Research Paper

Hematological and nonhematological toxicities of imatinib mesylate in patients with chronic myeloid leukemia and gastrointestinal stromal tumor

Mohammad Usman, Naveen Naz Syed, Ghulam Nabi Kakepoto, Salman Naseem Adil, Mohammad Khurshid

Section of Hematology, Department of Pathology and Microbiology, The Aga Khan University Hospital, Karachi, Pakistan

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Correspondence to:
Naveen Naz Syed
E-mail: naveen.naz@aku.edu

ABSTRACT

Objectives: To determine the hematological and nonhematological toxicities of imatinib mesylate in patients with chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST) and to review the literature to compile a list of the etiologic agents responsible for these events.

Materials and Methods: This was a prospective study conducted from May 2001 to February, 2007. Two hundred and thirty-two patients with CML and GIST treated with imatinib mesylate at the Aga Khan University Hospital were included in the study. Side effects were graded according to the common toxicity criteria of the National Cancer Institute version 3.0.

Results: Ninety-seven patients experienced various side effects which, in decreasing order of frequency, were: generalized hypopigmentation, periorbital edema, nausea, and weight gain. Hematological toxicities included mainly grade I/II anemia and thrombocytopenia. Grade III/ IV hematological adverse events were rare in our group. The frequency of all events is equally distributed in all phases of CML and GIST. The side effects rarely lead to permanent discontinuation of therapy.

Conclusion: Imatinib mesylate is a well-tolerated drug with some adverse events that are only rarely a permanent barrier to therapy.

KEY WORDS: Chronic myeloid leukemia, gastrointestinal stromal tumor, imatinib mesylate, toxicity

Chronic myeloid leukemia (CML) is a clonal disorder with a characteristic cytogenetic abnormality—the Philadelphia chromosome—the molecular sequence of which is generation of fusion protein BCR/ABL which induces leukemogenesis.[1]

Imatinib (imatinib mesylate, STI571, Gleevec), a selective inhibitor of BCR/ABl tyrosine kinase, has brought about a paradigm shift in the treatment of Ph-positive CML.[2,3] The drug also inhibits the tyrosine kinase associated with c-ABL, ARG, PDGF-R, and c-Kit.[4,5]

Imatinib mesylate, 4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]-phenyl]-benzamide, functions through competitively binding with the ATP site of the enzyme, which leads to the inhibition of tyrosine phosphorylation of the BCR/ABl signal transduction.[6]

It was first administered to a patient with CML in 1998 and later, phase II and phase III trials suggested that hematologic as well as cytogenetic responses can be obtained in all phases of CML.[7] It was found to have acceptable pharmacokinetic and toxicity profiles and hence was introduced into clinical practice.[8,9] The drug can be given orally, is well tolerated, and has manageable side effects.[2,10] The common side effects reported were nausea, rash, superficial edema, muscular cramps, myelosuppression, and deranged liver function tests.[11]

This article compiles the various adverse effects of imatinib reported by patients with CML and gastrointestinal stromal tumor (GIST) who were treated in our center.

Materials and Methods

This was an observational, prospective study conducted over a period extending from May 2001 to February 2007. Patients with Ph and/or BCR/ABL positive CML (chronic, accelerated, or blast crisis, according to WHO criteria)[12] and GIST in all age-groups and both sexes, who were treated with imatinib mesylate at the Aga Khan University Hospital were included in the study.

The diagnosis of CML was based on the characteristic peripheral blood smear and bone marrow findings and was confirmed by the presence of the Philadelphia chromosome on bone marrow cytogenetic studies or detection of BCR/ABL translocation by polymerase chain reaction (PCR).

GIST was diagnosed on the basis of the morphological assessment of the biopsy material and confirmed by CD117 positivity of the immunohistochemical stain.

The doses of imatinib were 400 mg daily for the chronic phase of CML and GIST and 600-800 mg daily for the accelerated and blast phase of the disease. Patients received continuous daily therapy unless unacceptable adverse events were recorded or disease progression had occurred. Before starting imatinib mesylate, complete blood count, serum creatinine, and electrolytes were checked.

While on therapy, complete blood counts were monitored weekly for the first month and fortnightly thereafter till the patient achieved hematological response, after which it was done monthly. Treatment was withheld if the absolute neutrophil count dropped below 1000/cumm and platelets to less than 75,000/cumm in the chronic phase and less than 20,000/cumm in the aggressive phase. On recovery, therapy was resumed at the 50% of the initial dose with close monitoring.

