiation, amplification, and propagation. Hemostasis is initiated by the formation of a complex between TF exposed as a result of endothelial cell injury, and FVIIa present in the circulating blood. The TF/FVIIa complex activates factor X (and IX) on the TF-bearing cell; FXa, in turn, activates factors V and II (prothrombin), leading to the generation of small amounts of thrombin. The initially formed thrombin also activates platelets, FV, VIII, and FXI, and releases FVIII from von Willebrand factor (vWF) (amplification step). Once activated, FVa, FVIIIa, and FIXa are rapidly bound to specific sites on the platelet surface. During the propagation step, FXa along with FVa on the platelet surface produce the subsequent thrombin burst necessary to convert fibrinogen to fibrin to form the hemostatic plug.

after two doses of 90 µg/kg of rFVIIa. However, DAH relapse with clinical deterioration occurred after stopping rFVIIa for 24 h. An additional 16 doses were administered that resulted again in clinical improvement. The patient was eventually discharged from the ICU.¹¹ Unfortunately however, the patient was readmitted 2 weeks later with progressive respiratory failure and new bilateral pneumothoraces and died 92 days after transplantation.

The administration of rFVIIa in the present case highlights the difficulties that clinicians face when choosing to administer a new and expensive agent (approximately \$6,000 per dose for a 70-kg adult) outside of the recommended indication.¹² First, the dosage schema of rFVIIa approved by the US Food and Drug Administration and used in our patient was developed from hemophilia patients with inhibitors, and not from experience in transplant patients. Second, the potential adverse effects of rFVIIa on the transplant process itself are not known. These issues suggest that further study would be required to determine whether rFVIIa is indeed beneficial in this population and, if so, what the adequate dosage and frequency of administration would be.

CONCLUSION

This case illustrates the successful use of rFVIIa in an allogeneic HSCT patient with DAH. We propose that rFVIIa be considered in any patient with pulmonary

hemorrhage after HSCT, in addition to standard therapy, particularly when hemoptysis is massive and/or recurrent. Additional data are necessary to further assess the efficacy and safety of rFVIIa to treat bleeding episodes in this high-risk patient population.

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