

# Response to trabectedin in a patient with advanced synovial sarcoma with lung metastases

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Trabectedin is an alkylating agent registered in Europe for the treatment of advanced metastatic soft-tissue sarcomas, whose activity has been documented mainly in liposarcomas or leiomyosarcomas. Here, we report the response achieved in a patient with lung metastases from synovial sarcoma. A man with a large synovial sarcoma of the axilla underwent three cycles of neoadjuvant epirubicin + ifosfamide before complete excision, followed by three additional cycles of chemotherapy and radiotherapy. After 14 months, bilateral lung metastases appeared and were first treated with a prolonged 14-day continuous infusion of high-dose ifosfamide without response, and then with second-line trabectedin. A partial radiological response was achieved; dosage was reduced to 1.1 mg/m<sup>2</sup> because of mild asthenia, grade 3 neutropenia, grade 3 nausea and vomiting, and reversible transaminase elevation. After 9 months of treatment, the lung nodules progressed, the patient received sorafenib, but further progressed and died 19 months after the first appearance of lung metastases. Trabectedin was the only

drug that led to a radiological response in this patient with synovial sarcoma, despite being administered at 75% of the standard dose because of dose-limiting nausea and vomiting, in line with more recent data demonstrating activity in translocated sarcomas. We believe that trabectedin represents an attractive option for the treatment of metastatic synovial sarcoma and further clinical studies are warranted. *Anti-Cancer Drugs* 25:1227–1230 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

Trabectedin is an antineoplastic alkylating agent approved in Europe in 2007 for the treatment of advanced metastatic soft-tissue sarcomas, after failure of anthracyclines and ifosfamide, or in those who are unsuited to receive these agents [1]. It is considered that trabectedin has multiple mechanisms of action, including induction of DNA damage through alteration of specific DNA repair pathways, transcriptional interference, and selective immunomodulatory and anti-inflammatory activities resulting from inhibition of tumor growth-promoting factors, angiogenesis, and metastasis [2–4].

Although the survival rates in these patients are low, systemic therapy can provide palliation in patients with unresectable metastatic tumors and may prolong survival. Trabectedin has been shown to be effective in advanced soft-tissue sarcomas, especially for liposarcoma and leiomyosarcoma [5–7]; however, some evidence suggests that other translocation-related sarcomas, such as synovial sarcomas, may also be sensitive to trabectedin [6,8–10]. Translocation-related sarcomas represent about a quarter

of sarcoma cases [11]. Recently, a retrospective study evaluating the efficacy of trabectedin in translocation-related sarcomas provided additional data of effectiveness in synovial sarcoma [8]. In another retrospective analysis of 61 patients with advanced synovial sarcoma, trabectedin induced an overall response rate of 15%, a 6-month progression-free survival (PFS) rate of 23%, and a median PFS in responding patients of 7 months [9].

Here, we report the use of trabectedin in an adult man with advanced unresectable metastatic synovial sarcoma.

## Case report

We present the case of a 37-year-old man without significant previous medical history, who presented in March 2009 with a rapidly growing axillary mass. MRI indicated a deep enhancing mass of more than 5 cm adjacent to the axillary artery. Biopsy indicated a biphasic synovial sarcoma; a chest and abdomen computed tomography (CT) scan showed no distant metastases.

The patient was treated with neoadjuvant chemotherapy consisting of epirubicin 60 mg/m<sup>2</sup> of body surface area on day 1 and 2 and ifosfamide 3 g/m<sup>2</sup> on days 1–3, every 21 days, for three cycles, with coadministration of prophyllactic granulocyte colony-stimulating factor to reduce

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the risk of neutropenia. The most relevant toxicities were nausea and vomiting grade 3.

The diameter and density of the tumor appeared unchanged at the MRI performed in June. Complete excision was performed with conservative surgery; pathology confirmed a poorly differentiated synovial sarcoma, harboring the typical t(X;18) translocation involving *SS18-SSX1* genes, with the presence of necrotic areas. Three cycles of the same chemotherapy schedule were delivered postoperatively, followed by local radiotherapy. The treatment was completed in September 2009.

