Trabectedin in advanced synovial sarcomas: a multicenter retrospective study from four European institutions and the Italian Rare Cancer Network

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Treatment options for patients with metastatic synovial sarcoma are limited. Over recent years, trabectedin has emerged as an effective agent for patients with advanced soft tissue sarcomas resistant to anthracyclines and ifosfamide. The aim of this retrospective analysis was to study the efficacy of trabectedin in the subgroup of synovial sarcomas. A retrospective analysis was carried out on patients with advanced synovial sarcoma treated with trabectedin at four European reference sarcoma centers and within the Italian Rare Cancer Network between 2000 and 2013. Radiological response, progression-free, and overall survival, as well as serious and unexpected adverse events were retrospectively assessed. Sixty-one patients with metastatic synovial sarcoma were identified. The median number of previous chemotherapy regimens was 2 (range 1–6). Nine patients had a partial response, in addition to two minor responses, and 19 patients had stable disease, for an overall response rate of 15% and a tumor control rate of 50%. The median progression-free survival was 3 months, with 23% of patients free from progression at 6 months. The median progression-free survival in responding patients was 7 months. Trabectedin is a therapeutic option for palliative treatment of a subset of patients with metastatic synovial sarcoma. *Anti-Cancer Drugs* 26:678–681

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Introduction

Synovial sarcoma accounts for ~10% of all soft tissue sarcomas [1]. The most frequent anatomic location is represented by the limbs; however, it can arise everywhere in the body including visceral sites. Synovial sarcoma presents morphologically as three main variants, namely, spindle cell monophasic, biphasic, and poorly differentiated. A characteristic chromosomal translocation, namely t(X; 18), resulting in the fusion of SYT with either SSX1 or SSX2 (very rarely with SSX4) is observed in the vast majority of cases [1]. Synovial sarcomas can arise at any age, but mainly occur during adolescence and early adulthood [1]. Surgery alone or in combination with radiotherapy, depending on prognostic factors, is the main treatment for localized synovial sarcoma [2]. Despite adequate localized treatment, about 50% of patients relapse, with a median survival after first documented metastases of about 1 year [3].

Synovial sarcomas are considered to be more chemosensitive than some other soft tissue sarcoma subtypes. Doxorubicin and ifosfamide have been considered the drugs most active in synovial sarcoma, with an objective response rate of ~30% or more and better prognosis in responding patients [4–6]. In addition to anthracyclines ± ifosfamide, recommended treatment for patients with advanced disease includes trabectedin and, most recently, pazopanib [2,7]. Trabectedin is approved in Europe for the treatment of adult patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or those who are unfit to receive these agents. The benefit has been mainly documented in liposarcoma and leiomyosarcoma [8, 9]. Among others, there are reported cases of partial responses in patients with synovial sarcoma in clinical studies or retrospective series evaluating the activity of trabectedin [10]. The aim of this retrospective analysis was to review all patients with advanced synovial sarcoma treated with trabectedin at four European sarcoma reference centers and within the Italian Rare Cancer Network (RTR; 'Rete Tumori Rari'), a clinical collaborative effort aimed at improving the quality of care in adult rare solid cancers in Italy.

Methods

A retrospective analysis of all cases of advanced synovial sarcoma treated with trabectedin at four sarcoma referral

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centers and within the Italian Rare Cancer Network from 2000 to 2013 was carried out. From 2000 to 2008, patients were treated within an expanded access program provided by PharmaMar. In 2008, after approval from the European Medical Agency and national agencies, trabectedin became available for the treatment of all soft tissue sarcomas.

Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Bilirubin/aspartate aminotransferase/alanine aminotransferase and alkaline phosphatase had to be up to 2.5 times the upper normal limit, renal function had to be normal, and full recovery from the toxicity of previous therapies had to be documented. Patients' age was more than 18 years. Written informed consent to treatment and data collection for research purposes was available. Authorization from reviewing/ethics committees was obtained according to the local rules of each institution.

