Trabectedin in synovial sarcoma: a retrospective case series analysis from two reference centers

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Abstract

Background Synovial sarcomas (SS) are high grade tumors of mesenchymal origin. Although rare, they represent one of the most common soft tissue sarcoma (STS) in children and young adults. Responses were consistently seen amongst patients with metastatic SS with trabectedin (T). Here we report on the activity of T in patients with SS treated in 2 Italian referall centers.

Patients and methods We retrospectively reviewed the medical records of patients with metastatic SS treated with T at Humanitas Clinical and Research Center, Rozzano, Milan and Santo Stefano Hospital, Prato, between January 2010 and June 2014.

Results Between January 2010 and June 2014, 10 patients with metastatic SS received T, administered as 24-hour continuous infusion at a dose of 1.5 mg/m^2 every 3 weeks (9 patients at Humanitas Clinical and Research Center, Rozzano, and 1 at Santo Stefano Hospital, Prato.
Six were female, four male. Median age at diagnosis was 44 years (range 26-65). Primary sites of disease were upper limb (n=1), lower limb (n=6), right atrium (n=1), pleura (n=2). Nine patients had local disease at diagnosis. Among these patients, 8 received surgery, 6 radiotherapy, and 4 anthracycline-based chemotherapy, of whom 1 in the adjuvant and 3 in the neoadjuvant setting.
Median time to metastasis was 12 months (range 6-146). Upon the development of metastatic disease, all patients received chemotherapy. Median number of chemotherapy regimens in the metastatic setting before trabectedin was 1 (range 0-2).
Amongst the evaluable patients 3 PR, 2 SD and 4 PD were seen for a RR of 33% and CBR of 55%.
Median PFS was 3 months (range 1-10). As of June 2014, one patient is still receiving T. The most common G3-4 adverse events related to trabectedin were transaminitis (G3 in 2:10, 20%), neutropenia (G3 in 2:10, 20% and G4 in 1:10, 10%).

Conclusions Trabectedin showed significant activity in patients with metastatic SS although in our series responses were short lasting without any relevant toxicity.

Key words: medical therapy, soft-tissue sarcoma, synovial sarcoma, trabectedin

Introduction

Synovial sarcomas (SS) are high grade tumors of mesenchymal origin. Although rare, they represent one of the most common soft tissue sarcoma (STS) in children and young adults, accounting for almost 8% of STS [1].
Histologically, two major subgroups of SS exist, monophasic and biphasic, based on the absence or presence of epithelial differentiation within the predominat spindled cell component; poorly differentiated SS forms have been described [1].
SS is characterized by the specific t(X;18) (p11;q11) translocation, which is present in more than 90% of the cases. The translocation leads to two fusion genes, *SYT-SSX1* and *SYT-SSX2*, with the resulting chimeric proteins acting as transcription factors. Contrasting results on the prognostic role of the different fusion genes exist: although early retrospective studies reported on the favorable prognosis of SYT-SSX2 SS [2], more recent analysis did not [3].
SS affects mainly the deep tissue of the extremities, although any site can be affected. It is locally invasive with a propensity to metastasize. Surgery is the mainstay of treatment of patients with localized disease; radiation

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therapy may be added to improve local control based on the specific disease characteristics, i.e. tumor dimension and location. Adjuvant chemotherapy with anthracyclines and ifosfamide, which does not represent the standard, may be offered on an individual basis [4, 5].

Despite adequate local treatment, roughly 50% of patients with local disease will recur, more commonly to the lungs. Retrospective series showed 5 and 10-year OS of 60-80% and 40-50% respectively [4-7]. Of note, late metastases are not uncommon [8]. Hence the need for long-term follow-up.

Anthracycline, ifosfamide, gemcitabina ± docetaxel [9], trabectedin [10-13] and pazopanib [14] are active agents in the metastatic setting, although surgery and radiation therapy may have a role in patients with limited burden, slow growing disease.

Trabectedin is a chemotherapeutic agent derived from the Caribbean tunicate *Ecteinascidia turbinata*. It possesses peculiar antitumor activities ranging from DNA minor groove binding capability to transcriptional regulation and modulation of tumor microenvironment [15].

