Efficacy of trabectedin for advanced sarcomas in clinical trials versus compassionate use programs: analysis of 92 patients treated in a single institution

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Trabectedin was recently approved for patients failing doxorubicin, the standard treatment for advanced/metastatic sarcoma. This retrospective study aimed to compare trabectedin efficacy between compassionate use in unselected patients and clinical trials. From May 1999 to January 2006, 92 patients were treated at the Centre Léon Bérard, either in phase II studies or on a named patient compassionate basis. All cases were retrospectively analyzed to assess trabectedin efficacy in terms of response, progression-free, and overall survival.

The objective response rate was 10% ($N=9$): 4% ($N=2$) for patients treated in compassionate use program and 16% ($N=7$) for those in clinical trials ($P=0.18$); 26 (28%) patients had stable disease for at least 6 months, 11 (23%) in the compassionate group and 15 (33%) in clinical trials. Median progression-free and overall survivals were, respectively, 2.2 [95% confidence interval (CI): 1.9–3.6] and 8.9 (95% CI: 6.4–14.2) months for all patients, 2.3 (95% CI: 1.9–4.3) and 10.4 (95% CI: 6.9–24.2) months for patients in clinical trials and 1.8 (95% CI: 1.4–3.4) and 6.4 (95% CI: 3.3–14.2) months for patients under compassionate treatment. In this retrospective analysis, the reported grade 3–4 toxicities were increased transaminase (34 patients, 37%) and neutropenia (38 patients; 42%). Higher efficacy was observed in phase II studies than with compassionate treatment, but no significant difference remained after adjustment in multivariate analysis for performance status, a well-established prognosis factor. The safety and tolerability of trabectedin shown in clinical trials is confirmed for patients in real-life situation treated in compassionate use programs, but its benefit is higher for patients with performance status 0–1. *Anti-Cancer Drugs* 21:113–119 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Soft-tissue sarcomas (STS) are a group of rare and heterogenous tumors of mesenchymal origin. Approximately 30–50% of patients experience metastatic relapse despite optimal locoregional treatment [1]. For advanced or metastatic disease, systemic chemotherapy is indicated, although long-term survival may also be achieved in selected patients with local therapy, such as surgery and radiation therapy [2,3]. Doxorubicin alone or combined with ifosfamide has been the backbone of systemic chemotherapy for metastatic or advanced STS for more than 20 years, with objective responses observed in 15–35% of patients [4–6]. No standard treatment has yet emerged after the failure of doxorubicin-containing chemotherapy, though some agents, such as gemcitabine and gemcitabine-docetaxel combination, have shown promising results [7–9]. Trabectedin (ET743, YONDELIS, PharmaMar, Madrid, Spain), a tetrahydroisoquinoline alkaloid, is a natural product derived from the marine tunicate *Ecteinascidia turbinata*. Trabectedin has shown potent antitumor activity in preclinical studies both *in vitro* and *in vivo*, in several solid tumors, including ovarian and breast cancers, melanoma, and sarcoma. These preclinical data have been confirmed in several phase II trials in breast and ovarian carcinomas, and mostly in STS [10–13]. The overall response rate is low, around 8% but a high proportion of patients remain free of disease after 6 months. Trabectedin recently received European approval for the treatment of STS after failure of doxorubicin-based chemotherapy.

Results of phase II trials are often better than those observed in phase III trials performed in nonselected patients after registration of the agent and expanded use

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in the general population of cancer patients [14]. The objective of this study was to compare the antitumor activity of trabectedin when given in clinical trials or in compassionate use programs in a series of 92 patients treated at a single institution with trabectedin. The main objective of the study was to show the potential benefit of trabectedin for nonselected patients.

Patients and methods

Patient population

Forty-five (49%) patients received trabectedin in phase II trials [12,13] and 47 (51%) on a named patient compassionate basis. All had histologically proven unresectable advanced or metastatic STS. Most patients had received at least one previous chemotherapy regimen including doxorubicin, and were progressive at the time of starting trabectedin.

