Imatinib-Induced Bone Edema: Case Report and Review of Literature

Lucas Vieira dos Santos, MD; João Paulo Lima, MD, PhD; Kathia Cristina Abdalla, MD; Arinilda Campos Bragagnoli, MD; Florinda Almeida Santos, MD; Alexandre dos Anjos Jácome, MD; and Fabiano Elias Porto, MD

Abstract
Imatinib mesylate represents a revolution in the management of patients with metastatic gastrointestinal stromal tumors (GISTs). More recently, postoperative imatinib has been shown to improve both disease-free and overall survivals in patients with a high risk of recurrence. This article presents a well-documented case of a patient with painful and reversible bone edema related to imatinib. (JNCCN 2013;11:1187–1191)

NCCN: Continuing Education

Accreditation Statement
This activity has been designated to meet the educational needs of physicians and nurses involved in the management of patients with cancer. There is no fee for this article. No commercial support was received for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians.

NCCN designates this journal-based CME activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Learning Objectives
Upon completion of this activity, participants will be able to:
• Describe the management of severe bone pain in patients with GISTs receiving imatinib
• Distinguish between the signs and symptoms of bone pain associated with imatinib therapy versus bone metastasis in patients with GISTs

From ‘Hemomed - Instituto de Oncologia e Hematologia & IEP Sao Lucas, Sao Paulo, and the ‘Gastrointestinal Cancer Unit, Medical Oncology Department and ‘Radiology Department, Hospital de Cancer de Barretos, Barretos, Brazil.
Submitted September 28, 2012; accepted for publication May 7, 2013.
The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.
Correspondence: Lucas Vieira dos Santos, MD, Hemomed - Instituto de Oncologia e Hematologia & IEP Sao Lucas, 121 Arnofo de Azevedo Ave, Sao Paulo, Brazil 01238-030. E-mail: lucasvsantos@yahoo.com

EDITOR
Kerrin M. Green, MA, Assistant Managing Editor, JNCCN—Journal of the National Comprehensive Cancer Network
Ms. Green has disclosed that she has no relevant financial relationships.

CE AUTHORS
Deborah J. Moonan, RN, BSN, Manager, CE Supporter Outreach
Ms. Moonan has disclosed the following relationship with commercial interests: AstraZeneca: Stockholder/Former Employee.
Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations
Ms. Gregory has disclosed that she has no relevant financial relationships.
Background

Gastrointestinal stromal tumors (GISTs) are the most common nonepithelial cancers of the digestive tract.\(^1,2\) Imatinib mesylate, a tyrosine kinase inhibitor, represents a revolution in the management of patients with metastatic GIST. More recently, postoperative imatinib has been shown to improve both disease-free and overall survival in patients with a high risk of recurrence.\(^3\) Imatinib, which has also been used successfully in chronic myeloid leukemia (CML), is well tolerated, with few severe adverse events.\(^3,5,7,9\) Bone-related events have been described in some series involving patients with late-phase CML, but it is not clear whether these symptoms are related to the drug or the baseline condition itself.\(^10\) In GIST, bone-related adverse events are far less frequently reported.\(^9\) This article describes a patient with GIST who developed severe bone pain secondary to bone edema caused by adjuvant imatinib. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Case Report

A 45-year-old otherwise healthy man was referred to the authors’ hospital because of a painful, enlarged abdominal mass associated with mild weight loss in the previous 6 months. CT scans showed a 9-cm cystic mass arising in the jejunum. No evidence was seen of metastatic disease. Laparoscopic surgery identified a 10.2 × 8.0-cm mass arising from the jejunum, with overt invasion of right colon and some foci of spontaneous rupture of the tumor. The surgical team performed a right hemicolectomy and enterectomy, with end-to-end anastomosis in both segments. All visible tumor was removed.

The pathologic findings showed a c-KIT–positive fusocellular-pattern GIST, with 14 mitoses per 50 high-power fields, harboring a c-KIT gene point mutation (exon 11 p.val560asp). The patient was considered at high risk of relapse according to current risk-assessment classifications.\(^11,12\) Postoperative CT scans showed no evidence of disease. Six weeks after surgery, the patient started imatinib, 400 mg/d, which was planned to continue for 3 years.\(^7,8\)

Fifteen days after starting imatinib, the patient developed mild pain in the left leg. The vascular duplex scan and neurologic examination ruled out any relevant abnormalities and therapy was continued. Two months later, the patient returned to the office complaining of worsening left leg pain despite optimized analgesic treatment. He also noted right arm pain with no history of trauma. At that moment, the leg pain was impairing his gait. A left leg CT scan showed no abnormalities. The levels of serum C-reactive protein, parathormone, calcium, phosphorus, and hemosedimentation velocity were all within the normal range.