Side effects were retrieved from previous studies[11,13] and events were graded according to the common toxicity criteria of the National Cancer Institute version 3.0.[14]

Results

Two hundred and thirty-two patients were registered in GIPAP (Gleevec international patient assistance programme) over a period of five years. The median age at the time of presentation was 36 years (range 12-65 years). Among these, 160 were males and 72 were females (M:F ratio 2.2:1). One hundred and thirty-six were in the chronic phase of CML, while 59 and 24 were in accelerated and blast crisis, respectively. Thirteen patients received imatinib mesylate for a diagnosis of GIST. Median time from diagnosis was almost one year (22 months; range 15 days to 108 months).

Ninety-seven (44.3%) patients experienced minor or major hematological and nonhematological toxicities; many of them experienced more than one adverse effect. Major nonhematological toxicities, in decreasing order of frequency, were hypopigmentation, periorbital edema, nausea, weight gain, leg cramps, fatigue, and dryness of mouth. Hematological side effects were anemia, leucopenia/neutropenia, and thrombocytopenia. Grade III/ IV hematological adverse events were noted in only 14 patients. The incidences of various nonhematological and hematological toxicities reported by our patients are listed in Tables 1 and 2, respectively.

At median follow-up at 21 months there were no deaths due to toxicity.

Discussion

Imatinib mesylate has changed the approach to the management of CML and is currently approved as a first-line

Table 1

Incidence of nonhematologic toxicities

Toxicity	*Chronic phase*	*Accelerated phase*	*Blast crisis*	*Gastrointestinal stromal tumor*	*Total (%)*
Hypopigmentation	60	22	3	8	93 (40)
Fluid retention					
Periorbital edema	30	11	2	6	49 (21)
Weight gain	17	4	1	2	24 (10.3)
GIT symptoms					
Nausea	26	7	0	5	38 (16.4)
Dyspepsia	9	2	0	3	14 (6.4)
Anorexia	6	1	1	2	9 (4.1)
Dry mouth	12	4	0	2	19 (8.7)
Diarrhea	5	0	0	1	6 (2.7)
Constipation	2	0	0	0	02 (0.9)
Abdominal pain					
Musculoskeletal					
Leg cramps	16	8	1	3	28 (12.8)
Body aches	8	5	0	3	16 (7.3)
Joint pain	9	3	1	2	15 (6.8)
Fatigue	16	7	0	1	24 (11)
Weakness	7	3	2	0	12 (5.5)
Nasopharyngitis	8	0	0	0	8 (3.7)
Headache	3	3	0	2	8 (3.7)
Alopecia	3	2	0	1	6 (2.7)
Cough	5	1	0	0	6(2.7)
Depression	2	0	0	1	3 (1.4)
Fever	2	0	0	0	02 (0.9)
Skin manifestations					
Rash	3	2	1	0	6 (2.7)
Pruritis	2	3	1	0	6 (2.7)
Exfolative dermatitis	1	2	0	0	3 (1.4)
Dizziness	1	2	2	1	6 (2.7)

Table 2

Incidence of haemtological toxicities in three phases of chronic myeloid leukemia and gastrointestinal stromal tumor

Toxicity	*Chronic phase*	*Accelerated phase*	*Blast crisis*	*Gastrointestinal stromal tumor*	*Total (%)*
Anemia					
Grade I-II	22	9	3	4	38 (17)
Grade III-IV	2	1	0	0	3 (1.3)
Leucopenia					
Grade I-II	17	6	1	0	24 (10.9)
Grade III-IV	0	0	0	0	0
Neutropenia					
Grade I-II	11	2	0	0	13 (5.9)
Grade III-IV	2	3	1	0	6 (2.7)
Thrombocytopenia					
Grade I-II	16	9	0	0	25 (11.4)
Grade III-IV	2	2	1	0	5 (2.2)
Subconjunctival hemorrhage	1	2	0	0	3 (1.4)
Central nervous system bleed	—	—	1	—	1 (0.5)
Epistaxis	—	—	1	—	1 (0.5)

treatment in all patients.[15] The mode of action, dosing, and side effects differ from that of the conventional cytotoxic drugs.

Herein, we discuss the various hematological and nonhematological toxicities associated with imatinib and compare our data with that of other international studies. The possible mechanisms associated with these symptoms are also reviewed. In the present study, two hundred and thirty-two patients were analyzed, making this one of the largest studies to compile the toxicities of imatinib mesylate from our region. Various minor and major adverse events have been reported with imatinib, including periorbital puffiness, nausea, skin rash, cramps, and hematological toxicities.[10,15]

Compared to reports from other studies,[16] the drug was relatively well tolerated in our population. Among 232 cases, 97 (44.3%) reported side effects.