Inclusion criteria in clinical trials

Patients older than 18 years and with WHO performance status (PS) less than 2 were to have adequate bone marrow reserve (neutrophil count $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l), normal renal function with clearance (Cockroft formula) ≥ 60 ml/min, and normal hepatic function [bilirubin $\leq$ upper limit of normal (ULN), alkaline phosphatase $\leq$ ULN or 5′ nucleotidase $\leq$ ULN, aspartate aminotransaminase/alanine aminotransaminase $< 2.5 \times$ ULN]. Fertile males and females were to use medically approved contraception. All patients were required to have an indwelling central venous access device (e.g. port-a-cath) for drug administration. The protocols were approved by a French national ethics committee and written informed consent was obtained from all patients.

Patients treated in the phase II trials and on the compassionate program were pooled for the purpose of this retrospective analysis, then analyzed separately.

Treatment plan

Trabectedin was supplied as a sterile lyophilized product in clear vials containing either 40 or 250 μg of trabectedin in 0.05 mol/l phosphate buffer, pH 4, with mannitol as an excipient. The vials were reconstituted by adding sterile water for injection. This solution was further diluted in the desired amount of normal saline.

Trabectedin was used at a dose of 1500 μg/m^2 administered as a 24-h continuous intravenous infusion, repeated every 3 weeks. In patients with creatinine elevation or mild elevation of 5′ nucleotidase, the starting dose of trabectedin was reduced to 1200 mg/m^2. If the reduced dose was well tolerated, the following cycle could be given at a higher dose level. Antiemetic prophylaxis was not routinely administered during the first course of treatment. If needed, antiemetic therapy included setrons, corticosteroids, and/or metoclopramide. Laboratory tests were monitored two times a week in both arms. Treatment was postponed until recovery in the case of insufficient hematological parameters (neutrophils $< 1.5 \times 10^9$/l, platelets $< 100 \times 10^9$/l), when creatinine, transaminase, and bilirubin failed to return to normal baseline values, or when grade 4 nonhematological toxicity did not resolve. The dose of trabectedin was reduced to 1200 μg/m^2 then to 900 μg/m^2 after febrile neutropenia, grade 4 neutropenia lasting more than 5 days, grade 4 thrombocytopenia, any grade 3 or 4 nonhematological toxicity (except grade 3–4 elevation of aspartate aminotransaminase/alanine aminotransaminase), and $\geq$ grade 1 increase of bilirubin or alkaline phosphatase. Secondary prophylactic use of granulocyte colony-stimulating factor was allowed in case of previous febrile neutropenia.

Treatment with trabectedin was continued until disease progression, toxicity, or patient refusal. Response was evaluated every two to four cycles by repeated clinical and appropriate radiological assessments based on the extent of the disease at presentation. Antitumor activity was evaluated according to Response Evaluation Criteria In Solid Tumors criteria.

Statistical design

The main objective of this retrospective study was to compare the therapeutic activity and toxicity of trabectedin between patients with advanced STS included in a compassionate use program and patients included in phase II trials in the same center. The response rate was estimated as the proportion of patients who achieved a complete or partial response in the total number of patients who received at least one cycle of trabectedin. Overall survival (OS) was defined as the time from date of first trabectedin injection to date of death. Progression-free survival (PFS) was calculated from the date of first trabectedin injection to the date of disease progression or death or to the date of last follow-up for patients alive at last contact. Survival distributions in prognostic groups were estimated by the Kaplan–Meier method. To evaluate the relationship between survival and baseline characteristics, prognostic factors described by Van Glabbeke *et al.* [15] were included in a multivariate Cox proportional hazard regression models. Candidate prognostic factors for OS and PFS with a 0.05 level of significance in univariate analysis were then entered in a multivariate Cox model. The final model was obtained by backward selection. The date of analysis was October 2006; OS was updated in September 2007.

