

## Retinal Neovascularization and Hemorrhage Associated with the Use of Imatinib (Gleevec®) in a Patient Being Treated for Gastrointestinal Stromal Tumor (GIST)

ANTHONY PAUL GULATI and MUHAMMAD WASIF SAIF

*Columbia University College of Physicians and Surgeons at New York,  
Presbyterian Hospital, New York, NY, U.S.A.*

**Abstract.** *Background: Gastrointestinal stromal tumor (GIST) is a mesenchymal malignancy of the gastrointestinal tract. Imatinib mesylate (Gleevec®, ST1571, Novartis Pharmaceuticals, Basel, Switzerland) is a selective inhibitor of break point cluster-Ablason (BCR-ABL), c-Kit, and platelet-derived growth factor receptor alpha (PDGFRα) tyrosine kinases. Imatinib has been approved in the U.S. for the treatment of Philadelphia-chromosome positive chronic myeloid leukemia, KIT (CD117)-positive unresectable and metastatic malignant GIST and adjuvant treatment of adult patients following resection. Ocular side effects are commonly reported with Gleevec®, the most common being periorbital edema and epiphora. Case Report: Here we present the case of a 62-year-old male with a history of GIST in the jejunum who was started with imatinib mesylate at 400 milligrams daily. Seven months into his therapy, he reported blurry vision. He was evaluated by an ophthalmologist, and was ultimately found to have retinal hemorrhage and neovascularization. His dose was reduced by 50% to 200 milligrams daily with an almost complete resolution of symptoms within several weeks. No recurrence of symptoms or signs was noticed at 6 months follow-up. Discussion: This patient's Naranjo scale was calculated to be 7, indicating a probable adverse drug reaction. Our patient's symptoms significantly improved with a dose reduction of imatinib, and this hints that there was a dose-dependent effect. The World Health Organization has categorized retinal hemorrhage as an unlikely side-effect of therapy, and to our knowledge this has never been reported before in a patient receiving*

*imatinib mesylate for GIST treatment. Neovascularization also has not been previously reported in patients receiving this medication. It is important to identify less common ocular toxicity in patients receiving imatinib.*

Gastrointestinal stromal tumor (GIST) is a mesenchymal malignancy of the gastrointestinal tract. It is characterized by activating Kit or platelet-derived growth factor receptor (PDGFRα) mutations, and consequently these tumors over express KIT or PDGFRα protein. While the preferred treatment for GIST is surgical resection, up to 47% of patients are reported to have distant metastases at the time of presentation (1). Therefore, targeted therapy with imatinib mesylate (Gleevec®), a selective inhibitor of break point cluster-Ablason (BCR-ABL), c-KIT, and PDGFRα tyrosine kinases, is an effective treatment for patients who are not candidates for surgery. It can also be used in the adjuvant setting, and studies looking into the use of this medication after surgery are ongoing. Imatinib mesylate is also commonly used in the treatment of chronic myelogenous leukemia (CML) (2, 3).

The most commonly reported drug-related adverse events with imatinib mesylate are fatigue, mild to moderate nausea, diarrhea, liver function test abnormalities, myalgia, peripheral edema, and skin rash. In addition, the most commonly described ocular abnormalities were periorbital edema (70%) and epiphora (18%) (4). Interestingly, there have been no reported issues with retinal neovascularization in association with imatinib mesylate. Furthermore, there are only a few cases of retinal hemorrhage in patients on imatinib mesylate reported in the literature, and these are referred to patients being treated for CML (5).

### Case Report

Our patient is a 62-year-old male with a history of GIST in the jejunum. He initially presented with a jejunal mass and underwent a laparoscopic resection. The tumor was well

*Correspondence to:* Wasif Saif, MD, MBBS, Professor of Clinical Medicine, Director, Cl. Sec. of GI Cancers, Medical Director, Pancreas Center, Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital, New York, NY, U.S.A. Tel: +212 3050592, Fax: +212 3053035, e-mail: mws2138@columbia.edu

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Table I. *The Naranjo algorithm.*

Naranjo	Description	Score
1	Are there previous conclusive reports on this reaction?	0
2	Did the adverse event appear after the suspected drug was given?	2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	1
4	Did the adverse reaction appear when the drug was re-administered?	0
5	Are there alternative causes that could have caused the reaction?	2
6	Did the reaction reappear when a placebo was given?	0
7	Was the drug detected in any body fluid in toxic concentrations?	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was reduced?	1 (less severe when dose reduced)
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	0
10	Was the adverse event confirmed by any objective evidence?	1