Follow-up visits were performed every 4 months up to November 2010, when a CT scan indicated multiple and unresectable bilateral lung metastases, maximum diameter 1.5 cm. Given the choice of close observation or treatment, the patient opted to start a first-line regimen of systemic chemotherapy, possibly with low acute toxicities. We therefore chose a prolonged 14-day continuous infusion of high-dose ifosfamide 1 g/m<sup>2</sup>/daily, along with an equal dose of mesna.

Restaging after three cycles showed asymptomatic progression of all lung metastases. Following some reports of activity of trabectedin in this histotype of sarcoma [8,9] and considering the good performance status of the patient, in April 2011, we decided to start second-line treatment with trabectedin, with standard dexamethasone premedication. Prudently, the dose of the first cycle of trabectedin was reduced from the standard dose of 1.5 to 1.3 mg/m<sup>2</sup> in consideration of his previous exposure to the alkylating drug ifosfamide. Even with this lowered dose, the patient developed mild asthenia, grade 3 neutropenia, grade 3 nausea, and vomiting, plus some episodes of reversible transaminase elevation (>2.5× upper limit of normal), and so the dose of trabectedin was further reduced to 1.1 mg/m<sup>2</sup>, with resulting attenuation of toxicity.

After the first three cycles of treatment, a CT scan showed that the lung metastases had reduced in size; thus, trabectedin was continued at the same dose of 1.1 mg/m<sup>2</sup> for three additional cycles. A partial radiological response according to Response Evaluation Criteria in Solid Tumors criteria was achieved on August 2011, when some lesions had even disappeared (Fig. 1). Multifocality discouraged metastasectomy and therefore the patient continued chemotherapy for three additional cycles, with persistence of grade 2 nausea.

Unfortunately, in December 2011, after 9 months of trabectedin, the lung nodules appeared increased in size and number. Despite this, the patient had Eastern Cooperative Oncology Group performance status 0, no functional impairments, with only a moderate cough attributable to the presence of the lung metastases, and was, therefore, motivated to continue with further

treatments. Third-line treatment with sorafenib was initiated on the basis of a previous personal observation of significant response in a similar patient [12], but the patient rapidly progressed after 2 months of therapy. At this stage, we openly discussed with the patient the limited benefits from further cytotoxic treatment [13], which were therefore not proposed. We performed some palliative transcatheter radiofrequency procedures on painful lung metastases adjacent to the pleura, but without clinical benefit. The patient was referred to home care and died on June 2012, 19 months after the initial relapse and appearance of the lung metastases.