Results

Patient characteristics

Until July 2006, 92 patients with STS were treated in phase II studies (45 patients, 49%) [12,13] or on a compassionate basis (47 patients, 51%). All patients were treated at a single institution, the Centre Léon Bérard, in Lyon, France. Patient characteristics are summarized

Table 1 Patients' characteristics at baseline

	All	Compassionate	Phase II	*P* value
Median age, year (range)	52.5 (18–82)	51 (18–74)	53 (20–82)	0.463
Sex				1.000
Female	42	21	21	
Male	50	26	24	
Histology				0.464
Leiomyosarcoma	18	6	12	
Unclassified sarcoma	15	8	7	
Liposarcoma	11	8	3	
Osteosarcoma	9	4	5	
Ewing's sarcoma	4	2	2	
Other	35	19	16	
FNCLCC grade				0.457
1	7	3	4	
2	17	6	11	
3	25	14	11	
Unknown	43	24	19	
Performance status				**0.011**
0	22	7	15	
1	49	22	25	
2	13	11	2	
3	4	3	1	
Unknown	4	2	2	
Initial localization				0.177
Lower limbs	29	15	14	
Retroperitoneum	10	8	2	
Uterus	10	5	5	
Pelvic girdle	10	5	5	
Abdomen	7	1	6	
Upper limbs	9	4	5	
Head and neck	5	1	4	
Other	12	8	4	
Metastases				
Lung	65	35	30	0.643
Bone	23	11	12	0.810
Liver	22	8	14	0.142
Other	5	3	2	1.000
None	8	4	4	1.000
Previous chemotherapy	87	47	40	**0.025**
Anthracyclin	85	47	38	**0.005**
Ifosfamide	67	39	28	**0.035**

Numbers set in bold signify range of data.
FNLCC, Fédération Nationale des Centres de Lutte Contre le Cancer.

in Table 1. The median age was 52.5 years (range: 18–82 year) and most patients were in good general condition at initiation of treatment: 69 patients had PS 0–1, 13 had PS 2, and four patients had PS 3 (PS was not available for four patients). The three most common tumor types were leiomyosarcoma (18 patients, 20%), unclassified sarcoma (or malignant histocytofibroma) (15 patients, 16%), and liposarcoma (11 patients, 12%). The most common site of the primary tumor was the lower limbs (29 patients, 32%). Histological grade of the primary tumor was unknown for half of the patients but, when available, histological data indicated that the majority of tumors were intermediate or high grade according to the Fédération Nationale des Centres de Lutte Contre le Cancer grading system. Eighty-three patients were metastatic. The most common sites of metastases were lung (65 patients, 71%), bone (23 patients, 28%), and liver (22 patients, 24%).

Patient characteristics were significantly different between the two sets: patients included in the compassionate program had worse PS: seven had PS 0 and 14 had PS 2–3, versus 15 and 3, respectively, in the phase II trials ($P = 0.011$).

The majority of patients had received prior chemotherapy; only five patients in phase II studies were given trabectedin as first-line therapy in metastatic phase and patients included in compassionate program were significantly more pretreated ($P = 0.025$). The great majority of patients received anthracyclins ($N = 84$; 95%), often in combination with ifosfamide (72%). Some patients were heavily pretreated with up to five prior regimens. All patients had documented disease progression before initiation of treatment. The starting dose was 1500 μg/m^2 continuous infusion over 24 h given as monotherapy.

Drug delivery and safety

Patients received a median of three cycles [1–25]. Sixty-three patients (68%) experienced grade 3–4 toxicity leading to 20–50% dose reduction in 29 patients (32%). Seven patients (8%) had to discontinue treatment because of toxicity. The most frequent grade 3–4 toxicities are summarized in Table 2. The two most frequent grade 3–4 toxicities were neutropenia in 38 patients (42%) and increased transaminase in 34 patients (37%). Only three patients experienced febrile neutropenia. No toxic deaths occurred. Other frequent toxicities were grade 1–2 asthenia, diarrhea, anorexia, and fever. The main cause of discontinuation of treatment was progression (71 patients, 77%). No significant difference in toxicity was observed between patients included in phase II studies and in the compassionate program.

