Granulocyte–Colony-Stimulating Factor (Filgrastim) May Overcome Imatinib-Induced Neutropenia in Patients with Chronic-Phase Chronic Myelogenous Leukemia

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Received November 3, 2003; revision received March 15, 2004; accepted March 18, 2004.

BACKGROUND. Imatinib mesylate administration has become standard treatment for patients with chronic myelogenous leukemia (CML). Although the safety profile of imatinib is favorable, Grade ≥ 3 neutropenia (according to the National Cancer Institute Common Toxicity Criteria) occurs in 35–45% of patients with CML in chronic phase who receive standard-dose imatinib. Myelosuppression results in treatment interruptions, which may compromise responses to imatinib. The authors investigated the ability of granulocyte–colony-stimulating factor (filgrastim) to reverse imatinib-associated neutropenia, thereby allowing for more continuous imatinib administration.

METHODS. Thirteen patients with chronic-phase CML and Grade ≥ 3, imatinib-induced neutropenia were treated with filgrastim. Treatment with filgrastim was initiated after a median of 22 months from the start of imatinib. Eleven patients received filgrastim 5 μg/kg 1–3 times weekly, and 2 patients received filgrastim 5 μg/kg daily; doses were titrated to maintain an absolute neutrophil count (ANC) $\geq 10^9$/L.

RESULTS. Seven of 11 patients (64%) who began treatment with an ANC $< 1.5 \times 10^9$/L had responses (i.e., their ANC improved to $\geq 2 \times 10^9$/L within 21 days); the other 4 patients experienced slower recovery but were able to continue receiving imatinib uninterrupted. Before filgrastim administration was initiated, patients did not receive imatinib (due to neutropenia-related treatment interruptions) for an average of 21% of the total time since the start of imatinib. This figure decreased to 6% after the start of filgrastim treatment ($P = 0.0008$). Before filgrastim treatment was initiated, only one patient had achieved a major (partial) cytogenetic response. After the start of filgrastim treatment, five patients had major cytogenetic responses (including two complete responses).

CONCLUSIONS. The authors concluded that filgrastim may overcome imatinib-associated neutropenia and allow improved delivery of imatinib. Some patients may experience improvements in their responses to therapy as a result. ***Cancer* 2004;100:2592–7.** © *2004 American Cancer Society.*

KEYWORDS: absolute neutrophil count, cytogenetic response, imatinib-induced neutropenia, myelosuppression, filgrastim.

Imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) is a potent and selective tyrosine kinase inhibitor with activity against Bcr-Abl, the protein tyrosine kinase that arises from the Philadelphia chromosome (Ph) in chronic myelogenous leukemia (CML).[1,2] c-Kit and platelet-derived growth factor receptor[3,4] also can be inhibited by imatinib mesylate at concentrations that are achiev-

DOI 10.1002/cncr.20285
Published online 7 May 2004 in Wiley InterScience (www.interscience.wiley.com).

able in vivo. Imatinib therapy induced major cytogenetic (CG) responses in 65–90% of patients with CML after failure to respond to interferon α (IFN-α)[5–7] and in 80–90% of patients with previously untreated CML in early chronic phase.[8,9] Imatinib therapy generally is well tolerated. Nonhematologic adverse effects, although they are relatively common, are usually mild (Grade 1–2) and manageable. These effects include nausea, skin rash, peripheral edema, muscle cramps, and elevated liver transaminase levels. Hematologic toxicity occurs more frequently, with National Cancer Institute (NCI) Grade 3 or 4 neutropenia reported in 35–45% of patients who were treated with 400 mg daily.[5,10] Grade $\geq$ 3 thrombocytopenia and anemia occur in up to 35% and 10% of patients, respectively.[5,10] Treatment guidelines for patients receiving imatinib include the withholding of therapy for patients who develop Grade 3 neutropenia (i.e., absolute neutrophil count [ANC] $< 10^9$/L) or thrombocytopenia (i.e., platelet count $< 50 \times 10^9$/L) and dose reduction for patients who require more than 2 weeks to recover from these effects.[11]Thus, patients who develop Grade $\geq$ 3 myelosuppression receive imatinib at a reduced dose intensity. This leads to a reduced probability of achieving a major CG response.[10,12]

Filgrastim (granulocyte–colony-stimulating factor; Neupogen; Amgen, Thousand Oaks, CA) can reduce the severity and duration of neutropenia, the need for parenteral antibiotics, and the risk of infection associated with intensive chemotherapy in patients with solid tumors and lymphomas. This allows the delivery of chemotherapy at optimal doses in a timely fashion.[13,14] The efficacy and safety of filgrastim after chemotherapy for acute myeloid leukemia also has been established in several studies, accelerating neutrophil regeneration and reducing the frequency of episodes of neutropenic fever.[15,16] We investigated whether filgrastim could be used to mitigate the neutropenia associated with imatinib treatment in patients with chronic-phase CML and in turn improve responses to therapy with imatinib.

