

## LETTERS TO THE EDITOR

# Recombinant Factor VIIa to Treat Diffuse Alveolar Hemorrhage following Allogeneic Stem Cell Transplantation

We report a female patient who developed volume overload and diffuse pulmonary infiltrates on day +14 following a myeloablative stem cell transplant (SCT) from an HLA identical sibling for acute myelogenous leukemia (AML). Empiric antibiotics and antifungal treatment was started immediately, but on day +16 she required intubation; diffuse alveolar hemorrhage (DAH) was suspected and subsequently confirmed by bronchoscopy. Intravenous methylprednisolone, 100 mg daily, was started and ventilatory function improved. However, on day +20 gas exchanges worsened and a single 90  $\mu\text{g}/\text{kg}$  dose of recombinant factor VIIa (rFVIIa) was given. Bronchoscopy the next day confirmed a further hemorrhage and another dose of rFVIIa was administered 17 hours after the first dose. Her condition rapidly improved, and she was extubated 4 days after the first dose of rFVIIa. She is now doing well 9 months posttransplantation.

Although DAH affects a minority of patients post-transplant, it carries a high mortality. In a retrospective analysis of 60 SCT patients, DAH was the second leading cause of respiratory failure (37%), with an overall survival (OS) of 19% [1]. Although steroids, transfusion support, and treatments directed at the underlying condition (often infectious) remain the mainstays of therapy, recent case reports document success with Aminocaproic acid (Amicar) or rFVIIa. Wanko et al [2] reviewed 14 patients who experienced 15 episodes of DAH after SCT. All were treated with steroids. Amicar, 1 g every 6 hours, was given concurrently in 1 patient and following treatment failure with steroids in 8. One hundred-day mortality was 44% in Amicar recipients compared to 83% for those receiving steroids alone; but 1 patient who received Amicar had a recurrent episode of DAH.

Recombinant FVIIa has been used with success to treat severe bleeding in thrombocytopenic patients [3-5]. Hicks et al [6] used rFVIIa to treat DAH after failure of 9 days treatment with steroids, desmopressin

(DDAVP), fresh frozen plasma (FFP), and Amicar. Hemorrhage stopped after 3 doses of rFVIIa 90  $\mu\text{g}/\text{kg}$  given 3 hours apart, recurred 24 hours later, but resolved completely after a total of 24 doses of rFVIIa were administered. Pastores et al [7] used rFVIIa 90 mg/kg every 2 hours in addition to standard therapy to treat DAH within 6 hours of diagnosis, with resolution of bleeding after the second dose and extubation 6 days later. Blatt et al [8] used rFVIIa 90  $\mu\text{g}/\text{kg}$  every 6 hours, to treat a child with DAH, hemorrhagic cystitis, and gastrointestinal bleeding post-SCT. Although there was pulmonary improvement the patient died of a massive gastrointestinal bleed.

Recombinant FVIIa, first approved for treatment of bleeding in patients with hemophilia A or B with inhibitors, was initially thought to work by binding to tissue factor and increasing effects through the extrinsic pathway; however, more recent in vitro data favors a tissue factor-independent pathway. rFVIIa is postulated to bind to activated platelets and activate factor X, leading to thrombin generation independent of tissue factor [9,10]. Additionally, given that this thrombin burst is isolated to the surfaces of activated platelets, effects of rFVIIa can be localized to the areas of tissue injury with minimal systemic thrombogenic side effects. Indeed, none of the cases reviewed documented any ill effects from rFVIIa despite repetitive doses.

The half-life of rFVIIa is only 2.3 hours. Thus, to be effective, frequent administration early in the course of hemorrhage is needed. The literature cited supports the use of a dose of 90  $\mu\text{g}/\text{kg}$  rFVIIa for DAH, but the optimum dose and schedule of rFVIIa remains to be elucidated.

These promising results from case reports suggest that rFVIIa should be considered early in the course of DAH. Although rFVIIa is an expensive treatment, the cost of early administration with prompt resolution of DAH could potentially be offset against a lengthy period in intensive care. Controlled trials comparing steroids with or without other treatments and rFVIIa would be required to clearly identify the therapeutic role of rFVIIa in DAH, but realistically, given the rarity of the complication, such trials are unlikely to be initiated.

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## Autologous Stem Cell Transplantation as Part of First-Line Treatment of Waldenström's Macroglobulinemia

In the August 2006 issue of BBMT, Anagnostopoulos and coworkers [1] reported superior outcome of autologous (autoSCT, n = 10) over allogeneic stem cell transplantation (alloSCT, n = 26) in 36 patients

with Waldenström's macroglobulinemia (WM). Referring to data of our group, the authors discussed that the results of autoSCT in WM might further be improved by using this modality earlier during the course of the disease. We would like to take the opportunity to give an update of our approach, which was originally published in 1999 [2].

WM patients were treated on subsequent prospective protocols aimed at investigating the feasibility and efficacy of autoSCT as part of first-line treatment of indolent lymphoma. The protocols, including the informed consent forms, were approved by the responsible institutional review board (Ethics Committee of the University of Kiel). Patients gave written informed consent using study-specific forms. Patients with symptomatic disease were eligible if they were between 18 and 65 years old, had an adequate performance status (Karnofsky  $\geq 80\%$ ), and never received WM-specific cytotoxic treatment. After an optional initial cytoreduction with alkylators or fludarabine, patients were treated with 1-3 cycles of Dexamethasone-BEAM chemotherapy for stem cell mobilization and remission induction, followed by myeloablative therapy with total body irradiation (TBI)/high-dose cyclophosphamide and stem cell reinfusion. In the first 5 patients, grafts were vigorously B cell-depleted by immunomagnetic CD34<sup>+</sup> and/or negative B cell selection [2].

Between March 1995 and September 2003, 12 consecutive patients fulfilling eligibility criteria were included. Median age was 49 (39-61) years. Prior to treatment, serum IgM levels were 46.7 (17.4-92.3) g/L, and all patients had symptomatic disease because of anemia, bulky lymphadenopathy, hyperviscosity, and/or B symptoms. Four patients proceeded directly to Dexamethasone-BEAM mobilization, whereas the remainder received 3-6 cycles of CHOP (4), R-CHOP (2), chlorambucil (1), or fludarabine (1) beforehand, resulting in partial remission (5) or no response (3). Mobilization failure did not occur. After myeloablative therapy and stem cell reinfusion (median CD34<sup>+</sup> cell number 5.3 (2.1-13.2)  $\times 10^6/\text{kg}$ ), engraftment was prompt, and toxic deaths did not occur. Although autoSCT induced strong reduction or normalization of serum IgM levels in all patients (5.4 [2.1-23.2] g/L at 100 days posttransplant), immunofixation remained monoclonal in all but 2 patients, suggesting persistence of residual disease. Disease progression was observed in 6 patients, translating into a median progression-free survival of 69 months (Figure 1). Median time to retreatment was 82 months, and all patients are still alive after a median follow-up of 69 (25-123) months after autoSCT.

In conclusion, these results show that first-line high-dose radiochemotherapy with autoSCT is highly effective in patients with symptomatic WM. Even though complete eradication of the disease