Efficacy

All 92 patients were evaluable for response (Table 3). According to Response Evaluation Criteria In Solid Tumors criteria, no complete response was observed, but nine patients achieved partial response (PR) with a response rate of 10% [95% confidence interval (CI): 5–18]. Stabilization of disease (SD) for more than 2 months (first evaluation) was achieved in 34 (37%) patients, of whom three had minor responses. Overall, 43

Table 2 Major grade 3–4 toxicities

Type of grade 3–4 toxicity	Total ($N=92$)(%)	Compassionate program ($N=47$)(%)	Phase II study ($N=45$)(%)	*P* value
Hepatic				
Increased ASAT/ALAT	34 (37)	16 (35.6)	18 (40.0)	0.667
Increased GGT	4 (4)	3 (6.7)	1 (2.2)	0.616
Hematologic				
Neutropenia	38 (42)	17 (37.8)	21 (46.7)	0.522
Anemia	15 (17)	10 (22.2)	5 (11.1)	0.258
Thrombocytopenia	10 (11)	3 (6.7)	7 (15.6)	0.315
Other				
Nausea/vomiting	10 (11)	4 (8.9)	6 (13.3)	0.739

ALAT, alanine aminotransaminase; ASAT, aspartate aminotransaminase; GGT, gamma-glutamyl transferase.

patients [47% (95% CI: 36–57)] had a clinical benefit (complete response + PR + SD) from trabectedin and 49 (53%) progressed on treatment at first evaluation. A clinical benefit was obtained in, respectively, 20 of 47 (43%) and 23 of 45 (51%) patients included in the compassionate program and phase II clinical trials, whereas progression occurred in, respectively, 27 of 47 (57%) and 22 of 45 (49%) patients ($P = 0.18$).

Table 3 Best response to trabectedin

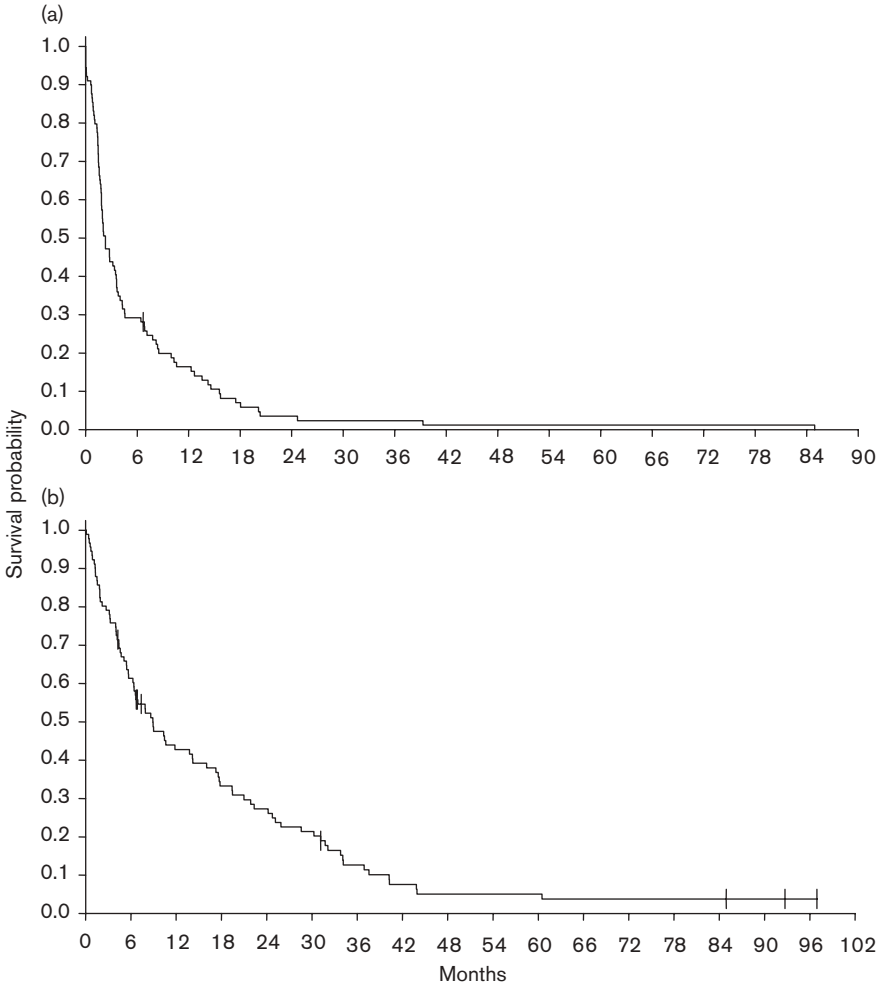
Response	Total ($N=92$)	Compassionate program ($N=47$)	Phase II study ($N=45$)
CR	0	0	0
PR (%)	9 (10)	2 (4)	7 (16)
SD (%)	34 (37)	18 (38)	16 (36)
PD (%)	49 (53)	27 (57)	22 (49)