MATERIALS AND METHODS

The current trial was a pilot study investigating the feasibility as well as the efficacy and safety of filgrastim in the setting of imatinib-induced neutropenia. Patients with chronic-phase CML who developed Grade $\geq$ 3 neutropenia over the course of therapy with imatinib were eligible. Patients were eligible regardless of the time from their diagnosis to the start of therapy with imatinib or whether they had received other treatment before imatinib therapy. The starting dose of imatinib was 400 mg daily for 11 patients and 800 mg daily for 2 patients, as described previously.[17,18] All patients signed informed consent statements in accordance with institutional guidelines.

Doses of imatinib were adjusted as described previously.[5,11] In brief, patients who developed Grade $\geq$ 3 or persistent Grade 2 nonhematologic toxicity had treatment discontinued until toxicity improved to Grade $\leq$ 1. Imatinib then was resumed at 300 mg daily (600 mg for patients who were receiving 800 mg) but was never reduced to $<$ 300 mg daily. Patients who developed Grade $\geq$ 3 neutropenia or thrombocytopenia had treatment interrupted until neutrophil counts recovered to $\geq 10^9$/L and/or platelet counts recovered to $\geq 50 \times 10^9$/L. Imatinib treatment subsequently was resumed at the same dose if counts recovered within 2 weeks, but the dose was reduced to 300 mg daily if myelosuppression persisted for $>$ 2 weeks. If myelosuppression recurred, then imatinib was discontinued again, and administration was restarted at 300 mg daily. No dose reductions to $<$ 300 mg daily were allowed.

A complete blood count (CBC) and differential were obtained weekly for the first 12 weeks and every 2–6 weeks thereafter. Patients who developed myelosuppression were followed with a CBC and differential at least once weekly until recovery. Bone marrow morphology and cytogenetics were evaluated every 3 months. A major CG response was defined as either *complete* (0% Ph-positive) or *partial* (1–34% Ph-positive). Evaluation of CG response was based on examination of at least 20 metaphases in bone marrow samples.

Patients received filgrastim in doses of 5 μg/kg. The frequency of administration varied depending on the ANC and was titrated to maintain an ANC $> 10^9$/L. If imatinib had to be discontinued for reasons other than neutropenia, then filgrastim also was discontinued and then reintroduced when imatinib was reinitiated, at the same dose used before interruption. Toxicities were graded according to the NCI Common Toxicity Criteria (Version 2.0).

RESULTS

The clinical characteristics of the 13 patients treated are summarized in Table 1. The median patient age was 56 years (range, 31–79 years), and the median time from diagnosis to the start of imatinib therapy was 27 months (range, 0–60 months). Ten patients had CML that previously failed to respond to therapy with IFN-α, and 3 patients were previously untreated. The starting dose of imatinib was 800 mg daily for 2 patients and 400 mg daily for all other patients. The median time to development of the first episode of Grade 3–4 neutropenia was 67 days from the start of imatinib treatment (range, 4–174 days), and there was

TABLE 1
Clinical Characteristics before and after Administration of Granulocyte–Colony-Stimulating Factor

