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## Editorial

# Hypocalcemia with imatinib treatment in chronic myeloid leukemia patients

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## 1. Introduction

Imatinib mesylate is a tyrosine kinase inhibitor targeted to BCR-ABL, PDGFR, and KIT mutations. It plays a pivotal role in treatment of chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours (GISTs), and has dramatically changed the clinical management of these tumour types.<sup>1-4</sup>

The adverse effects of imatinib are mostly mild and manageable.

Various side effects are as follows:

1. Anemia
2. Oedema
3. Fatigue
4. Nausea
5. Diarrhoea
6. Cramps
7. Rash
8. Myalgia
9. Arthralgia
10. Granulocytopenia

Musculoskeletal effects of imatinib are reported in 25% of GIST patients and 20–40% of CML patients, including arthralgia, myalgia, and muscle cramps, but are rarely dose-limiting.<sup>2,5-8</sup>

The pathophysiology of these effects is uncertain. Various pathophysiological mechanisms proposed are :

1. Firstly, although KIT is expressed on renal tubular cells, their functions there are unknown. Imatinib could therefore be exerting a direct effect on renal tubular KIT receptors, resulting in relative hypocalcaemia.
2. Secondly, imatinib is a member of a family of protein tyrosine kinase inhibitors which can induce marked changes in cell excitability and ion homeostasis. Indeed, imatinib blocks low voltage-activated T-type calcium channels in human embryonic kidney cells.<sup>9</sup> Thus imatinib could have a nonspecific effect on calcium homeostasis that is not KIT receptor-mediated.
3. Thirdly imatinib might be causing nonspecific inhibition of calcium channels in tubule which might be leading to hypocalcemia.

Musculoskeletal complaints are a common side effect of imatinib and are manifested as muscle cramps and bone pain. The muscle cramps occur mainly in the hands, feet, calves, and thighs. The pattern, frequency, and severity of cramps are usually constant over time, and they may resemble titanic contractions. Some patients relate cramps to exertion or describe night time occurrence. Bone pain and arthralgias have been reported by 20% to 40% of patients. Their onset tends to be in the first month of therapy, and they frequently abate after a few months. The symptoms most frequently affect the femurs, tibias, hips, and knees.

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Bone or joint pain can be severe and disabling and may be strikingly asymmetric. In some cases, imaging studies were done but failed to detect abnormalities.

Various electrolyte imbalances common in imatinib treatment

1. Hypophosphatemia: This is the most common electrolyte imbalance associated with imatinib. The clinical manifestations of mild hypophosphatemia include myalgias, weakness, anorexia. Chronic severe depletion may be manifested by pain in muscles and bones.
2. Hypocalcemia: This is the second most common abnormality which was detected in patients on imatinib, hypocalcemia increases excitation of nerve and muscle cells, primarily affecting the neuromuscular and cardiovascular systems. Extensive spasm of skeletal muscle causes cramps and tetany.<sup>9</sup>
3. Hypokalemia: Described only in case reports in patients who are on imatinib, this is also a possible cause of myalgia and muscle spasms but does not cause arthralgia /bony pains.

The treatment which has been advised by NCCN and other literature evidence states that calcium supplementation is an important treatment aspect in the management of musculoskeletal pain along with fluids supplementation.<sup>10,11</sup>

## 2. Conclusion

Myalgia and musculoskeletal is the one of the common nonhematological side effect in patients of chronic myeloid leukemia who are initiated on imatinib. This side effect must be efficiently taken care of in order to increase the compliance of patients for better outcome.

## 3. Conflict of Interest

None.

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