Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study

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Summary

Background **Previous studies have suggested that trabectedin (ecteinascidin-743) could have antitumour activity in soft-tissue sarcoma. We aimed to study the usefulness of trabectedin in the treatment of patients with myxoid liposarcomas, a subtype of liposarcoma that is associated with specific chromosomal translocations t(12;16)(q13;p11) or t(12;22)(q13;q12) that result in the formation of DDIT3-FUS or DDIT3-EWSR1 fusion proteins.**

Methods **51 patients with advanced pretreated myxoid liposarcoma who started treatment with trabectedin between April 4, 2001, and Sept 18, 2006 at five institutions in a compassionate-use programme were analysed retrospectively. Centralised radiological and pathological reviews were done for most patients. Trabectedin was given either as a 24-h continuous infusion or as a 3-h infusion, every 21 days, at 1·1–1·5 mg/m². 558 courses of trabectedin were given in total, with a median of ten courses for each patient (range 1–23). The primary endpoints were response rate and progression-free survival, and the secondary endpoint was overall survival.**

Findings **According to Response Evaluation Criteria in Solid Tumors (RECIST), after a median follow-up of 14·0 months (IQR 8·7–20·0), two patients had complete responses (CR) and 24 patients had partial responses (PR); the overall response was 51% (95% CI 36–65). Five patients had early progressive disease. In 17 of the 23 patients who achieved PR or CR as defined by RECIST and who had centralised radiological review, tissue-density changes, consisting of a decrease in tumour density on CT scan or a decrease in contrast enhancement on MRI (or both), preceded tumour shrinkage. Median progression-free survival was 14·0 months (13·1–21·0), and progression-free survival at 6 months was 88% (79–95).**

Interpretation **Trabectedin was associated with antitumour activity in this series of patients with myxoid liposarcoma. The noted patterns of tumour response were such that tissue density changes occurred before tumour shrinkage in several patients. In some patients, tissue-density changes only were seen. Long-lasting tumour control was noted in responsive patients. The compassionate-use programme is still ongoing. This analysis has resulted in the initiation of two prospective studies to assess the role of trabectedin in the treatment of patients with myxoid liposarcoma in preoperative and metastatic settings. Furthermore, the selective mechanism of action for trabectedin in this translocation-related sarcoma is being studied.**

Introduction

Soft-tissue sarcomas are rare malignancies of mesenchymal origin, and which encompass more than 50 different histological subtypes. These sarcomas can arise anywhere in the body, but mainly in limbs, girdles, and the abdominal cavity.[1] Surgical excision is the mainstay of treatment, but despite curative surgery, around half of patients develop distant metastases and die from their disease.[2] The chemosensitivity of soft-tissue sarcoma cells is limited, and only anthracyclines and ifosfamide have shown activity, with response rates of 20–40% in previously untreated patients.[3] No other medical option is currently available, and the median survival of patients with soft-tissue sarcoma metastases is less than 1 year.[3]

Trabectedin (previously known as ecteinascidin-743; PharmaMar, Madrid, Spain) is a marine-derived alkaloid that binds covalently to the DNA minor groove, interfering with transcriptional factors in a promoter-dependent way. Trabectedin is active in several malignancies, including sarcomas and ovarian carcinomas.[4–6] Although the objective response rate in patients with anthracycline-resistant advanced soft-tissue sarcoma has not exceeded 10% in multiple phase I and II clinical trials, this drug does result in meaningful control of disease with progression-free survival (PFS) exceeding 20% at 6 months.[7] A higher proportion of objective responses and better PFS with trabectedin treatment have been documented for patients with liposarcomas and leiomyosarcomas, compared with those of other soft-tissue sarcoma subtypes.[8] A European Organisation for Research and Treatment of Cancer (EORTC) study[9] in previously treated patients and a US study in chemotherapy-naive and refractory patients confirmed this finding.[10] For example, in the US study, three of nine patients with liposarcoma responded, and all three responsive patients had the myxoid variant.[10]

Three important liposarcoma subtypes are identified by morphology and genetics: well-differentiated or de-differentiated, myxoid, and pleomorphic. Myxoid liposarcoma accounts for about 30–35% of liposarcomas, and almost 10% of all adult soft-tissue sarcoma. The aggressiveness of the

