vates *c-myc* expression) but not with imatinib's pro-apoptotic effects. In summary, *c-myc* expression is not linked to CML cell proliferation as the growth of cells can be arrested in the presence of high *c-myc* expression, indicating that c-Myc is not sufficient to trigger cell proliferation. However, *c-myc* expression could serve as a molecular marker of imatinib activity.

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Disorders of Hemostasis

Recombinant factor VIIa for the management of severe hemorrhages in patients with hematologic malignancies

Seven patients with hematologic malignancies were treated with recombinant activated factor VII (rFVIIa) for severe bleeding episodes complicating diagnostic procedures or high-dose chemotherapy associated or not with stem cell transplantation. All patients were thrombocytopenic and refractory to standard support. After administration of rFVIIa, 2 complete responses, 3 partial responses and 2 failures were documented.

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Severe bleeding can be a fatal complication of intensive treatment for acute leukemia, and is thus associated with reduced survival. Administration of platelet concentrates is the most common treatment but substantial limitations frequently make this approach unsatisfactory. Recently, recombinant activated factor VII (rFVIIa, Novoseven) has been successfully used for the management of bleeding in patients with hemophilia A and B with inhibitors, congenital or acquired platelet disorders, severe thrombocytopenia associated with hematologic malignancies, or bleeding complications after bone marrow transplantation.[1-6] The mechanism by which rFVIIa can stop bleeding in patients with thrombocytopenia and the doses needed are currently being investigated.[7] From March 2001 to December 2002, seven patients with hematologic malignancies were treated with rFVIIa for severe bleeding episodes that were refractory to standard anti-hemorrhagic therapies. The clinical characteristics, the type and probable cause of the hemorrhage and the planned treatment are reported in Table 1. Two patients affected by acute myeloid leukemia (AML) received rFVIIa during or before induction therapy. Five patients received rFVIIa during the course of allogeneic stem cell transplantation. The initial indications for rFVIIa were a post-liver biopsy hemorrhage and uterine bleeding in the two AML patients; subsequently, gastrointestinal bleeding in the context of severe acute graft-versus-host disease (GVHD) in 3 cases, gastrointestinal bleeding and hemorrhagic cystitis in 1 were treated during the course of allogeneic stem cell transplantation. The type of bleeding was evaluated through a score proposed by Nevo *et al.*[8] Hemorrhages were diffuse in all cases, except in 1 patient in whom bleeding followed a liver biopsy, and were objectively assessed by instrumental procedures. All patients were thrombocytopenic at the time of rFVIIa infusion and had proved refractory to standard anti-hemorrhagic measures, including intravesicular administration of prostaglandin in the patients with hemorrhagic cystitis. No patient had evidence of disseminated intravascular coagulation or a history of a prior bleeding diathesis. Informed consent for the experimental use of rFVIIa was obtained from all the patients or the minor's legal guardian.

The planned administration of rFVIIa was 100 μg/kg (or 40 μg/kg in the case of the presence or a history of thrombosis) every 6 hours, for a total of 6 doses (Table 2). Platelet transfusions were continued during rFVIIa administration to provide a substrate useful for the action of the drug.[9] Treatment efficacy was evaluated 96 hours after the last dose of rFVIIa and was based on daily clinical records and on the number of red blood cell units required to maintain the hemoglobin lev-

Table 1. Patients and bleeding characteristics.

Patient	Age/ Sex	Diagnosis	Phase	Treatment of disease	Therapy planned	PLTS $\times 10^9$/L	Bleeding site	Probable cause of bleeding	Bleeding score
1	52/M	AML	Diagnosis	Induction CHT	No	15	Liver	Biopsy	3
2	47/F	AML	Diagnosis	Induction CHT	Induction CHT	20	Uterus	AML localization	4
3	36/M	AML	2nd relapse	1 Ag mism. SCT	Bu + Cy	20	GI	aGVHD	4
4	7/M	AML	1st relapse	CBT	TBI + Cy	40	HC	Cy toxicity	4
5	28/M	ALL	1st CR	Id. Sibl. SCT	TBI + Cy	50	GI	aGVHD	4
6	28/M	ALL	2nd relapse	MUD SCT	TBI + Cy	20	GI + HC	aGVHD + Cy toxicity	4
7	38/F	MM	2nd relapse	3 Ag mism. SCT	Mel + Fluda + Thiot. + ATG	40	GI	aGVHD	3

