



## Research Article

# Ethnic Differences in Hematologic Toxicity from Imatinib in Patients with Gastrointestinal Stromal Cell Tumor (GIST): Coincidence or a Real Phenomenon

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### Abstract

**Objectives:** There is a wide variability in the pharmacokinetics, pharmacodynamics and tolerance of anticancer drugs based on ethnicity. GIST is a rare cancer, (~1% of GI cancers). Imatinib is used in the neo-adjuvant, adjuvant and metastatic setting. The purpose of this study was to report the difference in hematologic toxicities to imatinib among different ethnicities when treated for GIST either in the adjuvant or metastatic setting.

**Methods:** We performed a retrospective study to collect data on patients with GIST (in any stage), who were on imatinib and presenting with grade 2 or more anemia, neutropenia and/or thrombocytopenia from July 1, 2005 to January 31, 2018. The degree of cytopenia was graded as per National Cancer Institute Common Toxicity criteria; version 4.0. We collected included age, gender, ethnicity, pathology, adverse effects-hematologic and non-hematologic, management of toxicities including dose modifications and administration of pegfilgrastim.

**Results:** Among 57 patients (median age 61 years, M: F=41:16 (F); ethnicities: White 65%, African-American (AA) 19%, Asian 12% and Hispanic 4%), neutropenia (Grade 3 & 4) was seen in 6 patients (10%): 5 AA and 1 Asian. 45% of all AA patients developed neutropenia. Median absolute neutrophil count (ANC) nadir was 700/ $\mu$ L, median duration on drug prior to onset of neutropenia was 4.5 weeks and median duration of neutropenia was 4 weeks. One patient developed febrile neutropenia. Dose interruptions were needed in 3, dose-reductions in all patients, and 3 patients required pegfilgrastim. One patient had to discontinue imatinib, while one patient was escalated back to 400mg daily dose.

**Conclusion:** This is the first study to examine ethnic variations in myelosuppression following imatinib in patients with GIST.

**Keywords:** Anemia, ethnicity, gastrointestinal stromal tumors, imatinib, neutropenia

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Imatinib (Glivec or Gleevec) usually considered as a miracle drug in the history of cancer therapy, is a 2-phenylaminopyrimidine compound that specifically interacts with the adenosine triphosphate (ATP) binding site of multiple tyrosine kinases (TK) including BCR-ABL, ABL-related gene product (ARG), and certain subgroup III receptor tyrosine kinases (c-kit receptor, platelet-derived growth factor (PDGF) receptor, and stem cell factor receptor).<sup>[1]</sup> The Food

and Drug Administration (FDA) have approved Imatinib for the treatment of patients with chronic myeloid leukemia (CML) as well as gastrointestinal stromal tumor (GIST) that express the tyrosine kinase receptor c-kit.<sup>[2, 3]</sup> The most common adverse effects (>10% associated with imatinib include superficial edema, muscle cramps, musculoskeletal pain, rash, fatigue, headache, abdominal pain, and joint pain. Less frequent adverse effects (<10%) include pancy-

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topenia, febrile neutropenia, flushing, and liver function test abnormalities. Myelosuppression is significantly more common in CML patients on Imatinib than in patients of gastrointestinal stromal tumors (GISTs).<sup>[3]</sup>

With an extensive experience with this agent in both cancer and non-cancer fields, we have gathered a better understanding of both the short and long-term toxicities of imatinib. However, there is a wide variability in the pharmacokinetics, pharmacodynamics and tolerance of anticancer drugs based on ethnicity. Previous data have revealed very limited about the differences in toxicities among different ethnic groups. One study tried to investigate the bone marrow morphology in imatinib treated CML patients presenting with persistent cytopenias but no ethnic disparity was reported at all.<sup>[4]</sup>

The objective of this study is to report the difference in hematologic toxicities to imatinib among different ethnicities when treated for GIST either in the adjuvant or metastatic setting.

## Patients and Methods

Using pharmacy records and ICD code for GIST, we collected data on patients with GIST (in any stage), who were on imatinib and presenting with grade 2 or more anemia, neutropenia and/or thrombocytopenia from July 1, 2005 to January 31, 2018. The degree of cytopenia was graded as per National Cancer Institute Common Toxicity criteria; version 4.0. Information was obtained through review of electronic medical records. Data collected included age, gender, ethnicity, pathology, adverse effects-hematologic and non-hematologic, management of toxicities including dose modifications and administration of pegfilgrastim.

