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Case Report of Suspected Rhabdomyolysis during Treatment with Trabectedin in a Patient with Metastatic Leiomyosarcoma

W. Lamm[a] G. Amann[b] T. Brodowicz[a]

[a]Clinical Division of Oncology, Department of Medicine I, and [b]Department of Pathology, Medical University of Vienna, Vienna, Austria

Key Words
Leiomyosarcoma · Trabectedin · Rhabdomyolysis

Abstract
Trabectedin has been reported to occasionally induce rhabdomyolysis. In the present case, continuation of trabectedin was maintained despite suspected rhabdomyolysis related to trabectedin. Creatinine kinase levels dropped to normal levels. We suggest that continuation of trabectedin despite suspected rhabdomyolysis was safe in this specific patient.

Introduction

Leiomyosarcomas are rare malignant tumors. Trabectedin is an antineoplastic compound isolated from the Caribbean tunicate *Ecteinascidia turbinate*. It induces tumor regression and inhibits tumor growth. This agent is approved as second-line therapy after failure of available standard-of-care therapies in leiomyosarcomas. The most common grade 3/4 side effects are anemia, thrombocytopenia and transient elevation of liver enzymes.

Case Report

We describe a case of a 37-year-old male who was admitted to the Vienna General Hospital, Medical University Vienna, due to abdominal pain. Magnetic resonance imaging showed a right-sided retroperitoneal tumor, infiltrating the right kidney, the right adrenal gland and the inferior caval vein. Additionally, an abdominal computed tomography (CT) was performed, which showed further metastases in the lymph nodes and ascites. In February 2008, the patient underwent debulking surgery

Thomas Brodowicz, MD

Clinical Division of Oncology, Department of Medicine I
Medical University of Vienna, Waehringer Guertel 18–20
AT–1090 Vienna (Austria)
Tel. +43 1 40400 4429, Fax +43 1 40400 4451
E-Mail thomas.brodowicz@meduniwien.ac.at

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of the tumor, resection of the right kidney and of the inferior caval vein with gore-tex replacement. Histopathology revealed a marginally resected leiomyosarcoma G3 of 20 × 11 × 16.5 cm in size. Immunohistochemical analysis showed tumor cells positive for vimentin, smooth muscle actin (1A4) and, to a lesser extent, for desmin. Reactions with antibodies against CD117 (c-kit), CD34 and p53 were negative. A chest CT scan showed multiple metastases also in the lung. The patient rejected initial conventional chemotherapy and asked for experimental therapy. Within this context, sorafenib treatment [1] was suggested to the patient and subsequently started. Best overall response was stable disease, which lasted for 6 months. Subsequent to progression, second-line therapy with doxorubicin 75 mg/m^2 every 3 weeks was administered. Due to progressive disease after 2 cycles, ifosfamide (1,500 mg/m^2, day 1–5, every 21 days) was given as third-line therapy with subsequent progression of disease after 3 cycles. Thereafter, trabectedin (1.5 mg/m^2 continous infusion over 24 h every 3 weeks) was started. Dexamethasone 20 mg and 5HT3 antagonists were administered 30 min before trabectedin application. Best overall response was stable disease (SD), which lasted for 11 cycles. In the 8th cycle of trabectedin, creatinine kinase (CK) level was elevated to 1,119 U/l (normal range <319 U/l), which was confirmed by repetitive measures. Levels of TnT, CK-MB, LDH were within normal values and the electrocardiogram showed no abnormalities. Thus, a cardiac causality of the CK elevation was ruled out. The patient complained of general muscle pain, but he did not report any previous excessive muscle training or trauma. A biopsy of the muscle cell, in order to verify suspected rhabdomyolysis, was refused by the patient. Due to the limited availability of further therapeutic options and after careful consideration of risks related to continuation of trabectedin and the potential benefit of SD after 8 cycles of trabectedin, trabectedin was continued under the condition of extensive monitoring of the patient. Three additional cycles of trabectedin were applied. All 3 cycles were dose reduced (1.2 mg/m^2) due to elevated serum creatinine levels of 2.12 mg/dl (normal value <1.2 mg/dl). CK levels, which were still elevated (≥1.5 × ULN) after the 9th and 10th cycle dropped to 78 U/l, which is normal after the 11th cycle. The most recent creatinine level was 2.05 mg/dl, and the patient is doing well. He still has an ECOG PS of 0, and a recent CT scan showed SD.

Discussion

Leiomyosarcomas are rare malignant tumors of smooth muscle differentiations that may arise in any organ or tissue that contains smooth muscle. They comprise less than 2–9% of sarcomas. Leiomyosarcomas are most frequently found in the stomach and small intestine and may also be commonly found in the abdomen and retroperitoneum. However, besides the walls of the gastrointestinal tract, they normally arise in the walls of large vessels [2].

Trabectedin is a marine-derived antineoplastic compound isolated from the Caribbean tunicate *Ecteinascidia turbinate* and currently produced synthetically [3]. This agent induces tumor regression and inhibits tumor growth [4]. The efficacy of trabectedin at a dose of 1.5 mg/m^2, given intravenously over 24 h every 3 weeks in patients with advanced soft tissue sarcomas was previously evaluated in 4 phase II studies [5–8]. In a study by the French study group, the most common grade 3/4 toxicities were anemia, thrombocytopenia, and transient elevation of liver enzymes (AST/ALT) [9].

To the best of our knowledge, this is the first reported case of a continuation of trabectedin despite a severe trabectedin-related CK elevation. In this specific case, this specific toxicity was reversible and not repetitive under treatment with trabectedin. However, reported findings should not be interpreted as suggestion to continue treatment regardless of drug-related toxicity. They should rather serve as a description of specific findings related to a relatively new drug.

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Disclosure Statement

Thomas Brodowicz is an advisory board member at PharmaMar. Wolfgang Lamm and Gabriele Amann indicated no potential conflict of interest.

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