M: male; F: female; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; MM: multiple myeloma; CR: complete remission; CHT: chemotherapy; Ag mism SCT: antigen mismatched stem cell transplantation; CBT: cord blood transplantation; Id sibl SCT: identical sibling stem cell transplantation; MUD SCT: matched unrelated donor stem cell transplantation; Bu + Cy: busulphan + cyclophosphamide; TBI: total body irradiation; Mel + Fluda + Thiot + ATG: melphalan + fludarabine + thiotepa + anti-thymocyte globulin; PLTS: platelets; GI: gastrointestinal; HC: hemorrhagic cystitis; aGVHD: acute graft-versus-host disease.

Table 2. Treatment and results.

Patient	rFVIIa dosage mg/kg	RBC units Pre-rFVIIa	RBC units Post-rFVIIa	Response	Outcome after rFVIIa treatment (days)	Cause of death
1	100×6	5	0	Complete	Alive (360)	
2	100×6	19	4	Complete	Death (20)	Disease progression + MOF
3	100×3	7	6	None	Death (5)	Hemorrhage + aGVHD
4	40×3	7	2	Partial	Death (60)	CMV pneumonia
5	40×6	15	5	Partial	Death (10)	Hemorrhage + aGVHD
6	40×6	15	15	None	Death (4)	Hemorrhage + aGVHD
7	100×6	10	6	Partial	Death (30)	Pneumonia infection

RBC units: red blood cell units; MOF: multi organ failure; aGVHD: acute graft-versus-host disease; CMV: cytomegalovirus.

el > 8 g/dL in the 4 days after discontinuation of rFVIIa treatment compared to the requirement in the 4 days prior to the drug's administration. Clinical response was rated as complete (no transfusion requirement, or change from severe to minor type of bleeding), partial (reduction of bleeding from severe to moderate) or failure (no change in transfusion requirement).

The two AML patients treated during or before induction chemotherapy shown a rapid and complete response of their bleeding complications and an increase of hemoglobin level in the 4 days following rFVIIa treatment (Table 2). Four out of the 5 transplanted cases were in an advanced phase of disease, had received mismatched related or unrelated stem cells and showed grade 3-4 acute GVHD before the start of the bleeding episodes (Table 1).[10] Only 1 patient (# 7) followed the planned rFVIIa dosage and schedule, which was administered for an acute GVHD-related diffuse gastrointestinal bleed, confirmed endoscopically. The other 4 patients received reduced dosages of rFVIIa infusions. Overall, 3 were considered partial responders (# 4, 5 and 7) and 2 cases failed to respond (# 3 and 6) (Table 2).

In conclusion, patients treated in an early phase of disease showed better results than did transplanted patients with acute GVHD. In four cases, in fact, 3-4-grade acute GVHD was the main cause of hemorrhage, and only 1 case could receive the planned treatment. Despite this, 3 patients showed a partial response with a marked reduction in their requirement of red blood cell units and a significant improvement in their general condition. rFVIIa appears to be an effective complementary drug for the treatment of hemorrhages in thrombocytopenic patients with hematologic malignancies during chemotherapy or complicating the course of stem cell transplantation. The impressive results achieved in the two patients treated in an early phase of the disease indicate that treatment could be started early after the development of the bleeding episodes, while the lesser efficacy shown by rFVIIa in the transplanted patients necessitates an accurate analysis of all the factors that may be involved in the pathogenesis of bleeding in such cases.

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Chronic Myeloproliferative Disorders

Incidence of pulmonary hypertension in patients with chronic myeloproliferative disorders

Pulmonary hypertension (PH) has been reported to be a common finding in chronic myeloproliferative disorders (CMPD); nevertheless, there is a paucity of data regarding its exact incidence in these patients. We conducted a prospective study in order to assess the incidence of PH in patients with CMPD.