## Results

A total of 57 patients with diagnosis of GIST (all had KIT overexpression) were identified. The median age was 61

years (range 32-87) and 58% of patients were over 65. Genders included 41 male and 16 female. Ethnicities included White 37 (65%), African-American (AA) were 11 (19%), Asian 7 (12%) and Hispanic 2 (4%). Majority of the patients had unresectable or metastatic disease (40/57) and 17 patients were administered in adjuvant setting. All patients were prescribed imatinib at 400 mg oral daily and were followed closely every two weeks for two times and then every 4 weeks thereafter, unless more frequent visits were required due to toxicities.

Grade 3 and 4 neutropenia was witnessed in 6 patients (10%), consisting of 5 AA patients and 1 Asian patient (Table 1). Overall, 45% (5/11) of all AA patients developed grade 3 and 4 neutropenia. Median absolute neutrophil count (ANC) nadir was 700/ $\mu$ L (488-840), median duration on imatinib prior to onset of neutropenia was 4.5 weeks (3-12). Median duration of neutropenia was 4 weeks (range 2-10). Only one patient developed febrile neutropenia. Concomitant anemia was seen in 4 patients and pancytopenia in 1 patient (Table 1).

Dose interruptions were needed in 3 patients, and dose reduction in all patients. One patient had to discontinue imatinib altogether due to persistent neutropenia. Three patients required growth factor support with pegfilgrastim (Table 2).

To rule out other causes responsible for disparity in hematologic toxicities, review of medical records showed no history of previous malignancy requiring chemotherapy or other drugs such as carbimazole, clozapine, methimazole, penicillin G, quinidine, hydralazine, procainamide, propylthiouracil, or sulfasalazine. We also tried to collect previous laboratory records on these patients to rule out benign ethnic neutropenia (BEN), a known hematologic condition associated with people of African ancestry and specific Middle Eastern ethnic groups. We were successful in securing records in 4 of the 5 AA patients and one Asian patient;

**Table 1.** Grades of cytopenia in the patients as per NCI CTCAE 4.0

Grade	Grade 2	Grade 3	Grade 4	Total
Anemia (gm/dl)	4	1	0	5
Neutropenia (ANC-/cmm)	0	5	1	6
Thrombocytopenia (Platelet/cmm)	1	0	0	1
Bicytopenia				5
Anemia + Thrombocytopenia				0
Anemia + Neutropenia				4
Neutropenia + Thrombocytopenia				1
Pancytopenia				1
Anemia + Neutropenia + Thrombocytopenia				1

**Table 2.** Characteristics of the patients who developed myelosuppression

No.	Age	Sex	Ethnicity	Location	M/A	Wks. on Rx	ANC	ANC Nadir	Plts	Hg	Febrile neutropenia	Dose interruption	Dose reduction	Final dose (mg) daily	Use of Pegfilgrastim (Y/N)
1	63	F	AA	Gastric		3	518	518	54	8.9	Y	Y (2wk)	200->200 Once a day	200	Y
2	51	F	AA	Small Bowel		5	760	760	106	9.6	N	Y (2wk)	200	200	N
3	38	F	AA	Gastric		12	900	790	142	8.7	N	N	200->100	D/C	N
4	76	F	AA	Rectal		7	840	840	>150	>12	N	N	200->400	200	N
5	42	M	AA	Gastric		4	480	488	103	7.9	N	Y (4wk)	200->100->100 Once a day	100	N
6	43	M	Asian	Gastric		3	960	640	113	9.4	N	N	200	400	Y
Median						4.5	700	700	106	8.9					

M: male, F: female, Y: yes, N: no, wk: weeks, ANC: absolute neutrophil count, PLT: platelets, Hg: hemoglobin.

no previous history of neutropenia was identified.

We were able to escalate the dose of imatinib to 400mg daily in only one patient. Bone marrow biopsy was performed in 2 patients with prolonged neutropenia; results were for dysplasia, fibrosis or other etiology and negative for hematologic malignancy.

Most importantly, we did not find any differences in the number of cycles received, relative dose, relative time, or relative dose intensity for AA and other patients.