CR, complete response; PD, progressive disease; PR, partial response; SD, stabilization of disease.
Chi-square $P=0.18$.

The PFS and OS of the 92 patients are presented in Fig. 1. Median PFS was 2.2 months (95% CI: 1.9–3.6): 2.3 months (95% CI: 1.9–4.3) in phase II studies versus 1.8 months (95% CI: 1.4–3.4) in patients receiving compassionate treatment, $P = 0.17$ (Fig. 2). Median OS was 8.9 months (95% CI: 6.4–14.2), with significantly better results in phase II studies: 10.4 months (95% CI: 6.9–24.2) versus 6.4 months (95% CI: 3.3–14.2), $P = 0.0165$.

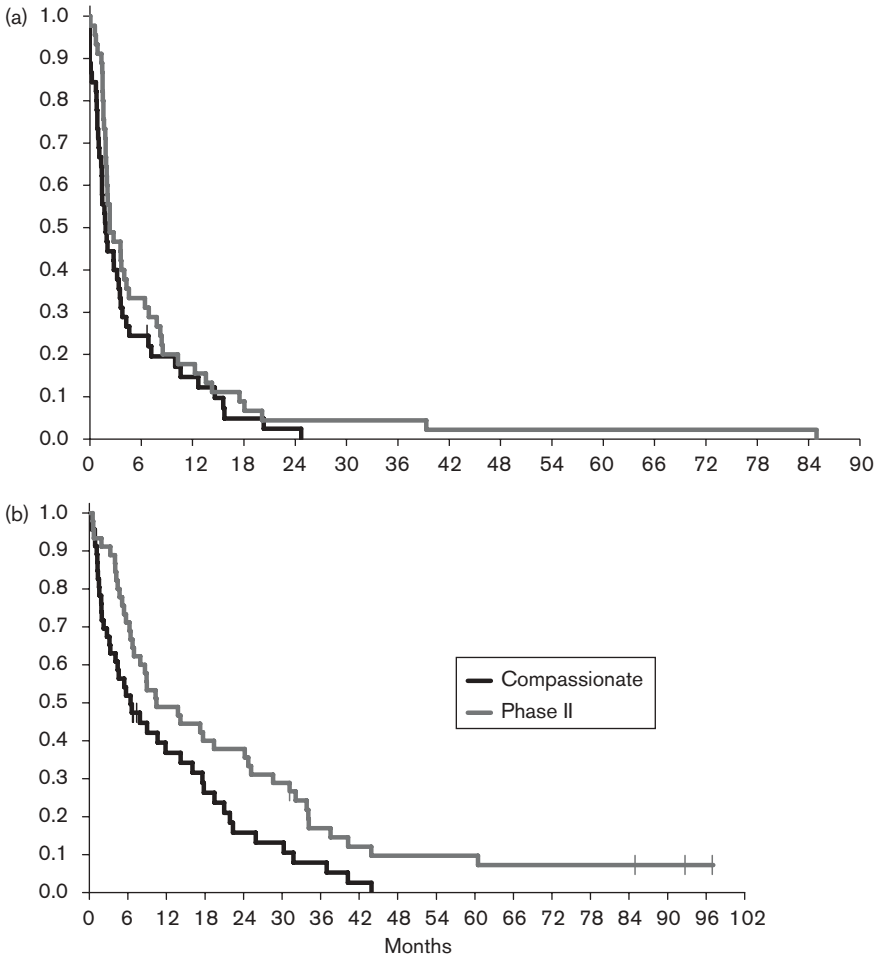
Cox analyses were made including well-established prognostic factors in sarcoma (PS, liver metastases, histological grade, age) [15], previous treatment, and type of management (phase II study or compassionate program). As indicated in Table 4, good PS and inclusion in phase II study were favorable prognostic factors for OS in univariate analysis. However, in multivariate analysis, only PS remained a strong independent prognostic factor ($P < 0.0001$): compared with PS 0–1, the hazard ratio for

