

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

An unexpected and devastating adverse event of dasatinib: Rhabdomyolysis



ARTICLE INFO

Keywords:

Dasatinib
Rhabdomyolysis
Creatine kinase

ABSTRACT

We, herein, describe a 52-year-old male whom developed rhabdomyolysis and acute renal failure likely related to dasatinib shortly after the administration of treatment. After withdrawal of dasatinib, the myalgia reduced, and his CK returned to normal levels within a week. On follow-up acute renal failure did resolve without requiring dialysis, but unfortunately the patient died of severe respiratory distress. We recommend that musculoskeletal symptoms should be monitored during therapy with dasatinib, and CML patients with musculoskeletal symptoms should have CK levels checked in order to prevent this unexpected but devastating adverse event.

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To the Editor,

Dasatinib, a second-generation BCR-ABL inhibitor that has 325-fold higher potency in vitro compared with imatinib [1], is used for the treatment of Philadelphia chromosome-positive (Ph⁺) chronic myeloid leukemia (CML) and Ph⁺ acute lymphoblastic leukemia. Its common side effects (myelosuppression, fluid retention, and diarrhea) are most often mild and manageable [2]. All grades of adverse reactions under dasatinib treatment including musculoskeletal pain, myalgias, and muscle spasms are 13%, 6%, and 5% respectively, based on the manufacturer's labeling. However, no grade 3/4 adverse reactions of musculoskeletal system are described, as well as rhabdomyolysis [3]. In the 2-year follow-up of phase 3 DASISION (dasatinib versus imatinib study in treatment-naïve CML patients) study, one patient in the dasatinib arm discontinued treatment because of elevated skeletal creatine phosphokinase with no evidence of myocardial ischemia [1].

Among tyrosine kinase inhibitors (TKIs), imatinib mesylate-induced two [4,5], and erlotinib-induced one [6] rhabdomyolysis cases are documented. However, no dasatinib- or nilotinib-induced rhabdomyolysis cases are reported in the current literature. To the best of our knowledge, this is the first report of rhabdomyolysis which had been occurred under dasatinib treatment.

We describe here a case of a 52 year-old male who received dasatinib (Sprycell[®], Bristol-Myers Squibb) at a daily dose of 100 mg for the treatment of chronic phase CML with no hematologic or molecular response to imatinib-mesylate. Approximately 4 months ago he had been diagnosed as de novo chronic phase CML, and imatinib mesylate (Glivec[®], Novartis) 400 mg/day was initiated. However, the patient's compliance to treatment was not adequate. 4 months after imatinib therapy, he admitted to our institution. At that time neither hematologic nor molecular response was achieved under imatinib therapy. Therefore, imatinib was stopped and second-generation TKI (dasatinib) was given instead in order to prevent disease progression. Two weeks after the administration of dasatinib treatment, he had severe lassitude and muscle weakness, and an elevated level of serum creatine kinase (CK:

2600 U/L, normal range: 25–195). His renal function tests on admission were as follows: urea: 143 mg/dL (10–50), creatinine: 3.0 mg/dL (0.6–1.2). His CK level peaked at 3831 U/L on the day following admission. The patient's medical history was unremarkable for chronic diseases and he was not taking any drugs that may affect dasatinib metabolism or trigger rhabdomyolysis. There was no history of trauma, direct injury, or excessive physical activity. Myocardial infarction, stroke, medications (statins, antidepressants, antipsychotic drugs, colchicine), or other common causes of rhabdomyolysis were ruled out. He had not been using any alcohol or other substances (e.g. herbal medicines). Dasatinib was stopped and he was given aggressive hydration, allopurinol and diuretics. Because of the patient's low performance status, a muscle biopsy was deferred at this point. After withdrawal of dasatinib, the myalgia reduced, and the CK returned to normal levels (156 U/L) within a week (Fig. 1). On follow-up acute renal failure did resolve without requiring dialysis. Unfortunately, the patient died after clinical deterioration while receiving palliative therapy had progressive severe respiratory distress, with a rapid decline in performance status ultimately leading to cardiorespiratory arrest. The leading cause of death was thought to be severe pulmonary infection.

Although a clear association cannot be made between the administration of dasatinib and the CK elevations based on this case alone, we considered his rhabdomyolysis to be induced by dasatinib. Our objectives are (a) the rhabdomyolysis occurred shortly after the initiation of dasatinib therapy, (b) his CK levels normalized after withdrawal of the aforementioned drug. The exact mechanism whereby dasatinib could cause rhabdomyolysis remains unclear. It has been suggested that platelet-derived growth factor receptor and c-abl which are expressed by muscle tissue are inhibited by imatinib mesylate treatment, and the reduction of these enzymes could lead to CK elevation [7,8]. Because of the potency of dasatinib over imatinib mesylate, the same mechanism should also be suggested in this case.

An uncommon adverse event of dasatinib, rhabdomyolysis, should be considered in the clinical setting of persistent muscle

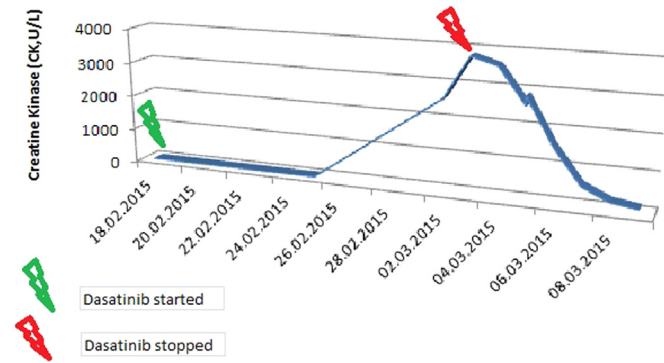


Fig. 1. Close monitoring of creatine kinase (CK) levels of the patient during follow-up.

pain and elevated CK levels. We, therefore, recommend examining musculoskeletal symptoms for CML patients during treatment with dasatinib. CML patients with musculoskeletal symptoms should have CK levels checked in order to prevent this devastating complication.

Conflict of interest statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Received 9 April 2015; accepted 29 November 2015

Available online 3 December 2015

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