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liposarcoma depends on the percentage of the round-cell component within the tumour. Myxoid liposarcoma has characteristic chromosomal translocations, namely t(12;16)(q13;p11), resulting in the formation of DDIT3-FUS transcript fusion protein and the rarer t(12;22)(q13;q12), resulting in the DDIT3-EWSR1 fusion protein.[11] Nine molecular variants of the DDIT3-FUS fusion transcript have been previously described, but with no demonstrable prognostic effect.[12,13] Unlike other soft-tissue sarcoma histotypes, myxoid liposarcoma tends to spread to serosal membranes (peritoneum, pleura, and pericardium), the abdominal cavity, distant soft tissues, and bones, even in the absence of lung metastases.[14] Surgery alone or in combination with radiotherapy, depending on prognostic factors, is the main treatment for localised myxoid liposarcoma. Despite adequate localised treatment, about 40% of patients relapse.[13] Median survival after first documented metastasis is about 2 years.[15] Chemotherapy is usually administered to patients with advanced or unresectable disease.[16,17] A higher sensitivity to standard chemotherapy than with other soft-tissue sarcoma histotypes has been suggested, but overall long-term tumour control is far from optimum.[18–20]

New drugs to treat advanced soft-tissue sarcoma are needed. After early studies showed the antitumour activity of trabectedin in soft-tissue sarcoma, a compassionate-use programme was made available at referral centres for the use of trabectedin to treat this rare group of tumours. In this setting, a higher response rate and better tumour control for myxoid liposarcoma was noted. Anecdotal data were also reported, adding to this clinical impression.[10] Therefore, we aimed to review retrospectively data on all patients with myxoid liposarcoma who were treated with trabectedin at five referral institutions around the world.

Methods

Compassionate-use treatment programme

All patients included in this retrospective analysis were treated in a compassionate-use programme that was open to patients with all types of sarcoma who had failed conventional chemotherapy for advanced disease. Patients were included in the programme because they did not meet eligibility criteria for ongoing phase II trials or because they were seen in referral institutions involved in this study when no clinical trial was ongoing. Inclusion into the programme required approval from the Institutional Review Board or Ethics Committee (or both), according to local rules, and approval by PharmaMar; PharmaMar checked that patients met all inclusion criteria, and no patient was refused treatment. Before entering the programme, each patient had to give written informed consent to treatment and data collection. A treatment protocol had to be followed, and eligibility criteria were: histological diagnosis of sarcoma, advanced disease, previous treatment with anthracyclines and ifosfamide, life expectancy of at least 3 months, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, full recovery from any toxicity from previous treatment, and at least 18 years of age.

Compassionate-use treatment protocol

Trabectedin was supplied by PharmaMar as a lyophilised powder in glass vials containing 0·25 mg or 1·0 mg of trabectedin and was allowed to be given at different doses (1·10–1·65 mg/m²; none of the patients in this study received more than 1·50 mg/m² trabectedin) with the use of two different schedules: a 3-h infusion or a 24-h continuous infusion via a central venous line. The starting dose was selected according to baseline liver tests, performance status, and previous treatments. Routine antiemetic premedication included both dexamethasone (8–20 mg intravenously) and ondansetron (8 mg intravenously) or tropisetron (2 mg intravenously). Only patients treated in Milan, Italy, received steroid pre-medication (dexamethasone 4 mg orally twice a day) the day before treatment.[21] According to the compassionate-use treatment protocol, treatment cycles were repeated every 21 days. Each cycle was administered on day 21, provided that complete recovery from any haematological or hepatic toxicity was achieved (ie, to grade 1 or less). Additionally, recovery from any nonhaematological toxicity to grade 1 or less was required. If these criteria were not met on day 21, the next cycle was postponed by 1 week. A delay of 21 days was allowed, and if a persistent absence of recovery was documented the treatment was stopped, unless a clinical benefit was evident. According to the compassionate-use protocol, treatment was continued until disease progression, unacceptable toxicity (ie, resulting in postponement of treatment for longer than 21 days), or patient refusal.

Assessments and evaluation of response and outcomes

According to the compassionate-use programme protocol, all patients had to be assessed by full medical history, physical examination, full blood count, serum biochemistry, and a staging CT or MRI scan at entry into the study. Tumour assessment (by CT or MRI) was done every 2–3 cycles in all patients. Routine follow-up was similar across all centres. The Response Evaluation Criteria in Solid Tumors (RECIST) metrics were used by centres to assess response as part of their clinical practice.[22]