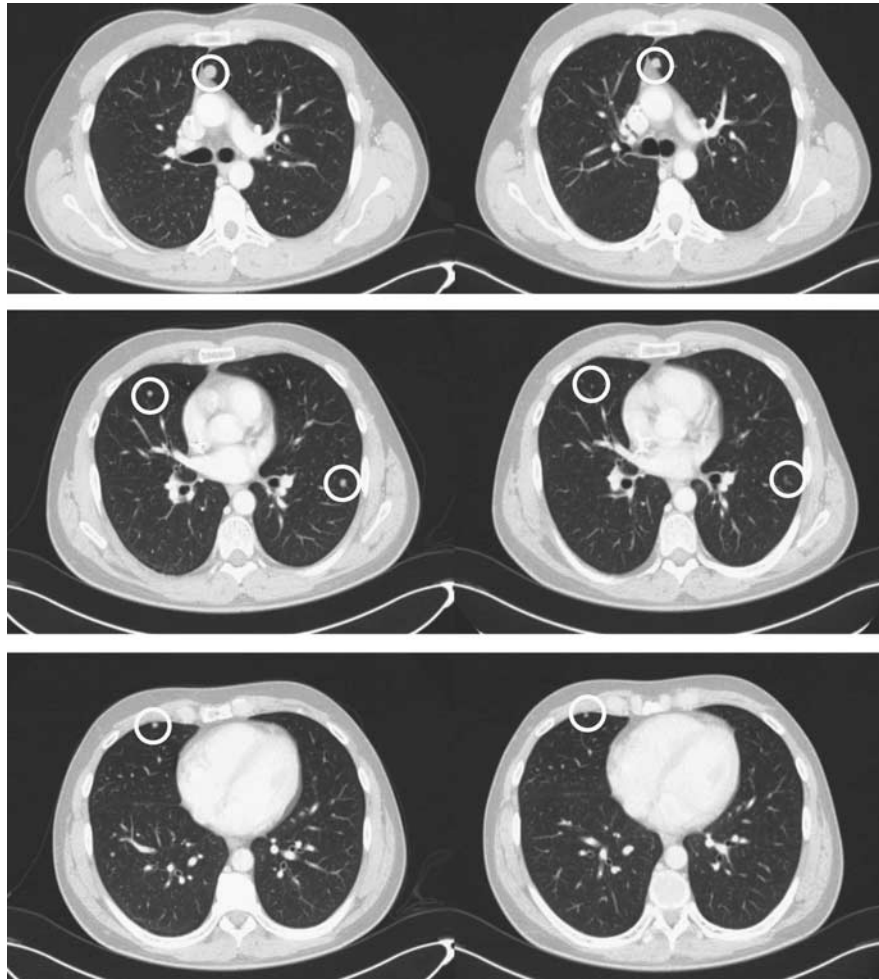
## Discussion

Ifosfamide is an effective drug for synovial sarcoma and it is currently considered the standard therapy for this histotype after the failure of anthracycline-based regimens [14]. There are different ways to administer this drug in terms of the doses and the duration of infusion. A prolonged continuous infusion schedule of 1 g/m<sup>2</sup>/day allows administration of higher doses with less acute toxicity, and is frequently applied in Italian Sarcoma centers. However, a recent multicenter phase II study carried out by the Italian Sarcoma Group reported a disappointingly low response rate of 9% in the subgroup of eleven synovial sarcomas [15]. Our patient did not respond to neoadjuvant chemotherapy with combination epirubicin plus ifosfamide, and both the size and the density of the primary tumor remained unchanged, a strongly negative prognostic factor as confirmed recently by a large neoadjuvant randomized trial by the Italian Sarcoma Group [16]. Furthermore, a continuous infusion schedule of ifosfamide did not halt tumor growth after the first relapse in the lungs.

Patients with advanced metastatic soft-tissue sarcomas and disease progression with or following doxorubicin or ifosfamide chemotherapy have limited therapeutic options and the prognosis is poor. In line with previous data from retrospective studies [8,9], trabectedin showed some efficacy in this patient and was the only drug that led to a response according to the Response Evaluation Criteria in Solid Tumors criteria, despite the fact that it was administered at 75% of the standard dose because of dose-limiting nausea and vomiting. The patient was particularly sensitive to the emetogenic effect of cytotoxic agents, and this was apparent from his first neoadjuvant treatment.

A phase III open-label, randomized, controlled multicenter study (NCT00796120) compared the safety and effectiveness of trabectedin 1.5 mg/m<sup>2</sup> administered intravenously over 24 h with doxorubicin-based chemotherapy (intravenous doxorubicin 75 mg/m<sup>2</sup> every 3 weeks, or 60 mg/m<sup>2</sup>, followed by ifosfamide 6–9 g/m<sup>2</sup> every 3 weeks) as first-line treatment in ~120 patients with unresectable locally advanced or metastatic translocation-related sarcomas, including synovial

Fig. 1



Computed tomography (CT) scans taken before trabectedin therapy showing lung metastases (left-hand images) and response to 5 months of trabectedin therapy showing lung metastases considerably reduced in size and density (right-hand images).

sarcoma patients. Preliminary results reported no significant differences in terms of PFS, but the high rate of censoring prevents us from drawing any relevant conclusion so far [15].

### Conclusion

On the basis of this case report and findings from previous studies, we believe that trabectedin represents an attractive option for the treatment of metastatic synovial sarcoma. We await the findings from an ongoing randomized phase III trial investigating the efficacy of trabectedin compared with doxorubicin-based chemotherapy as first-line therapy for translocation-related sarcomas. Combination trabectedin-containing chemotherapy regimens as well as the use of trabectedin as part of neoadjuvant strategies warrant further investigation in this population.

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### Conflicts of interest

There are no conflicts of interest.

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