Fig. 1



Progression-free survival (a) and overall survival (b) of all patients (a).

Fig. 2



Progression-free survival (a) and overall survival (b) of the 45 patients receiving trabectedin in a phase II study or the 47 patients treated in a compassionate program. $P=0.0165$.

death was 8.447 (95% CI: 4.16–17.16) for PS 2–3. For PFS, inclusion in a phase II study is not a predictive factor and only PS is significantly associated with a good PFS.

Discussion

Treatment of local sarcoma associates en bloc surgery and radiotherapy [1,3]. However, despite optimal management, 50% of patients relapse with unresectable locally advanced or metastatic disease. For advanced disease, standard chemotherapy regimens include doxorubicin and/or ifosfamide, although efficacy results remain disappointing. A large retrospective study has shown that the median OS of patients with advanced disease is 12 months [15] with few long-term survivors [2]. Increasing doses of chemotherapy, or combining doxorubicin and ifosfamide leads to enhanced response rates without benefit on OS, but with higher toxicities [16–20]. Single-agent doxorubicin currently remains the standard treatment for these patients. After failure of doxorubicin and ifosfamide treatment (sequential monotherapy or combination), the need for new drugs is crucial. The combination of gemcitabine and docetaxel has shown interesting results in some patients [7,8,21], mostly those with leiomyosarcoma, but the benefit is transient and new drugs are awaited.

Trabectedin was approved by the European Medicines Agency in July 2007 for the treatment of patients with advanced sarcoma after failure of doxorubicin-based chemotherapy. This new cytotoxic agent is active in a subset of previously treated patients with STS, with response rates ranging from 4 to 13% in phase I or II studies and in a compassionate program [10–13]. With a response rate of 10% and an OS of 8.9 months, the present results are consistent with these published data; actually, half of our patients had already been reported in these previous publications. Our study confirmed the

Table 4 Prognostic parameters for progression-free survival and overall survival

	Univariate analysis		
Progression-free survival	HR	95% CI	*P* value
Phase			0.175
Phase II vs. Compassionate	0.75	(0.49–1.14)	
Performance status			**<0.0001**
2–3 vs. 0–1	5.45	(3.01–9.88)	
Age	0.995	(0.98–1.10)	0.506
Anthracyclin as previous treatment			0.295
Yes vs. No	0.66	(0.30–1.44)	
Ifosfamide as previous treatment			0.939
Yes vs. No	1.02	(0.64–1.62)	
Overall survival			
Phase			**0.018**
Phase II vs. Compassionate	0.59	(0.38–0.91)	
Performance status			**<0.0001**
2–3 vs. 0–1	9.52	(4.99–18.16)	
Age	1.004	(0.99–1.02)	0.5999
Anthracyclin as previous treatment			0.3467
Yes vs. No	1.49	(0.65–3.43)	
Ifosfamide as previous treatment			0.8627
Yes vs. No	0.96	(0.59–1.55)	
	Multivariate analysis		
Phase			0.4442
Phase II vs. Compassionate	0.812	(0.48–1.38)	
Performance status			**<0.0001**
2–3 vs. 0–1	8.447	(4.16–17.16)	

Numbers set in bold signify 95% CI.
CI, confidence interval; HR, hazard ratio.

efficacy of trabectedin, with a PFS rate of 41% at 3 months and 28% at 6 months. Indeed, a drug is considered to be active against sarcoma if the PFS, the best surrogate endpoint for OS, is higher than 40% at 3 months and higher than 20% at 6 months [9].