	Patient no.												
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Age (yrs)	53	65	63	70	48	56	67	44	60	52	45	79	31
Sokal risk group	Low	Low	Low	Int	Low	Low	Low	Low	Low	High	Low	Int	Low
Initial imatinib dose (mg/day)	400	400	400	400	400	400	400	400	400	400	800	800	400
Neutropenia (CTC grade)	3	4	4	3	3	4	3	3	3	3	4	4	3
Neutrophils at start of G-CSF ($\times 10^9$/L)	1.1	0.9	0.8	1	1.1	0.9	0.9	1.7	4	1.5	0.2	0.2	0.8
Platelets at start of G-CSF ($\times 10^9$/L)	98	220	77	151	93	180	159	218	782	100	10	8	146
Days from start of imatinib to start of G-CSF	749	995	564	1053	776	646	620	752	560	724	62	13	96
Imatinib dose at start of G-CSF (mg/day)	300	300	300	400	400	300	400	300	300	300	800	600	300
Days imatinib was withheld before G-CSF (% of treatment days)	78 (10)	232 (36)	76 (14)	68 (10)	5 (5)	9 (10)	10 (11)	16 (15)	31 (39)	14 (14)	4 (47)	2 (54)	15 (9)
Starting G-CSF dose (μg)	300 (biw)	300 (biw)	300 (biw)	480 (qw)	300 (biw)	300 (biw)	300 (biw)	300 (qw)	300 (tiw)	480 (tiw)	300 (qd $\times$ 7d)	300 (qd $\times$ 7d)	300 (tiw)
Days from start of G-CSF to last F/U	477	646	372	182	434	581	571	451	626	91	30	190	89
Days imatinib was withheld after G-CSF (% of treatment days)	0 (0)	29 (5)	0 (0)	13 (7)	30 (6)	6 (1)	26 (5)	0 (0)	77 (10)	0 (0)	28 (31)	29 (11)	0 (0)
Imatinib dose at last F/U (mg/day)	600	600	400	300	400	600	400	600	400	600	800	300	600
Ph+ metaphases (%)													
Before G-CSF	68	100	70	100	100	90	100	90	100	4	100	100	60
At last F/U	15	90	100[a]	0	70	42	70	30	100	4	40	100	0

Int: intermediate; CTC: National Cancer Institute Common Toxicity Criteria; G-CSF: granulocyte–colony-stimulating factor; Ph+: Philadelphia chromosome–positive; biw: twice weekly; qw: once weekly; tiw: three times per week; qd $\times$ 7d: once daily for 7 days; F/U: follow-up.

[a] Had initial improvement to 51% after start of granulocyte–colony-stimulating factor treatment.

no significant difference between patients who had received prior therapy with IFN-α and previously untreated patients (median, 65 days vs. 77 days, respectively).

At the time filgrastim treatment was initiated, patients had received imatinib for a median of 22 months (range, 0.5–35.0 months), and the median time from the first episode of neutropenia to the initiation of filgrastim was 18 months (range, 0.1–33.0 months). Eleven patients (84%) required more than 1 interruption of imatinib therapy, and 12 patients (92%) required dose reduction. The median dose of imatinib when filgrastim treatment was initiated was 300 mg (range, 300–800 mg). For 9 patients, the only reason for treatment interruption was neutropenia. Other causes of imatinib interruption were thrombocytopenia (Patients 10 and 11), anemia (Patient 5), and rash (Patient 6). Before filgrastim was used, the median time to recovery from previous episodes of neutropenia was 20 days (range, 4–49 days). The median ANC at the time filgrastim was initiated was 0.9 $\times$ 10^9/L (range, 0.2–4.0 $\times$ 10^9/L).

Eleven patients had ANCs $<$ 1.5 $\times$ 10^9/L at the start of filgrastim treatment, and all eventually experienced resolution to ANCs $>$ 2.0 $\times$ 10^9/L. Resolution occurred within 21 days for 7 patients (64%). Four patients experienced slow recovery of neutrophil counts (43 days, 44 days, 57 days, and 144 days, respectively); however, for all patients, recovery occurred during uninterrupted imatinib therapy. Overall, for 12 patients, imatinib treatment was continued or reinitiated at the same time that filgrastim was initiated, and it was continued without further interruption due to neutropenia. Patient 12 developed neutropenic fever and had his imatinib dose withheld for 16 days; filgrastim treatment was initiated after 9 days, and his neutropenia resolved 7 days later. Imatinib treatment then was resumed. Two patients (Patients 11 and 12) discontinued filgrastim treatment after having received the growth factor for 7 days and had