The activity of trabectedin has been extensively studied in STS since the early 2000s [16-19]. The drug was approved in 2007 in Europe, based on the results of a randomized phase II study [20] for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Although response rate to trabectedin has been <10% in unselected STS patients, the Progression-free survival (PFS) at 6 months consistently exceeded 20% amongst the different studies.

However, when patients with specific STS histologies were considered, remarkable improvements in response rate (RR) and PFS were seen. A pivotal retrospective analysis of patients with myxoid round cell liposarcoma (MRCL), now high grade myxoid liposarcoma, enrolled within a multicenter compassionate-use program, showed a RR in the 50% range, and the 6-month PFS in the 80% range [21]. Similarly, leiomyosarcoma showed peculiar sensitivity to the drug [22].

Although patients with liposarcoma and leiomyosarcoma benefitted the most from the drug, responses were consistently seen amongst patients with SS. Here we report on the activity of trabectedin in patients with SS treated in 2 Italian centers.

Material and methods

We retrospectively reviewed the medical records of patients with metastatic SS treated with trabectedin at Humanitas Clinical and Research Center, Rozzano, Milan and Santo Stefano Hospital, Prato, between January 2010 and June 2014.

Treatment regimen

Trabectedin was administered as 24-hour continuous infusion at a dose of 1.5 mg/m^2, with a top dose of 2.6 mg, every 3 weeks. All patients received steroid premedication with dexamethasone (4 mg twice daily on day –1); steroid administration was also given from day +1 to +3. Blood count, creatinine, CPK, bilirubin, ALP, GGT, AST and ALT were monitored weekly after trabectedin administration. Dose reductions were carried out as GCP.

Assessment of response

Patients who received one dose of trabectedin were assessable for toxicity and response. Although retrospectively, toxicity data were retrieved from the medical records and graded according to National Cancer Institute Common Toxicity Criteria version 4.0.

Response to treatment was assessed by CT scan after the first 2 cycles of therapy and 3 cycles thereafter. The primary endpoint of the study was overall response rate (ORR) according to RECIST criteria.

Statistical analysis

PFS was measured from the date of first dose of trabectedin to the date of documented progression or death, whichever came first. Survival analyses were carried according to the Kaplan–Meier method.

The study was approved by the institutional review boards of the participating institutions.

Results

Patient characteristics

Between January 2010 and June 2014, 10 patients with metastatic SS received trabectedin, 9 at Humanitas Clinical and Research Center, Rozzano, and 1 at Santo Stefano Hospital, Prato.

Six were female, four male. Median age at diagnosis was 44 years (range 26-65). Primary sites of disease were upper limb (n=1), lower limb (n=6), right atrium (n=1), pleura (n=2). Nine patients had local disease at diagnosis. Among these patients, 8 received surgery, 6 radiotherapy (RT), and 4 anthracycline-based chemotherapy, of whom 1 in the adjuvant and 3 in the neoadjuvant setting.

Median time to metastasis was 12 months (range 6-146). Upon the development of metastatic disease, all patients received chemotherapy. Median number of chemotherapy regimens in the metastatic setting before trabectedin was 1 (range 0-2). Two patients had been enrolled within a randomized phase III study comparing trabectedin to doxorubicin-based chemotherapy as first-line in patients with metastatic sarcoma [23].

A total of 40 cycles of trabectedin were administered with a median number of cycles per patient of 3.5 (range 1-10).

Activity

Nine patients received at least 2 cycles of chemotherapy. One patient received 1 cycle of chemotherapy due to toxic hepatitis related to trabectedin and was not evaluable for response.

Amongst the evaluable patients, 3 partial responses (PR), 2 stable diseases (SD) and 4 progression diseases (PD) were seen for a RR of 33% and clinical benefit rate (CBR) of 55%. Responses to trabectedin are shown in Figure 1 (A, B). Median PFS was 3 months (range 1-10). As of June 2014, one patient is still receiving trabectedin.