Final Score 7 (probable ADR)

Scoring: 7=probable Adverse Drug Reaction (ADR), > 9=definite ADR, 5-8=probable ADR, 1-4=possible ADR, 0=doubtful ADR.

circumscribed, found to be 3.5 cm in its greatest dimension, contained within the bowel wall, and had a low mitotic count and CD117 positivity with spindle cells, consistent with GIST tumor with low risk features. Three months after surgery, the patient was started on adjuvant therapy with imatinib mesylate at a dose of 400 milligrams daily. Initially this treatment was tolerated fairly well; computed tomography (CT) scans, carried out every three months during this time, showed stable disease.

After almost 7 months of therapy, the patient complained of new visual disturbances which included blurry vision and eye fatigue on the right. Prior to this, he had gone to annual visual examinations including fundus examination, which were unremarkable, and he did not wear glasses or corrective lenses. He did not have any personal history of diabetes mellitus, hypertension or any other medical conditions, and was not on any other medications. He denied the use of any smoking, alcohol, or drugs.

Laboratory data at that time was unremarkable and showed a stable complete blood count, basic metabolic panel, and liver function tests. A Positron emission tomography-computed tomography (PET/CT) and Magnetic resonance imaging (MRI) of the brain at that time did not show any evidence of metastatic disease.

He was evaluated by an ophthalmologist and on examination of the right fundus neovascularization and mild retinal hemorrhage (less than 1/5 total disk area) were revealed. Visual acuity was also slightly decreased at 20/25. The ophthalmologist reported no microaneurysms, no A-V crossing defects, no narrowing of the arterioles, and no exudates. In the left fundus there was a possible small area of neovascularization but it was otherwise unremarkable.

Given these findings, we decided to reduce the patient's dose of imatinib mesylate to 200 milligrams. The patient noted almost complete resolution of his symptoms within

several weeks. His symptoms from his GIST were also stable, and CT findings of the abdomen and pelvis have remained stable since then. In addition, further ophthalmologic exams showed resolution of the retinal hemorrhage with improvement in his visual acuity.

To further assess the potential association of imatinib and retinal hemorrhage and neovascularization, we used the *Naranjo algorithm*, which is a questionnaire designed for determining the likelihood of whether an adverse drug reaction is actually due to the drug rather than as the result of other factors (Table I) (6). The probability of an adverse drug reaction is assigned a score of definite (total score greater than 9, with a maximum possibility of 10), probable (total score ranging 5-8), possible (total score ranging 1-4), or doubtful (total score equal to 0). Our patient's total score according to the algorithm was 7, indicative of a probable adverse drug reaction.

## Discussion

We have reviewed the medical literature and found sparse data regarding either of these events in association with imatinib mesylate. In addition to the most common ocular findings of periorbital edema and epiphora, there have been sparse reports of optic disk edema as a possible complication of imatinib mesylate in a patient being treated for CML (7). In a retrospective review of 250 patients with CML treated with imatinib mesylate, there were two reported cases of retinal hemorrhage, and they occurred early (within 1-2 months) on starting treatment, and in one of them, the dose was reduced (5).

The WHO classification of ocular side-effects with imatinib mesylate is as follows: certain: periorbital edema; probable: epiphora; possible: extra-ocular muscle palsy, ptosis, blepharoconjunctivitis; unlikely: glaucoma, papilledema,

retinal hemorrhage, photosensitivity, abnormal vision, and increased intraocular pressure (8).

It appears that the association of retinal hemorrhage and neovascularization and imatinib mesylate is a rare complication. However, our patient's symptoms significantly improved with a dose reduction of his imatinib, and this hints that there was a dose-dependent effect. It has been reported in animal studies that the ocular toxicity of imatinib in rabbits is dose dependent (9). Although retinal metastasis has been rarely reported as a cause of retinal hemorrhage (and not in cases of GIST), this is unlikely in this case given that the hemorrhage resolved on further examination of the fundus and that MRI of the brain and PET/CT were unremarkable (10).

It is important to identify imatinib mesylate as a potential causative agent early and make an appropriate intervention as needed. Since imatinib mesylate is being used more frequently and ocular toxicity can be a cause of great morbidity in patients, it is important to be aware of these potential adverse ocular effects.

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