Manuscript processing
This manuscript was peer-reviewed by two external referees and by Dr. Marie-Christine Béné, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Béné and the Editors. Manuscript received August 19, 2002; accepted December 31, 2002.

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Appendix

**For the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto): Livio Pagano, Luca Mele, Luana Fianchi, Sergio Rutella Roberta Piscitelli, Giuseppe Leone (Istituto di Ematologia, Università Cattolica S. Cuore, Roma); Alessandro Pulsoni, Paolo de Fabritiis, Robin Foà, Franco Mandelli (Dipartimento di Biotecnologie Cellulari ed Ematologia, Università «La Sapienza», Roma); Giuseppe Visani, Paolo Piccaluga (Istituto di Ematologia, Università di Bologna); Eros Di Bona (Divisione di Ematologia, Ospedale S. Bortolo, Vicenza); Raffaella Cerri, Marco Risso (Ematologia I, Ospedale S. Martino, Genova); Maria Elena Tosti (Reparto di Epidemiologia Clinica, Istituto Superiore della Sanità, Roma); Adriano Venditti (Cattedra di Ematologia, Università di Tor Vergata, Roma).*

Granulocyte colony-stimulating factor reverses cytopenia and may permit cytogenetic responses in patients with chronic myeloid leukemia treated with imatinib mesylate

Imatinib mesylate induces major or complete cytogenetic responses in the majority of patients with chronic myeloid leukemia (CML) in chronic phase. However, 15-40% of patients develop neutropenia and/or thrombocytopenia that makes it necessary to reduce the dosage or to interrupt treatment. Patients with recurrent cytopenias may be less likely to obtain cytogenetic responses. We speculated that low doses of granulocyte colony-stimulating factor (G-CSF) in conjunction with imatinib might offer clinical benefit. Eleven patients with CML in chronic (n=9) or accelerated (n=2) phase who could not tolerate 300 mg/day and had no cytogenetic response after 6 months of imatinib treatment received G-CSF in combination with imatinib. Ten of the 11 patients could then tolerate doses of imatinib equal to or greater than 300 mg/day and 7 patients achieved major (n=6) or complete (n=1) cytogenetic responses. We conclude that G-CSF reverses the hematologic toxicity of imatinib and may thereby increase the proportion of cytogenetic responses.

haematologica 2003; 88:227-229
(*http://www.haematologica.org/2003_02/88227.htm*)

Imatinib mesylate (Glivec®) has remarkable activity in the chronic (CP) and accelerated phases (AP) of CML. Kantarjian *et al.*[1] reported that 41% of patients in CP who had failed to benefit from interferon-α achieved complete cytogenetic remissions after treatment with imatinib. Despite these promising results, 40-60% patients fail to achieve major cytogenetic responses and some CP patients progress to advanced phases of CML while on imatinib. A major problem during imatinib therapy is the development of cytopenias; thus 15%-40% of CP patients and a higher proportion of AP patients[2] develop grade III-IV cytopenias that require dosage reduction to below the accepted therapeutic levels[3,4] or indeed interruption of treatment. The development of cytopenia has been associated with lack of cytogenetic response[5,6] We speculated that poor tolerance of imatinib associated with cytopenias might be reversed by the use of G-CSF and that this might increase the proportion of cytogenetic responses. Patients with CML in chronic or accelerated phase who failed to achieve cytogenetic responses after 6 months of imatinib therapy and who did not tolerate a dose of 300 mg/day on account of grade III-IV neutropenia and/or thrombocytopenia were eligible for this trial of G-CSF (Filgrastrim®). For patients with *iso-*

Table 1. Conventional definitions of cytogenetic responses to treatment for chronic myeloid leukemia.

Ph-positive marrow metaphases (%)	*Designation*
0	Complete cytogenetic response (CCR)
1-35	Partial cytogenetic response (PCR)
36-95	Minor cytogenetic response
>95	None

Complete and partial responses are often grouped together as 'Major cytogenetic responses' (MCR).

Table 2. Features of the 11 patients before and after the onset of G-CSF.