Toxicity

All patients were evaluable for safety. The most common G3-4 adverse events related to trabectedin were transa-

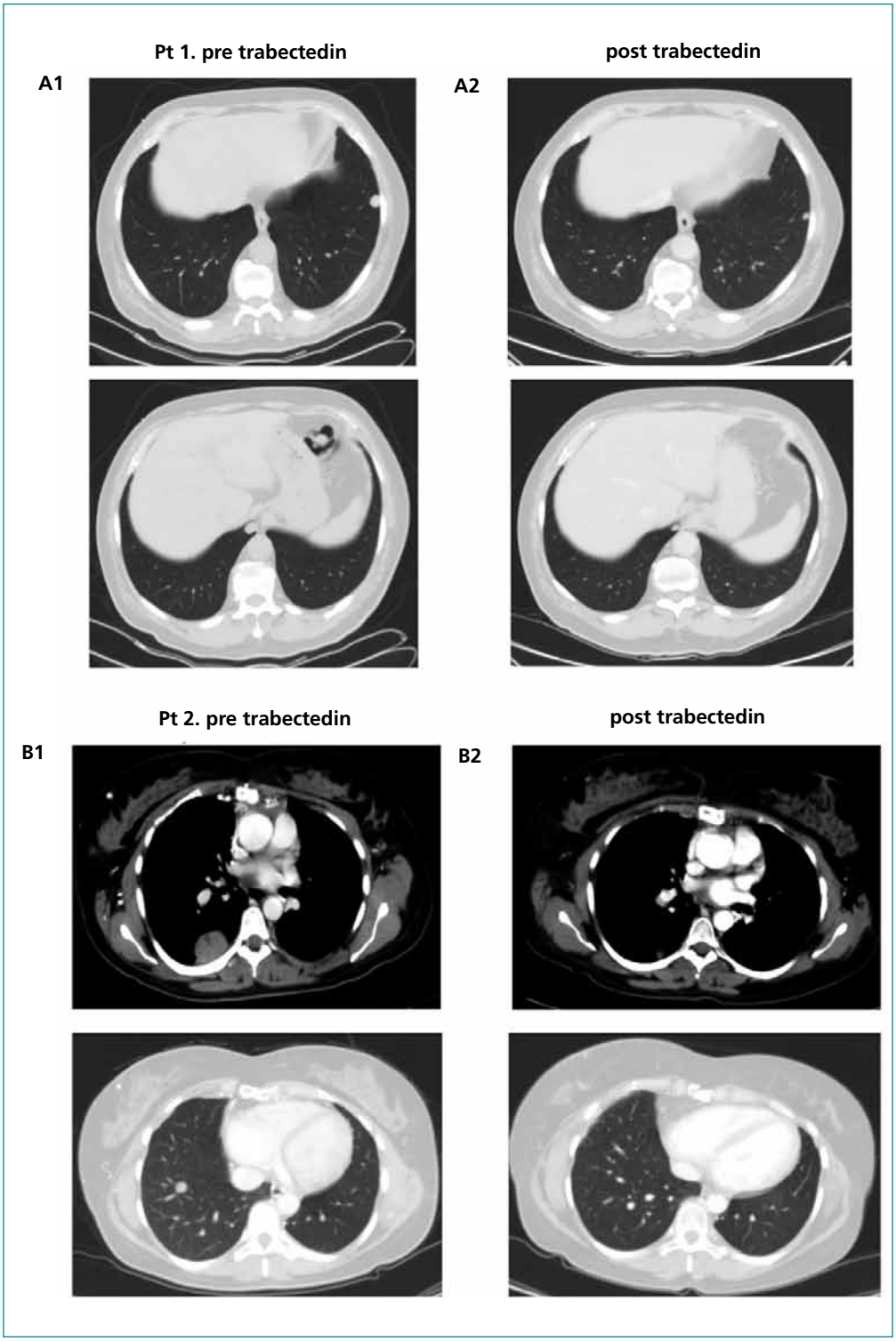

Fig. 1. Response to trabectedin. Computed tomography (CT) scan.
A. 66 year-old male patient with bilateral lung metastases from SS of the thigh. CT scans at baseline (A1) and 2 cycles of trabectedin (A2).
B. 37 year-old female patient with bilateral lung metastases from SS of the arm. CT scans at baseline (B1) and 9 cycles of trabectedin (B2).

minitis (G3 in 2:10, 20%), neutropenia (G3 in 2:10, 20% and G4 in 1:10, 10%). One of the patients with G3 transaminitis didn't recover from trabectedin toxicity within 2 months and discontinued treatment after 1 cycle. One patient had acute pulmonary embolism after the 2nd cycle of trabectedin.