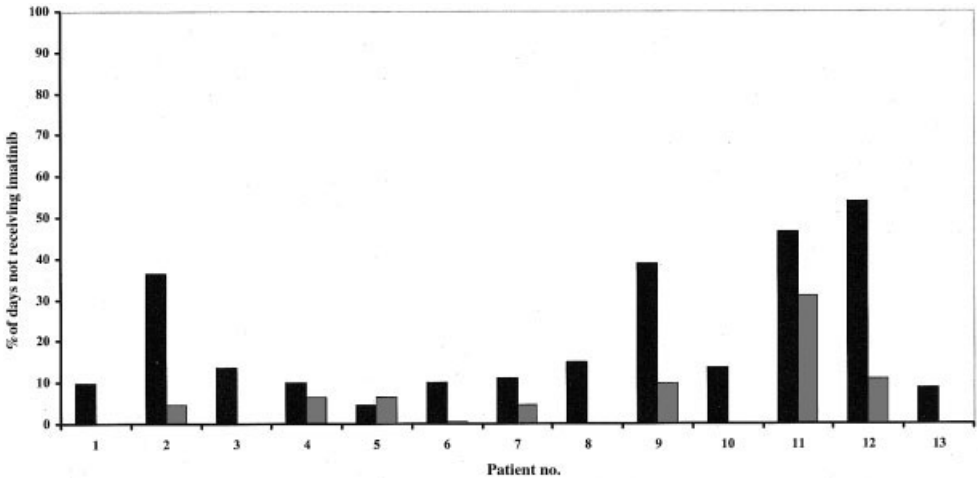

FIGURE 1. Length of time for which patients were not receiving imatinib before and after granulocyte–colony-stimulating factor (G-CSF) therapy. Black bars: before start of G-CSF therapy; gray bars: after start of G-CSF therapy.

no recurrence of neutropenia. Patient 11 continued to receive high-dose imatinib (400 mg twice daily), and Patient 12, who required a dose reduction to 300 mg daily, subsequently continued treatment at that dose. The remaining 11 patients continued to receive filgrastim for a median of 15 months (range, 3–22 months). The average percentage of days on which imatinib treatment was withheld due to neutropenia before the start of filgrastim treatment was 21% (range, 5–54%), compared with 6% (range, 0–31%) after the start of filgrastim treatment ($P = 0.0008$) (Fig. 1). After the start of filgrastim treatment, dose reduction due to neutropenia occurred in only 1 patient (Patient 2), and 8 patients (62%) were able to increase their imatinib doses after the addition of filgrastim.

Two patients had Grade $\geq$ 3 thrombocytopenia before the start of filgrastim treatment (Patients 11 and 12); 1 patient experienced a modest increase, to 41×10^9/L (best platelet count while receiving filgrastim), and the other patient had no response. Four other patients had Grade 1 thrombocytopenia (Patients 1, 3, 5, and 10), and platelet counts normalized in one of these patients. All other patients had baseline platelet counts that were within normal limits.

Imatinib therapy was well tolerated. The only adverse event attributed to filgrastim was transient Grade 1 bone pain, which was noted in 2 patients. No patient had to discontinue the use of filgrastim due to side effects.

All patients had achieved complete hematologic responses before filgrastim treatment was initiated, but only 1 patient (Patient 10) had achieved a major CG response (partial response, 4% Ph-positive). In addition, eight patients had minor CG responses, and four patients had no CG response. At the last follow-up, 5 patients (38%; Patients 1, 4, 8, 10, and 13) had achieved major CG responses (2 complete responses and 3 partial responses), and 5 patients had minor responses (all with a decreased percentage of Ph-positive metaphases compared with baseline). Three patients remained 100% Ph positive, although 1 patient had a transient improvement to 49% Ph-negative status while receiving filgrastim. Paradoxically, the 2 patients who began receiving filgrastim earlier during imatinib therapy (Patient 11, who began filgrastim treatment on Day 62, and Patient 12, who began filgrastim treatment on Day 13 after the start of imatinib therapy) failed to achieve a major CG response. Both patients stopped receiving filgrastim treatment after 7 days of therapy. None of the patients who were treated developed additional chromosomal abnormalities involving transformation to accelerated or blast phase.

DISCUSSION

Myelosuppression is the most common Grade 3 or 4 adverse event observed during therapy with imatinib. Grade 3 or 4 neutropenia has been reported in up to 58% and 64% of patients with CML in accelerated phase and blastic phase, respectively[19,20]; in many instances, patients already had severe neutropenia at the start of treatment. Among patients treated in chronic phase, Grade 3 or 4 neutropenia has been reported in 35–45% of patients who were treated with imatinib after IFN failure[5,10] and in 13% of previously untreated patients.[8,9] Other manifestations of hematologic toxicity also have been observed, with Grade $\geq$ 3 thrombocytopenia reported in 25–35% of patients and anemia reported in 5–10% of patients.