## Discussion

To the best of our knowledge, our study is the first one, which examined the ethnic differences in myelosuppression with imatinib in GIST. Despite having a small sample size, it brings out ethnic variation in degree of myelosuppression as an important factor to be studied in both retrospective and prospective manner. Neutropenia is a serious adverse complication of myelosuppressive chemotherapy that predisposes patients to life-threatening infection, hospitalization and delays in treatment. This is associated with significant mortality as well as increased health-care associated costs.

As mentioned above, a study by Paul et al.<sup>[4]</sup> studied the bone marrow morphology in imatinib treated CML patients presenting with persistent cytopenias. Of 638 imatinib treated CML patients, 60 patients (9%) showed persistent cytopenia: 46 patients with  $\geq$  grade 2 anemia, 25 patients with  $\geq$  grade 2 neutropenia and 37 patients with  $\geq$  grade 2 thrombocytopenia. Of these, 18 patients had bicytopenia and 13 cases had pancytopenia. The patients' characteristics showed the median age of 38 years (range: 21–75) and male:female ratio of 1:1. Bone marrow examination showed persistent marrow disease in 5 patients, marrow hypoplasia in 6 patients, fibrosis and other stromal changes in 5 patients, megaloblastic erythropoiesis in 11 patients and disease progression to accelerated or blast crisis in 3 patients.

It has been published previously that myelosuppression is significantly more common in CML patients on Imatinib than in patients of GIST,<sup>[5]</sup> probably the former patients in advanced phases of CML are more prone for myelosuppression. However, it is not known what underlines the observation why some patients develop myelosuppression and some do not. Sneed et al.<sup>[7]</sup> suggested that in addition to inhibitory effect on Bcr/Abl, imatinib also inhibits c-kit, which is involved in early hematopoiesis, thereby, leading to suppression of normal progenitors and causing myelosuppression.<sup>[6]</sup>

Investigators have been searching for causes of myelosuppression following imatinib in CML patients as bone marrow suppression has been identified as an independent

adverse risk factor for achieving a cytogenetic response.<sup>[7]</sup> Such studies have shown marrow with both hypoplasia or aplasia as well as fat replacement in such patients.<sup>[4, 7–9]</sup> These data suggests that bone marrow suppression could represent a potentially fatal toxicity of imatinib; especially in patients with CML. Stromal changes have also been seen in patients following imatinib in CML patients.<sup>[10]</sup> Serous atrophy also known as gelatinous transformation has been reported anecdotally in CML patients treated with imatinib.<sup>[11]</sup> Megaloblastosis in bone marrow in patients who developed cytopenias following imatinib has also been witnessed by other investigators.<sup>[12]</sup> Imatinib is not known to cause folate deficiency, however, it brings the idea of testing and replenishing these patients with therapeutic doses of vitamin B12 and folate as suggested by Braziel et al.<sup>[12]</sup> Imatinib has also been linked to myelodysplastic syndrome and acute leukemia in handful patients of CML on imatinib therapy.<sup>[13]</sup>

Though not performed in our patients as no evidence of BEN was found, but genetic studies in large such as rs2814778 in Duffy Antigen Receptor for Chemokines (DARC) gene, specifically DARC null red cell phenotype should be considered in patients of AA and middle eastern decent.<sup>[14]</sup>

## Conclusion

In summary, this is the first study to examine the ethnical differences in myelosuppression with imatinib in GIST. High incidence of neutropenia was seen in AA and none in white. Various degrees of cytopenias may occur in few patients of CML as well as GIST on imatinib therapy. Regular hematologic follow-up is required so that the drug may be stopped or dose modified as per the individual's needs. Despite having a small sample size, it brings out ethnic variation in degree of myelosuppression as an important factor to be studied in both retrospective and prospective manner.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.W.S.; Design – M.W.S.; Supervision – M.W.S.; Materials – M.W.S., S.P.; Data collection &/or processing – M.W.S., S.P.; Analysis and/or interpretation – M.W.S., S.P.; Literature search – M.W.S., S.P.; Writing – M.W.S., K.K., N.W., A.C., T.R., K.B.M.; Critical review – M.W.S., K.K., N.W., A.C., T.R., K.B.M.

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