Patient no.	Phase	Initial dose (mg)	Time from start of imatinib to start of G-CSF (days)	Pre G-CSF DI	Pre G-CSF Lowest ANC (×10⁹/L)	Pre G-CSF Lowest platelet count (day)	Pre G-CSF % Ph⁺ metaphases (day)	Post G-CSF DI	Post G-CSF Lowest ANC (×10⁹/L)	Post G-CSF Lowest platelet count (×10⁹/L)	Post G-CSF % Ph⁺ metaphases (day)
1	CP	400	577	216	0.3	170	100 (514)	600	1.6	180	100 (707)
2	CP	400	203	101	0.2	132	100 (182)	353	1.9	323	9 (366)
3	CP	400	238	124	0.3	22	97 (168)	319	1.1	56	7 (434)
4	CP	400	177	230	1.2	20	97 (210)	300	1.6	55	3 (349)
5	CP	400	189	158	0.4	82	100 (189)	219	1.3	34	100 (264)
6	CP	400	197	187	0.6	200	100 (137)	400	2.2	190	74 (335)
7	CP	400	161	249	0.3	160	100 (161)	509	2.1	60	7 (329)
8	CP	400	224	204	0.4	24	100 (173)	300	3	92	16 (417)
9	CP	400	343	243	0.3	125	96 (343)	495	1.4	75	15 (588)
10	AP	600	162	214	0.4	41	100 (70)	405	3	123	0 (413)
11	AP	600	162	266	0.3	245	100 (162)	400	0.9	162	100 (260)

DI: dose intensity; ANC: absolute neutrophil count. Patient #10 progressed to blastic transformation 5 months after achieving a complete cytogenetic response and died 2 months thereafter.

lated neutropenia the imatinib was continued at 300 mg daily and the G-CSF was administered subcutaneously at a dose of 300 μg 2-3 times per week; if patients were thrombocytopenic (with or without neutropenia) the imatinib was interrupted for 1 to 3 weeks and then re-introduced together the G-CSF at the above dosage. All patients gave informed consent to this study. CP and AP were defined by standard criteria.[7] The dose of imatinib was increased every 4 weeks by steps of 100 mg/day provided that patients maintained an absolute neutrophil count (ANC) >1.0×10⁹/L and a platelet count >50 ×10⁹/L. Imatinib was discontinued if the ANC fell below 1.0×10⁹/L or platelets fell below 50×10⁹/L. Once a patient was stable on a given dose of imatinib, the G-CSF was adjusted in order to administer the lowest effective dose - always trying to maintain the ANC >1.0×10⁹/L and platelets >50×10⁹/L. Eleven patients (9 CP and 2 AP) were treated with the combination of G-CSF and imatinib (Table 2). The dose intensity (DI) of imatinib before and after the onset of G-CSF therapy was defined as the sum of the daily doses divided by the number of elapsed days before and after the time of starting G-CSF. Before starting G-CSF all patients were receiving a DI below 300 mg/day (mean 199 mg/day). After G-CSF therapy 10/11 patients tolerated a DI ≥ 300 mg/day (mean DI 391). In 7 patients the reason for lack of tolerance to imatinib was isolated neutropenia; of these patients 7 patients, all but one (patient #5) tolerated 300 mg/day or more when imatinib was given in conjunction with G-CSF. The neutropenia in these patients was reversed within one week of starting treatment with G-CSF. In patient #5 the G-CSF reversed the neutropenia but the subsequent development of thrombocytopenia necessitated interruption of imatinib therapy. The three patients who did not tolerate imatinib because they had both neutropenia and thrombocytopenia, together with patient #7 who had isolated thrombocytopenia attributed to imatinib, all tolerated imatinib after the introduction of G-CSF. These 4 patients maintained both ANC and platelet counts at acceptable levels. In 8/11 patients it was possible to escalate the dose to above 300 mg/day and in patients #8 and #10 it was possible to discontinue G-CSF completely after 3 and 5 months, respectively. The achievement of at least a major cytogenetic response has been associated with higher progression-free survival in patients treated with imatinib who failed to benefit from interferon-α.[1] Moreover patients treated with imatinib tend to achieve cytogenetic responses early after beginning therapy and cytogenetic responses in patients who have had not obtained response by six months, although not impossible, are apparently rare.[6] In this small series 7 of the 11 patients achieved a major cytogenetic response (1 complete) after starting treatment with G-CSF. We have shown that the use of G-CSF can reverse the dose-limiting neutropenia and, more surprisingly, the thrombocytopenia caused by imatinib. Although the design of this study does not permit us to conclude unequivocally that the addition of G-CSF facilitates a cytogenetic response that would not otherwise have occurred, the kinetics of the cytogenetic response on imatinib together with the high proportion of responders in this series suggest that the cytogenetic responses are in fact due to the use of G-CSF rather than to an unrelated *spontaneous* event.

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Key words: imatinib, G-CSF cytopenia.

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Lucio Luzzatto, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Luzzatto and the Editors. Manuscript received September 3, 2002; accepted December 31, 2002.