In our series, a striking finding was the high incidence of generalized hypopigmentation, which was seen in 40% of the patients treated with imatinib; similar observations have been previously reported in Asian[15] and African patients.[16] This effect is naturally well marked in dark-skinned people. It occurred with similar frequency in patients in all phases of CML as well as in those with GIST. It does not affect the prognosis.[16] It seems to be related to the inhibition of the platelet-derived growth factor receptor and the c-kit tyrosine kinases that are involved in skin pigmentation.[17]

Symptoms related to fluid retention (periorbital edema, pedal edema, or weight gain) were found in 30.3% of the cases, similar to the finding of Hasan *et al*.[16] and others.[13] The etiology of this phenomenon is debatable. One postulated mechanism is defective integrity of capillaries due to inhibition of the kinases responsible for maintaining the integrity of the blood vessels, as there is a tendency to develop edema with deletion of PDGFR gene or in Al/Arg double knockout mice.[10] Generalized fluid retention (with pulmonary edema and pleural/pericardial effusion), a potentially life-threatening complication reported in 1-3% of patients,[10] was not observed in our series.

Savage *et al*.[8] reported nausea (43%) as the most frequent side effect in his series; in contrast, only 16% of our patients had this symptom. Nausea, the third most frequent adverse event in our study, might have been related to the local irritant effects of the drug[10] and usually improved when the drug was taken after meals or by splitting doses. Diarrhea, anorexia, dyspepsia, constipation, and dry mouth are relatively less frequent complaints. Inhibition of Kit on intestinal epithelium is the mechanism assumed to be responsible for the diarrhea.[2]

Musculoskeletal pain was seen in 27.6% of our patients, an observation that has been reported previously,[10] when 20-40% of cases had musculoskeletal complaints (muscle cramps, body aches, or arthralgias). These symptoms usually resolved after a few months or with the use of simple analgesics and calcium supplementation. However, two patients with intractable leg cramps and normal serum calcium levels were benefited by quinine in our group. The etiology of these symptoms is unclear.[10]

In contrast to other studies,[10,15] skin changes or dermatitis were less common in our group. Three subjects developed exfoliative dermatitis that required discontinuation of therapy and administration of systemic corticosteroids. Rechallenge with imatinib was well tolerated in two patients. However, in one case, due to the severity of the symptom, the drug was not restarted. Inhibition of Kit on skin basal cells, melanocytes, and mast cells, or histamine release from mast cells, is the probable mechanism for these effects.[18]

Weakness and fatigue were reported by a small number of patients in our study, similar to the findings of others.[10] No specific etiology was identified. It may have been secondary to the primary disease process or may have been related to mild anemia. Other less common nonhematologic adverse effects have been listed, including insomnia, depression, nasopharyngitis, weakness, and alopecia. As has been reported previously,[11] one patient developed gynaecomastia after taking imatinib; this patient also had signs of fluid retention.

Hematological toxicities were less common in our patients as compared to the findings in previous studies,[10,15] with most of them experiencing grade I/II anemia or thrombocytopenia. Grade III/IV adverse events consisted of neutropenia in 2.7%,

anemia in 1.3%, and thrombocytopenia in 2.2% and required temporary interruption of treatment and blood product transfusion in these patients.

Liver toxicity manifesting as deranged liver function tests has been reported previously.[10] This was observed in one patient in our series.

In this study, the observed hematological toxicities were equally distributed or, possibly, more prevalent in the chronic phase of CML; this observation is in contrast to prior data,[19] where myelosuppression was found to be less frequent in imatinib-treated GIST and the chronic phase of CML. Myelosuppression may be either a consequence of a pharmacologic effect of imatinib through inhibition of c-kit or a reflection of the underlying compromised hemopoiesis in this group.[6]

Other side effects, including hemorrhagic manifestations, were observed in less than 2% of our cases, which is similar to previous reports.[11] Cerebral hemorrhage was observed in one patient with the accelerated phase of the disease and subconjunctival hemorrhage, which resolved with temporary interruption of treatment, was seen in three . Rechallenge was well tolerated in two of them.

Conclusion

Imatinib mesylate is well tolerated in all phases of CML and GIST. The commonest hematological and nonhematological side effects are grade I or II and are manageable across the spectrum of severity, rarely acting as a permanent barrier to therapy.

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