The pain was considered a serious adverse event possibly related to imatinib, and the drug was halted. Leg and arm pain improved dramatically with imatinib stoppage, and 12 days later the symptoms had completely disappeared.

Considering the high risk of relapse, imatinib was resumed 6 weeks later. Within 2 weeks of imatinib use, the same severe symptoms reemerged. The bone scan showed moderate uptake in the diaphyses of the left tibia and fibula, the distal right humerus, and the proximal radii and femurs bilaterally (Figure 1). MRI performed during this round of imatinib showed ill-defined areas in bone marrow with mild

Figure 1  Bone scan showing moderate uptake in the diaphyses of left tibia and fibula, the distal right humerus, and the proximal region of radii and femurs bilaterally.
Imatinib-Induced Bone Edema

decrease in signal intensity on T1-weighted images, moderate hyperintensity on T2-weighted images, and contrast-enhancement in the proximal right ulna, right humerus diaphysis, left fibula, and left tibia, suggesting bone edema. No signs of osteonecrosis were seen (Figure 2).

Given the severity of pain, imatinib was definitively discontinued, and all symptoms faded entirely in 2 weeks. Repeat bone and MRI scans showed disappearance of almost all alterations (Figure 3). The authors considered this unusual and reversible adverse event definitively associated with imatinib, hence demanding drug suspension. Twelve months after initiation of therapy, the patient remains asymptomatic and free of relapse.

Discussion

Imatinib has become the backbone of CML and GIST management in the past decade, because of not only its high efficacy but also its good safety profile. Up to 14% of patients with GIST on imatinib therapy will develop bone pain or arthralgia, usually mild, which can be misdiagnosed as bone metastasis. Edema and fluid retention are the most common adverse events associated with imatinib, and are far more common in elderly and female patients. These reactions seem to be dose-related, especially with doses greater than 600 mg/d. The physiopathology of imatinib-triggered edema is not yet clearly understood; however, it may be caused by inhibition of platelet-derived growth factor receptor, which regulates interstitial fluid pressure.

This report presents a well-documented clinical case showing that bone pain and bone edema occurred and worsened during imatinib therapy, and that these signs and symptoms completely resolved with discontinuation of therapy. The symptoms were extremely intense, leading to the definitive discontinuation of imatinib therapy. To date, no evidence-based guidelines have been published suggesting how to manage infrequent adverse events, and therefore the authors chose a more conservative approach, discontinuing imatinib.

Figure 2  MRI showing ill-defined areas in bone marrow with moderate hyperintense signal intensity on T2-weighted image of left tibia.

Figure 3  Left tibia MRI showing disappearance of bone lesion described in Figure 2 after imatinib discontinuation.
To the authors’ knowledge, this is the first case of imatinib-related bone edema in a patient with GISTs reported in the literature; other groups have reported insufficiency fractures and bone necrosis possibly related to imatinib. The radiologic findings helped demonstrate that the bone pain may be caused by marrow edema, which is reversible.

Edema is one of the most common imatinib-related adverse events, and bone edema might share the same pathogenesis as edema in general. Clinicians must be aware that pain, accompanied by bone scan and MRI alterations, may be associated with imatinib itself. These signs and symptoms might be wrongly diagnosed as bone metastasis, which is a late and unusual event in patients with GISTs treated with imatinib, or other benign bone lesions, which would lead to unnecessary diagnostic interventions or therapy change for the primary condition.

Conclusions

For patients experiencing bone pain while receiving imatinib, a conservative workup with bone and MRI scans, accompanied by drug suspension, may be the optimal approach for managing this rare adverse event, which is reversible.

References

Instructions for Completion
To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at http://education.nccn.org/node/30367; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on “New Member? Sign up here” link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions
1. Bone-related adverse events have been described in some patients with CML and GIST treated with imatinib.
   a. True
   b. False
2. Which of the following are the most common adverse events associated with imatinib?
   a. Edema
   b. Fluid retention
   c. Arthralgia
   d. Bone pain
   e. Both a and b
3. Dose-reduction of imatinib is the optimal approach for the management of bone pain and bone edema associated with imatinib in patients with GIST.
   a. True
   b. False