In this study, half of the patients were included in phase II studies and the other half in a compassionate program. Two significant differences were observed between the two patient populations: more patients were PS 2–3 ($P = 0.011$) and had received prior chemotherapy ($P = 0.025$) in the compassionate group. PFS was similar in the two groups (2.3 months in the phase II studies vs. 1.8 in the compassionate group, $P = 0.17$), but OS was longer in phase II studies [10.4 months (95% CI: 6.9–24.2) vs. 6.4 months (95% CI: 3.3–14.2), $P = 0.0165$]. It is well established in oncology that results are better in phase II trials than in phase III trials or routine care. After adjustment for known prognostic factors in sarcoma, multivariate analysis showed that inclusion in a phase II trial or a compassionate program was not an independent prognostic factor, the only one retained by the Cox model being the PS. The better PS of patients included in phase II studies ($P = 0.011$) clearly explained the difference in OS between groups, and trabectedin seemed similarly efficient in phase II studies and in compassionate care. This data support the large use of trabectedin in routine practice, but only for patients with PS 0–1, and awaited results should confirm those of published clinical trials.

Leiomyosarcoma and myxoid liposarcoma are described as histological subtypes sensitive to trabectedin [12,13,22]. Our study confirmed this sensitivity, with nine of 18 (two PR, seven SD) patients with leiomyosarcoma and four of 11 (two PR, two SD) with liposarcoma (of whom two of five had myxoid liposarcoma) benefiting from the treatment at 6 months. However, we showed that six of 15 (40%, one PR, five SD) patients with unclassified sarcoma also benefited from the treatment, suggesting that the use of trabectedin could be extended to other populations.

The toxicity in our series was consistent with previously published data. Interestingly, we observed no significant difference between patients included in phase II studies or in the compassionate program. On account of the known liver toxicity of trabectedin, patients were equally monitored in the compassionate program as in the phase II studies, with laboratory tests two times a week. A recent study has shown that premedication with 4 mg dexamethasone twice a day over 3 days, beginning 24 h before trabectedin, dramatically reduces hepatotoxicity and myelosuppression [23]. This retrospective study has shown, as expected, an elevation of transaminases, neutropenia, and thrombocytopenia (all grade 3–4) in, respectively, 34, 24, and 25% of patients without premedication. For premedicated patients, these levels were 2, 2, and 0%, respectively. Dexamethasone diminishes the toxicity of trabectedin by increasing its elimination, but does not interfere with its clinical activity [24]. Today, premedication with dexamethasone should be recommended in routine practice. The toxicity of trabectedin compares favorably with that observed with other drugs known to be active in sarcoma: doxorubicin, ifosfamide, or the combination of docetaxel and gemcitabine. Doxorubicin at the standard dose of 75 mg/m^2 is associated with 77–84% grade 3–4 neutropenia and 16–19% febrile neutropenia [25,26], with ifosfamide (> 9 g/m^2) [17,27] rates 78–100 and 30–39%, respectively. After relapse, that is, the setting in which trabectedin is used, the combination of gemcitabine and docetaxel is associated with 40% thrombocytopenia (grade 3–4) and 5% febrile neutropenia (despite the prophylactic use of pegfilgrastim) [21]. There is no direct comparison of efficacy between this combination and trabectedin.

In conclusion, trabectedin is as efficient in routine practice as in phase II trials, but only for patients with PS 0–1. Weaker patients did not develop more toxicity than the general population but the benefit from the treatment is more limited. STS are rare tumors and it is difficult to conduct studies enrolling many patients. Therefore, the demonstration of safety and efficacy of trabectedin in a compassionate program supports its use in routine practice. This drug deserves further evaluation

in combination with cisplatin, capecitabine, paclitaxel, or docetaxel as second-line treatment [28], or with doxorubicin as initial treatment [29].

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