Diffuse Alveolar Hemorrhage After Allogeneic Hematopoietic Stem-Cell Transplantation*

TREATMENT WITH RECOMBINANT FACTOR VIIa

Stephen M. Pastores, MD, FCCP; Esperanza Papadopoulos, MD; Louis Voigt, MD; and Neil A. Halpern, MD, FCCP

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-

*From the Department of Anesthesiology and Critical Care Medicine (Drs. Pastores, Voigt, and Halpern), and Adult Bone Marrow Transplantation Service (Dr. Papadopoulos), Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY.

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Correspondence to: Stephen M. Pastores, MD, FCCP, Associate Attending, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave M-210, New York, NY 10021; e-mail: pastores@mskcc.org

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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Correspondence to: Stephen M. Pastores, MD, FCCP, Associate Attending, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave M-210, New York, NY 10021; e-mail: pastores@mskcc.org

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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 hypoxic 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 he 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 *Strep-

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

**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 develop-
Development 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 thrombocytopathies.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 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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