Trabectedin was supplied by PharmaMar (Madrid, Spain) as a lyophilized powder in glass vials containing 0.25 or 1 mg and was commenced at the recommended dose of 1.5 mg/m^2 using a 24 h continuous infusion through a central venous line. The starting dose was selected according to baseline liver function tests, performance status, and previous treatments. All patients received a liver-protecting steroid premedication consisting of dexamethasone 4 mg orally twice a day the day before therapy [11]. Routine antiemetic premedication included intravenous dexamethasone 8–20 mg and a 5HT$_3$-antagonist. Each cycle was administered on day 21, provided that complete recovery of any hepatic toxicity was achieved. Recovery from any hematological and nonhematological toxicity to at least grade 1 was required. If these criteria were not fulfilled on day 21, the next cycle was postponed by 1 week. A delay of 3 weeks was allowed, and if a persistent lack of recovery was documented, the treatment was stopped, unless a clinical benefit was evident. Treatment was continued until disease progression, unacceptable toxicity, medical decision, or patient refusal. Patient medical records were examined retrospectively to collect clinical data. All patients were evaluated by a full assessment of medical history, physical examination, full blood count and serum biochemistry, and a staging computed tomography or MRI scan. Tumor assessment was carried out every two to three cycles. The Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) [12] were used to assess response. Any radiological reduction in the sum of the longest diameters of target lesions that did not reach the criteria for an objective partial response was defined as a minor response. As the analysis did not focus on toxic effects, only serious adverse or unexpected events were sought.

Results

Patient characteristics

This retrospective analysis included 61 patients with metastatic synovial sarcoma treated between April 2000 and December 2013 at Istituto Nazionale Tumori, Milan, Italy; Royal Marsden Hospital, London, UK; Centre Leon Berard, Lyon, France; and Institut Gustave Roussy, Villejuif, France. This analysis also included all patients with synovial sarcoma treated within the Italian Rare Cancer Network.

The median age of the patients was 37 years (range 18–68 years). The primary disease site was the extremity in 35 (57%) patients, the trunk in 10 (16%) patients, the mediastinum in three (5%) patients, the pelvis in four (7%) patients, and other site in nine (15%) patients. All patients had metastatic disease when starting trabectedin and had been treated previously with chemotherapy. The median number of previous chemotherapy regimens was 2 (range 1–6). The clinical characteristics of these patients are summarized in Table 1.

Drug delivery

A total of 247 cycles were administered, with a median of three cycles per patient (range 1–22). The starting dose was 1.5 mg/m^2, as recommended by the manufacturer, and ranged from 1.1 to 1.5 mg/m^2 during the study.

One patient interrupted treatment after achieving a partial response after four courses of trabectedin, as a shared decision with the treating clinician, and underwent surgery of residual disease. Another patient withdrew consent to therapy after one cycle. Six (10%) patients received more than 10 courses of trabectedin and in particular one patient received a total of 22 courses.

Activity and efficacy

All patients except one were evaluable for response. Nine patients achieved a RECIST partial response (15%) and 21 patients had stable disease (35%), with two of these patients showing minor tumor shrinkage. Overall, tumor control (partial + minor responses + stable disease) was achieved in 50% of patients.

The progression-free survival of the entire patient group was 3 months (Fig. 1). The progression-free rate at

Table 1 Patient characteristics

	Patients ($n = 61$)
Age [median (range)]	37 (18–68)
Sex [*n* (%)]	
Male	26 (42.6)
Female	35 (57.4)
Primary disease site [*n* (%)]	
Extremity	35 (57.4)
Trunk	10 (16.4)
Mediastinum	3 (4.9)
Pelvis	4 (6.6)
Other	9 (14.8)
Previous chemotherapy regimens	
1	17
2	25
3	13
≥ 4	6

6 months was 23%. In the subgroup of responding patients, progression-free survival was 7 months (Fig. 2).

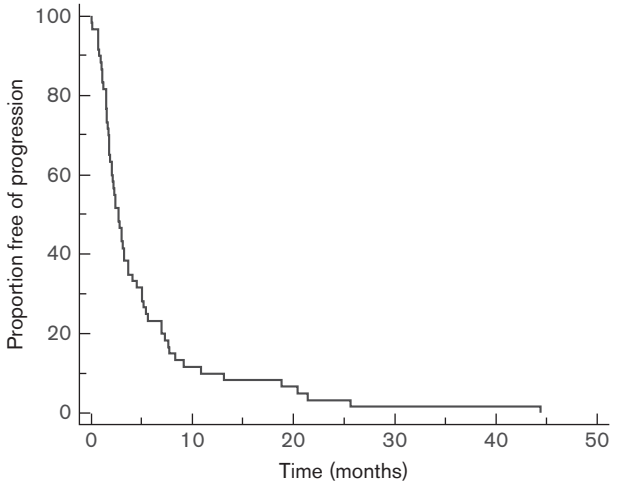
Discussion

In this multicenter, retrospective case-series analysis of 61 pretreated synovial sarcoma patients, trabectedin showed an objective response rate of 15% according to the RECIST response criteria, with an additional 35% of patients achieving disease stabilization. The progression-free survival of the entire patient group was 3 months, but it was 7 months in the subgroup of responding patients. The median number of cycles was three, but a subgroup of six responding patients received at least 10 cycles. Patients were heavily pretreated, with a subgroup (31%) receiving trabectedin as fourth/further line therapy.

