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 centers 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 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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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/m² 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 5HT3-antagonist. Each cycle was administered on day 21, provided that complete recovery of any hepatic toxicity was achieved. Recovery from any hematological and non-hematological 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 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/m², as recommended by the manufacturer, and ranged from 1.1 to 1.5 mg/m² 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 |
|--------------------------------|
| 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.

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...
References

Conflicts of interest

Acknowledgements

References

1 Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. World Health Organization classification of tumours of bone and soft tissue. Lyon, France: IARC; 2013.

2 ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3):ii102–ii112.

3 Lewis JJ, Antonescu CR, Leung DH, Blumberg D, Healey JH, Woodruff JM, Brennan MF. Synovial sarcoma: a multivariate analysis of prognostic factors in 112 patients with primary localized tumors of the extremity. J Clin Oncol 2000; 18:2087–2094.

4 Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shraki M, Frytak S, Parkinson DR. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol 1993; 11:1269–1275.

5 Le Cesne A, Antoine E, Spielmann M, le Chevalier T, Brain E, Toussaint C, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. J Clin Oncol 1995; 13:1600–1608.

6 Rosen G, Foscher C, Lowenbraun S, Elber F, Eckardt J, Holmes C, Fu YS. Synovial sarcoma. Uniform response of metastases to high dose ifosfamide. Cancer 1994; 73:2506–2511.

7 Van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379:1879–1886.

8 Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomised phase II study of two different schedules. J Clin Oncol 2009; 27:4188–4196.

9 Casali PG, Sanfilippo R, D’Incalci M. Trabectedin therapy for sarcomas. Curr Opin Oncol 2010; 22:342–346.

10 Garcia-Carbonero R, Supko JG, Maki RG, Manola J, Ryan DP, Harmon D, et al. Ecteinascidin-474 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. J Clin Oncol 2005; 23:5484–5492.

11 Grosso F, Dileo P, Sanfilippo R, Stacchiotti S, Bentulli R, Piovesan C, et al. Steroid premedication markedly reduces liver and bone marrow toxicity of trabectedin in advanced sarcoma. Eur J Cancer 2006; 42:1484–1490.

12 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92:205–216.

13 Le Cesne A, Blay JY, Judson I, van Oosterom A, Verweij J, Radford J, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol 2005; 23:576–584.

14 Panagopoulos I, Mertens F, Isakovsk M, Mandahl N, A novel FUS/CHOP chimera in myxoid liposarcoma. Biochem Biophys Res Commun 2000; 279:838–845.

15 Di Giandomenico S, Frapolli R, Bello E, Ubaldi S, Licandro SA, Marchini S, et al. Mode of action of trabectedin in myxoid liposarcomas. Oncogene 2014; 33:5201–5210.

16 Le Cesne A, Cresta S, Maki RG, Blay JY, Verweij J, Poveda A, et al. A retrospective analysis of antitumour activity with trabectedin in transllocation-related sarcomas. Eur J Cancer 2012; 48:3036–3044.

17 Blay JY, Leahy MG, Nguyen BB, Patel SR, Hohenberger P, Santoro A, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in transllocation-related sarcomas. Eur J Cancer 2014; 50:1137–1147.

18 Linch M, Mah AB, Thway K, Judson IR, Benson C. Systemic treatment of soft-tissue sarcoma-gold standard and novel therapies. Nat Rev Clin Oncol 2014; 11:187–202.