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Twenty-four patients with CMPD were included in the study (Table 1). The diagnosis of CMPD was established according to standard criteria.[1-3] Patients were excluded if any condition known to cause secondary PH was present. Eight patients were male and 16 were female. Their mean (±SD) age was 60.5±15.5 years, the mean age at diagnosis of CMPD was 56.1±16.1 years and the mean duration of CMPD was 4.7±4.5 years. Two patients had polycythemia vera (PV), 14 had essential thrombocythemia (ET), six had agnogenic myeloid metaplasia (AMM), and two had chronic myeloid leukemia (CML). Five patients reported the presence of dyspnea on exertion, which was mild except for in patients #11 and 14. No other symptoms compatible with the diagnosis of PH were reported. None of the patients had signs of right heart failure. All patients underwent transthoracic echocardiography (TTE). Pulmonary hypertension was diagnosed if the estimated right ventricular systolic pressure (RVSP) was higher than 35 mmHg.

Ten patients (41.7%), four males and six females, had PH, with a mean RVSP of 42.2 mmHg (range, 37 to 70 mmHg) (Table 2). Their mean age was 63.8±15.1 years. Six patients

Table 1. Characteristics of patients.

N.	*Sex*	*Age (yr)*	*CMPD*	*Age at diagnosis*	*Thrombosis† of CMPD (yr)*	*Treatment (past/current)‡*	*Hb (g/dL)*	*WBC (x10⁹/L)*	*PLT (x10⁹/L)*	*Splenomegaly*	*Symptoms*
1	F	43	ET	40	(–)	(–)/(–)	14.3	7.5	598	(–)	(+)
2	M	73	AMM	66	(–)	DAN/ EPO, G-CSF	9.9	1.1	66	(+)	(-)
3	M	71	AMM	68	(–)	HU/ DAN, PRE, EPO	10.9	8.4	65	(+)	(+)
4	F	50	ET	40	(–)	TIC, HU/ANA	13.2	8.6	702	(–)	(-)
5	F	50	ET	47	(–)	HU/IFN	13.0	5.0	457	(+)	(-)
6	F	52	ET	44	TIA	HU,TIC/IFN,ASA	10.4	3.0	523	(–)	(-)
7	F	70	ET	58	(–)	IFN/HU	12.8	4.1	607	(–)	(-)
8	F	53	ET	40	(–)	(–)/HU	15.2	6.3	580	(–)	(-)
9	F	72	ET	72	(–)	(–)/(–)	14.1	12.0	862	(–)	(-)
10	M	68	ET	67	(–)	(–)/ASA, ANA	13.2	5.1	500	(–)	(-)
11	M	78	AMM	77	(–)	DAN/EPO,G-CSF	6.2	2.4	600	(–)	(+)
12	F	34	ET	32	(–)	(–)/DIP	13.5	17.4	604	(–)	(-)
13	F	35	ET	34	(–)	(–)/ANA	13.6	14.7	388	(-)	(-)
14	M	65	AMM	63	(–)	DAN/EPO,G-CSF	8.5	2.5	150	(+)	(+)
15	F	77	CML	77	(–)	(–)/IMA	9.9	25.5	1422	(–)*	(+)
16	M	67	PV	66	(–)	(–)/HU, ASA, CLO	14	4.9	137	(–)	(-)
17	F	52	AMM	50	(–)	DAN/EPO,THAL,PRE	9.9	10.3	46	(+)	(-)
18	F	72	CML	72	(–)	IMA	8.3	75.0	590	(+)	(-)
19	F	58	ET	56	(–)	(–)/HU,ASA	12.4	4.8	384	(–)	(-)
20	F	77	ET	65	(–)	IFN/HU	12.6	4.4	367	(–)	(-)
21	M	75	AMM	75	(–)	DAN/EPO, G-CSF,PRE	9.2	2.0	17	(–)	(-)
22	F	51	ET	38	(–)	IFN / HU, ASA	14.5	5.6	354	(–)	(-)
23	F	81	ET	74	(–)	(–)/HU,ASA	12.5	9.8	688	(–)	(-)
24	M	27	PV	26	TMV, IS	(–)/ASA, WAR	15.3	9.8	224	(–)	(-)

*†TIA: transient ischemic attack; TMV: thrombosis of the mesenteric veins; IS: ischemic stroke; ‡DAN: danazol; EPO: erythropoietin; G-CSF: granulocyte colony-stimulating factor; HU: hydroxyurea; PRE: prednisolone; TIC: ticlopidine; ANA: anagrelide; IFN: interferon; ASA: acetylsalicylic acid; DIP: dipyridamole; IMA: imatinib mesylate; CLO: clopidogrel; THAL: thalidomide; WAR: warfarin; *splenectomy prior to the diagnosis of CML because of metastatic gastric carcinoma.*