This was a retrospective analysis. Of course, this is a limitation of this study, although it included a relatively high number of patients with a specific histology and included some of the main sarcoma reference centers in Europe. No prospective study of trabectedin specifically in synovial sarcoma is available.

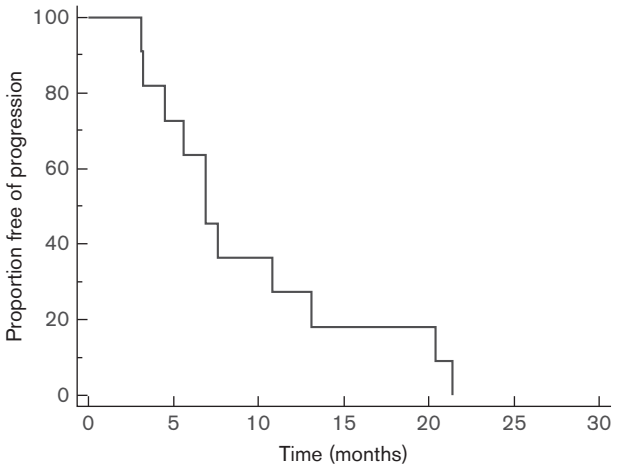
Synovial sarcomas are recognized to be a chemosensitive subtype within the soft tissue sarcoma family, with an objective response rate to anthracyclines and/or ifosfamide between 30 and 50% [4–6]. For patients with recurrent disease after anthracyclines and ifosfamide, trabectedin is an option. In a phase II study of trabectedin carried out in pretreated patients, 17% of patients had synovial sarcomas [13]. A radiological response was observed in one of these patients. A first-line study of trabectedin recruited one patient with a synovial sarcoma, who achieved a partial response lasting more than 1 year [10]. Recently, another therapeutic option has become available, that is, pazopanib, a vascular endothelial growth factor and multikinase inhibitor, which was approved for use in soft tissue sarcomas (except liposarcoma) after the failure of first-line chemotherapy [7]. The partial response rate in the randomized clinical trial that led to its approval was 6%, with notable activity against leiomyosarcoma and synovial sarcomas [13]. Another approved drug in soft tissue sarcoma is dacarbazine, even if its activity in synovial sarcoma is poorly documented. After failure of dacarbazine, trabectedin, and pazopanib, no other approved drugs are currently available.

Fig. 1



Kaplan–Meier curve for progression-free survival in all patients with synovial sarcoma treated with trabectedin ($n = 61$).

Fig. 2



Kaplan–Meier curve for progression-free survival in responding patients ($n = 9$).

The activity of trabectedin includes leiomyosarcomas and liposarcomas, with an excellent activity in myxoid/round-cell liposarcoma [8,9]. The latter is a translocation-related sarcoma, marked by the fusion gene FUS–DDIT3 [14]. The mechanism of action of trabectedin in this histology seems to be correlated with a specific mechanism, that is, to the ability of the drug to inhibit the biological activity of the chimeric oncoprotein [15].

Observation of the remarkable and apparently specific activity of trabectedin in myxoid liposarcomas led to the hypothesis that trabectedin might also be active against other translocation-related soft tissue sarcomas. This is supported by anecdotal observations of responses in other 'translocation-related' soft tissue sarcomas to the drug, such as endometrial stromal sarcomas and alveolar soft part sarcomas [16]. With respect to synovial sarcomas, these have a characteristic chromosomal translocation, namely t(X; 18), resulting in the SS18-SSX chimeric fusion protein.

Recently, a prospective randomized phase III study of first-line treatment in translocation-related soft tissue sarcomas was carried out comparing trabectedin versus

doxorubicin [17]. This trial showed no difference in progression-free survival, although it was underpowered, and the specific activity of trabectedin in synovial sarcomas was not reported.

Conclusion

Our retrospective case-series analysis supports the notion that trabectedin is active in a subset of patients with heavily pretreated synovial sarcomas, which thus adds to liposarcomas and leiomyosarcomas as a subgroup of soft tissue sarcomas potentially responsive to this agent. It remains to be explained whether there is a relatively specific mechanism of action of the drug in this translocation-related sarcoma, as has been seen in myxoid/round-cell liposarcomas. Future perspectives for the treatment of synovial sarcoma may include histone deacetylase inhibitors and targeted adoptive immunotherapy approaches [18].

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Conflicts of interest

P.G.C., A.P.D.T., JY.B., A.L.: advisory role and travel coverage for medical meetings from PharmaMar; R.S. and P.D.: travel coverage for medical meetings from PharmaMar. For the remaining authors there are no conflicts of interest.

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