The most notable complication of Grade $\geq$ 3 neutropenia is the development of potentially serious infection. In fact, two patients in the current series were hospitalized with fever (one case of unknown origin and one case associated with pneumonia). Both patients responded to the administration of filgrastim

with resolution of neutropenia and the associated infectious complications. Thus, early intervention with filgrastim in these instances may be indicated to reduce the risk of infection.

Another less recognized consequence of myelosuppression is its effect on response to imatinib. Patients with CML in chronic phase who developed Grade ≥ 3 neutropenia during imatinib therapy had a significantly lower probability of achieving a complete CG response compared with patients who did not develop this complication (44% vs. 62%; $P = 0.03$).[10] Patients who developed Grade ≥ 3 thrombocytopenia also had a significantly lower probability of achieving a complete CG response. The probability of response to imatinib was markedly decreased for patients who developed prolonged myelosuppression (i.e., myelosuppression lasting > 2 weeks). This adverse effect of myelosuppression was found to be significant on multivariate analysis.[10] Marin et al. also reported that neutropenia occurring 45–90 days after the start of imatinib therapy was associated with poor survival.[12]

The explanation for the adverse effect of myelosuppression on response and survival is not clear. One hypothesis is that normal progenitors have been suppressed by the malignant clone to the extent that they are no longer able to sustain hematopoiesis when the Ph-positive cells are suppressed. This suggests that hematopoiesis is dependent predominantly on the Ph-positive clone in these patients, and its elimination results in bone marrow that is unable to sustain normal blood production. Another possible explanation is that patients who develop Grade ≥ 3 myelosuppression receive imatinib at a lower effective dose intensity due to frequent treatment interruptions and dose reductions. Guidelines for the management of patients treated with imatinib suggest the withholding of therapy for patients with Grade ≥ 3 neutropenia (neutrophil counts $< 10^9$/L) or thrombocytopenia (platelet counts $\leq 50 \times 10^9$/L). Treatment is reinitiated when peripheral blood counts recover to above these levels, and dose reduction is recommended if the time to recovery is > 2 weeks.[11]

In either case, the use of hematopoietic growth factors may improve response by stimulating normal hematopoiesis and faster recovery. In the current study, we demonstrated that all patients with imatinib-induced neutropenia responded to filgrastim, and most patients continued to have normal neutrophil counts despite continuation of imatinib treatment. More notable was the finding that after filgrastim treatment was initiated, treatment interruptions were less common and usually were not related to neutropenia. Although some patients experienced slow recovery of neutrophil counts after the initiation of filgrastim treatment, this recovery was achieved during uninterrupted imatinib therapy (rather than imatinib therapy punctuated by the usual treatment interruptions necessitated by neutropenia) and was associated with an improved response to imatinib in 8 patients (62%; 2 complete responses, 2 partial responses, and 4 minor CG responses). One possibility is that these responses were attributable simply to the continuation of imatinib therapy and were independent of filgrastim treatment. However, the patients in question already had been treated with imatinib for an extended period (median, 22 months) before the initiation of filgrastim treatment, and the probability of achieving a major CG response when there is no response after 12 months of therapy is very low.[21] In fact, treatment interruptions became more frequent and prolonged for patients whose treatment extends beyond 12 months, making continuation of imatinib therapy increasingly difficult. The increased time receiving imatinib without further interruption after the start of filgrastim treatment was correlated with improved response. In addition, improved CG responses usually occurred after the dose of imatinib was increased. Increasing the imatinib dose for patients who have not experienced responses to the standard dose may improve the CG response in $> 50\%$ of patients.[22] However, this dose increase would not have been possible without the addition of filgrastim to the treatment regimen.

One recent report suggested a similar response to filgrastim in patients who developed neutropenia during imatinib therapy.[23] In that study, all 11 patients who were treated had responses to filgrastim, with observed improvements in neutrophil counts. In addition, CG responses improved in seven patients. It is noteworthy that the investigators who conducted that study reported improvements in platelet counts in four patients after the start of filgrastim treatment.[24] None of the patients who were treated in the current series experienced a significant improvement in platelet counts. In fact, two patients developed thrombocytopenia after filgrastim treatment was initiated; however, the imatinib dose was increased for one of these patients after the recovery of neutrophil counts, and it is likely that this dose increase accounted for the occurrence of thrombocytopenia.

We conclude that the administration of filgrastim to patients with chronic-phase CML who develop neutropenia during imatinib therapy improves neutrophil counts, allowing more-sustained administration of imatinib. Thus, the administration of filgrastim may allow dose escalations of imatinib and may lead to improvements in CG responses.

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