



Fig. 1. Transfusion rate prior to use of Novoseven.

Anecdotally Australia has reported a higher thrombosis rate than recorded in the world database. However comprehensive reporting from an individual center would suggest that the thrombosis rate is not increased. Australia uses Novoseven significantly later in massive hemorrhage than the rest of the world, which may conversely be contributory to an increase in thrombosis due to a poorer patient health status. Novoseven remains an effective and safe treatment of intractable bleeding.

We would like to thank the Australian hematologists whom contributed to the database.

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Successful treatment of cyclophosphamide induced intractable hemorrhagic cystitis with recombinant FVIIa (NovoSeven®) after allogenic bone marrow transplantation

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Hemorrhagic cystitis is considered a major cause of morbidity and mortality after allogenic bone marrow transplantation (BMT), and sometimes even invasive procedures, such as supravescical urinary diversion (ileal conduit) and cystectomy, may be needed [1]. It occurs after using high doses of cyclophosphamide as a condition regimen in patients who undergo BMT [1].

In this study, we evaluated the efficacy of recombinant factor VIIa (rFVIIa) in patients with severe hemorrhagic cystitis

Table 1 rFVIIa (NovoSeven®) therapy in cyclophosphamide induced severe hemorrhagic cystitis in bone marrow transplantation

	Age/sex	Diagnosis	Condition Rx† (mg g ⁻¹)	Start of hematuria (day post BMT)	Day and dose of NovoSeven® Rx (µg kg ⁻¹)	Stopping of bleeding
1	20/M	CML*	BU 16 CY 206	+ 23	+ 26 (200)	48 h later
2	26/M	CML	BU 16 CY 200	+ 36 + 74 (100)	+ 48 (100)	48 h later
3	9/M	Thalassemia major	BU 15 CY 200 AGT 40	+ 22 + 56 (400) + 66 (400)	+ 36 (400)	24 h later
4	11/F	Thalassemia major	BU 15 CY 200 AGT 40	+ 30 + 17 (severe GI bleeding)	+ 100 (150)	12 h later

*CML, chronic myelogenous leukemia. †Treatment.

following allogenic BMT, which can lead the patients to a better management, compared with risky procedures such as formalin instillation or artery ligation.

From May 1993 through September 2003, 182 patients underwent allogenic BMT in Nemazee Hospital, Shiraz, Southern Iran [(β-thalassemia major ($n = 113$), leukemia ($n = 55$), lymphoma ($n = 6$) and aplastic anemia ($n = 8$)]. Severe hemorrhagic was observed in eight patients (4.4%); one patient was expired, one needed suprapubic cystostomy and three underwent internal iliac artery ligation. The three remaining patients with severe hemorrhagic cystitis as well as the other one with mild hemorrhagic cystitis but with severe gastrointestinal bleeding received rFVIIa. These patients included three males of 21, 26 and 9 years of age and one 11-year-old female.

Patients received busulfan, 14–16 mg kg⁻¹ plus cyclophosphamide, 200 mg kg⁻¹ and ±-antilymphocyte globulin, 40–100 mg kg⁻¹ for thalassemia major and leukemia as a conditioning regimen with written consent.

Continuous bladder irrigation was applied as well as red blood cell transfusions as the first line of hemorrhagic cystitis therapy for all four patients without any significant response.

In the five patients for whom invasive procedures were used, in order to stop gross hematuria as well as repeated red blood cell transfusions we administered a dose of 150–400 µg kg⁻¹ of rFVIIa as a trial in four patients (three with severe hemorrhagic cystitis and one with mild hemorrhagic cystitis plus severe gastrointestinal bleeding) (Table 1).

Several studies have used rFVIIa in non-hemophilic patients with bleeding [2–6] and in hemophilic patients with inhibitor [7–9]. Induction of severe hemorrhagic cystitis by cyclophosphamide was reported to occur in about 5% of patients who underwent BMT [10]. Thus, we had convincing reasons to start rFVIIa as a first experience before beginning invasive procedures, which [10,11] we had used previously for five patients who developed morbidity and mortality. Indeed, we had to use repeated red blood cell transfusions due to severe gross hematuria, which caused the risk of induced infections and was dangerous in these immunologically compromised patients. In case 3, we had to use a higher dose (200 µg kg⁻¹)

and more frequent intervals to achieve hemostatic effects (total 1200 µg kg⁻¹) but in case 4, a single dose of 150 µg kg⁻¹ of rFVIIa could stop the bleeding after 12 h.

When rFVIIa is administered, the risk of thrombotic events seems to be low even in high risk clinical situations [2]. Several studies, including Baudo *et al.* showed the use of rFVIIa to be safe [12,13]. Moreover, it cannot be totally excluded that a plaque rupture occurring at the time of high plasma concentration of rFVII might facilitate the promotion of a thrombose formation at the site of the rupture plaque [14]. In our study, we did not encounter any thromboembolic or other side effects.

We can conclude that treatment with rFVIIa in the mid-range of a total dose of 150–1200 µg kg⁻¹ appears to be effective and safe in patients with severe hemorrhagic cystitis or mild hemorrhagic cystitis and severe gastrointestinal bleeding (three out of four) and recommend that other risky, painful and unacceptable procedures as well as repeated risky red blood cell transfusions should not be used.

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Hemophilia replacement products, clinical trials: inhibitors and pharmacokinetics—can they be done?

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Risk factors for the development of inhibitors in hemophilia include severity of disease, genetics, ethnicity and replacement therapy [1]. This information has been garnered by carefully carried out prospective clinical trials, either pre or postlicensing for biologicals in the USA and elsewhere. Initial previously untreated patient (PUP) studies with recombinant factors yielded similar results regarding these risk factors as well as the likelihood of developing inhibitors in this group of patients.

These findings led the Factor VIII & IX Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) to recommend that PUPs may not be the ideal candidates for evaluating this safety issue. They published that heavily treated [> 50 – 150 exposure days (EDs)] in previously

treated patients (PTPs) will serve us better to evaluate inhibitor induction [2].

A third-generation recombinant product, Advate, was recently licensed by the US Food and Drug Administration (FDA) and by the European agency for the Evaluation of Medicinal Products (EMA), based on prospective clinical trials which included pharmacokinetic and PTP studies [3–8]. More than 100 PTPs with > 150 EDs were evaluated. During the study, which included a minimum of 75 more EDs with the study agent, one patient developed a low-titer transient inhibitor. This study represents a longer observation period and/or represents a more rigorous laboratory monitoring program than was previously reported for other prelicensure clinical studies with both plasma-derived and recombinant factor (F)VIII.

On 21 November 2003, the FDA called a meeting to discuss guidelines for the acceptable number of inhibitors for licensure of a new product. The FDA proposal was the following:

- PTP: > 150 EDs, immunocompetent
- Sponsor to define: low, high, cut-off titers and assay
- Acceptable methodology/endpoint: sample size = 80 subjects; minimum of 50 EDs on study product; rule out 6.8% as upper bound of the two-sided 95% confidence interval for all inhibitors (high, low) by intent-to-treat analysis.

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