Discussion

This retrospective analysis confirms the activity of trabectedin in patients with advanced SS: among the 9 patients evaluable for response, RR was 33% and CBR 55% with a median PFS of 3 months. Of note, 2 of 3 patients with PR were chemotherapy naïve. Published prospective or retrospective studies of trabectedin in SS lack. A retrospective, multicenter series on 61 patients with advance SS, presented in abstract form at the Annual Meeting of the Connective Tissue Oncology Society in 2012, showed RR of 15% and disease control rate (DCR) of 50%. Median PFS was 3 months with 23% of patients free from progression at 6 months.

The results of our retrospective analysis make trabectedin a valid option for patients with SS progressing to and/or unfit for anthracyclines and ifosfamide. Combination chemotherapy with anthracyclines and ifosfamide in patients with unresectable or metastatic STS has consistently showed RR in the 20-30% range. However, although some studies reported higher RR for combination over single agent chemotherapy, this did not translate in improvements in overall survival (OS). Therefore, asymptomatic patients with advanced STS should be offered single agent chemotherapy.

The mechanism of action of trabectedin is partially known. Trabectedin is an alkylating agents that binds to the minor groove of the DNA. It also regulates transcription. Recently, the role of trabectedin in modulating the tumor microenvironment has been described. Some of the mechanisms of action of trabectedin appear to be histotype specific: in MRCL, for example, trabectedin promotes tumor differentiation through inactivation of the oncogenic FUS-CHOP resulting from the t(12;16)(q13;p11). No information on histotype-specific mechanism of action in SS exist.

Tumor response to trabectedin is peculiar [12]. Beside tumor shrinkage, which may require some time to be evident, some tumor showed non-dimensional tumor responses, like those observed in gastrointestinal stromal tumors treated with imatinib. Amongst our responding patients, tumor shrinkage was evident after 2 cycles of chemotherapy; no changes in tumor density were seen. Whether the specific pattern of response relates to the biology of SS or has clinical implications is currently unknown.

Trabectedin was well tolerated. Toxicity was as expected: G3 neutropenia was the most common hematologic toxicity, while moderate to severe transaminitis was the most common non hematologic toxicity. One patient experienced prolonged transaminitis, which did not resolve within two weeks despite supportive measures. Therapy was therefore discontinued. Mild asthenia, nausea and vomiting were common and controlled with supportive measures. Of note, all patients received steroid premedication to prevent and limit bone marrow and liver toxicity [13].

STS represent a heterogeneous group of diseases. Each sarcoma subtype is characterized by peculiar biology and natural history, which translates into different sensitivity to chemotherapeutic agents and targeted therapies. In the last years, the therapeutic armamentarium for patients with advanced STS improved with two drugs approved by the European Medicine Agency (EMA), trabectedin and pazopanib, thus improving the therapeutic options for patients with advanced SS although limited data are currently available for pazopanib. Our retrospective series confirms the activity of trabectedin in SS.

According with the European Society for Medical Oncology (ESMO) guidelines 2014, trabectedin is a second-line option [II, B] and is approved for advanced previously treated STS in the EU. It has proved effective in leiomyosarcoma and liposarcoma. In myxoid liposarcoma, a high antitumour activity was described. A peculiar pattern of tumour response has been reported, with an early phase of tissue changes preceding tumour shrinkage. Clinical benefit with trabectedin was also obtained in other histological types [24].

Conclusion

Trabectedin showed significant activity in patients with metastatic SS although in our series responses were short lasting. The toxicity profile of the drug makes trabectedin an option for patients unfit for anthracyclines and/or ifosfamide. The mechanisms of action of trabectedin in SS need to be better defined.

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