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Oral induction and consolidation chemotherapy with idarubicin and etoposide in elderly patients with acute myeloid leukemia

Exploring tolerable regimes for the treatment of acute myeloid leukemia (AML) in elderly patients is of interest. Twenty-two adults over 70 years of age with AML were treated with an oral schedule of idarubicin (30 mg/m^2/d) and etoposide (45 mg/m^2/d) for three consecutive days. Seven (32%) achieved complete remission, seven (32%) showed absolute resistance and eight (36%) died. The survival probability one year after diagnosis was 14%. Results are comparable to those described for standard intravenous regimens.

haematologica 2003; 88:229-230
(*http://www.haematologica.org/2003_02/88229.htm*)

Exploring more tolerable regimens is of interest in elderly patients (i.e. patients older than 70 years) with AML. The clinical status of some patients allows the use of standard full-scale intensive treatments but such chemotherapy results in excessive toxicity for most.[1] The aims of this study were to evaluate the feasibility of an oral induction and consolidation regimen with idarubicin and etoposide in elderly patients with AML and to determine the outcome of the patients treated in this way.

Patients 70 years of age or older with untreated *de novo* AML were eligible. Patients with acute promyelocytic leukemia, a prior history of myelodysplasia, or pre-existing severe conditions were excluded. The induction regimen consisted of oral idarubicin (30 mg/m^2 per day) and oral etoposide (45 mg/m^2 per day) for three consecutive days (1 to 3). Patients who obtained a partial remission (reduction to at least 50% of the initial marrow blast percentage) received a second induction course. Patients who did not obtain a complete remission (CR) after one or two induction cycles were removed from the study. Patients in CR were assigned to receive three consolidation courses of idarubicin and etoposide at the same doses used for induction approximately every 28 days or at least 1 week after peripheral blood recovery.

From January 1999 to December 2000, a total of 74 patients were diagnosed with *de novo* AML. Fifty-two patients were considered ineligible because of a poor performance status or associated conditions. Twenty-two patients (30%) were included in the study and treated (Table 1). Eight patients (36%), died during treatment-induced marrow hypoplasia and 7 (32%)

Table 1. Characteristics of the 22 elderly AML patients and toxicity of the treatment schedule.

Sex	Male/female	16/6
Age (years)	Median (range)	73 (70-89)
Performance status	ECOG 0-1 / 2-3	11/11
Leukocytes (×10^9/L)	Median (range)	6 (2-140)
Hemoglobin (g/L)	Median (range)	96 (42-122)
Platelets (×10^9/L)	Median (range)	77 (23-675)
AML Subtype	Myeloid with/without maturation	13
	Myelomonocytic/monocytic	6
	Other morphologic subtypes	3
Cytogenetics	Good risk[1]	3
	Intermediate	10
	High risk	2
	Unavailable	7

Treatment Schedule		*Induction*	*Consolidation*
Patients (evaluable courses)		*22 (27)*	*7 (12)*
Days of neutropenia[2]	Median (range)	21 (10-38)	15 (12-28)
Days of thrombocytopenia[3]	Median (range)	23 (10-65)	16 (8-25)
Major hemorrhage	Events (deaths)	4 (2)	2 (0)
Major infection	Events (deaths)	10 (4)	2 (1)
Other major toxicity (WHO grades 3-4)			
Mucositis/digestive		3	1
Respiratory		1[4]	–
Neurologic		1[4]	–

[1]"Good-risk" cytogenetics was associated with other alterations in the 3 cases: t(8;21)+del(9p), inv(16)+del(9)+add(17p) and inv(16)+trisomy 22. AML cytogenetic and morphologic subtype according to MRC[2] and WHO[10] criteria. [2]<0.5×10^9/L. [3]<20×10^9/L. [4]Pulmonary and cerebral hemorrhage. The same cases are also included in the major hemorrhage count, accounting for both deaths.

were withdrawn because of resistance after one or two induction cycles. The CR rate was 32%. The median (range) time to neutrophil count > 0.5×10^9/L was 21(10-38) days and to platelet count >20×10^9/L 23 (10-65) days (Table 1). Four CR patients (18%) received all the courses of consolidation therapy. Treatment was discontinued because of toxicity after induction in two patients. The median follow-up from diagnosis was 20 months. The probability of remaining alive one year after diagnosis was 14% (95% CI 1-20%), and the probability of being alive and disease-free for patients achieving CR after one year was 28% (95% CI; 0-60%) (Figure 1).

AML in aged patients is characterized by unfavorable prognostic features which are related not only to the patient's status but also to the disease.[1,3,4] Underlying diseases, organ dysfunction and poor tolerance of intensive treatment prevent most patients from entering clinical studies. Despite the substantial toxicity associated with antileukemic therapy, there is general agreement that cytotoxic chemotherapy is still the treatment of choice[5,6] although it is feasible for a minority of patients. The study protocol herein reported was designed to allow the inclusion of a greater proportion of elderly patients while still aiming to obtain and maintain CR. The drugs and route of administration had been tested before, although at lower doses, with encouraging results.[7,8] Thirty percent of all AML patients 70 years or older were treated. The first interim analysis revealed two facts that prompted discontinuation of the study. The first was a high rate of early deaths (36%). Hematologic toxicity was similar to any standard 3+7+3