Current retrospective study

This analysis was based on data retrieved retrospectively from medical records of patients with myxoid liposarcoma who were treated at five institutions, out of 15 in the programme worldwide. The ten centres that were excluded from the analysis had not treated any patients with myxoid liposarcoma at the time the analysis started, according to the PharmaMar database. The five institutions included in the analysis were: IRCCS Foundation—National Cancer Institute, Milan, Italy; Royal Marsden Hospital, London, UK; Dana-Farber Cancer Institute, Boston, MA, USA; Centre Leon Berard, Lyon, France; and Institut Gustave Roussy, Villejuif, France. These institutions are major referral centres for soft-tissue sarcomas, and agreed to cooperate for this retrospective analysis. All patients with myxoid liposarcoma who had been treated at these institutions in

	All patients (n=51)
Age, years	
Median (IQR)	50 (42–58)
Sex, n	
Men	35
Women	16
ECOG performance status, n	
0	31
1	18
2	2
Site of primary disease, n*	
Thigh	26
Leg	15
Pelvis	6
Other	4
Median number of sites involved (range)	2 (1–6)
Bulky or locally advanced disease, n	11†
Disease extent at diagnosis, n*	
Localised disease	40
Metastatic disease	11
Time to relapse since primary treatment, months	
Median (95% CI)	25·4 (18·9–68·0)
Range	3·0–189·0
Time between diagnosis and first cycle of trabectedin, months	
Median (IQR)	46·3 (31·4–120·1)
Range	7·0–248·0
Number of previous chemotherapy regimens, n	
0	3
1	15
2	17
3	8
4–6	8
Previous chemotherapy, n	
Anthracyclines	48
Ifosfamide	46
Both	46
Starting dose of trabectedin, n	
3-h infusion of 1·10 mg/m²	1
3-h infusion of 1·30 mg/m²	1
3-h infusion of 1·50 mg/m²	2
24-h infusion of 1·20 mg/m²	3
24-h infusion of 1·30 mg/m²	28
24-h infusion of 1·50 mg/m²	16

*Data as of initial diagnosis of disease, all other data are as of start of trabectedin treatment. †Seven patients had bulky disease and four patients had locally advanced disease.

Table 1: **Characteristics of patients**

the compassionate-use programme were included in this analysis. Only patients who had been included into prospective clinical studies were excluded. We analysed patients who started treatment between April 4, 2001, and Sept 18, 2006. During this period, only three additional patients with myxoid liposarcoma from the remaining ten centres joining the programme were registered in the database at PharmaMar, but these three patients are not included in this analysis. Therefore, most patients with myxoid liposarcoma who were treated with trabectedin in the compassionate-use programme were included in this retrospective analysis. For this retrospective analysis, patients' medical records were read between Nov 19, 2005, and Dec 31, 2006 at each institution (by FG, RLJ, GDD, JYB, ALC, RS, PD, SS) for details of full medical history at diagnosis of myxoid liposarcoma, previous treatments, physical examination, trabectedin administration, outcome assessment, and follow-up. This retrospective analysis did not focus on toxic effects, however treating physicians were asked to report serious adverse events or unexpected toxic effects. A serious adverse event was defined as any untoward medical occurrence or effect that resulted in persistent or substantial disability, death or a life-threatening situation, admission to hospital, or prolongation of existing time in hospital.

Additionally, a centralised review of radiological images was done (by FG and CS) in 41 patients in this retrospective analysis. CT scans were reviewed in all of these patients, apart from one for whom MRI was used. For this centralised review, RECIST criteria were used. According to these criteria, complete response (CR) is defined as disappearance measured on MRI or CT scan of all tumours and a partial response (PR) as a 30% decrease in the sum of the longest diameters of target tumour. A 20% increase in the sum of the longest diameter of target tumour is defined as progressive disease (PD), and stable disease (SD) as none of PD, PR, or CR criteria met.[22] In addition to the response categories defined by RECIST criteria, to study patterns of tumour response, any radiologically measured tumour shrinkage—ie, a decrease in the sum of the longest diameter of target tumours not reaching criteria for an objective PR—was defined as minor response (MR). However, for RECIST response rate quantification and for PFS correlations, MR were grouped with SD. Also, for exploratory purposes with regard to patterns of tumour response, occurrence of changes in tumour density measured qualitatively by CT scanning or consistent changes in MRI (consistent signal alterations or decrease in contrast enhancement, or both) were documented. If radiological images were not available for central review, response assessments were obtained retrospectively from the patients' medical records (FG, RLJ, GD, JYB, ALC), and changes in tumour density were not recorded.

For the subgroup of patients who were treated in Milan, Italy, and London, UK, data were available to calculate previous PFS referring to the last chemotherapeutic treatment administered before trabectedin. PFS was calculated from the date of starting previous chemotherapy until the date of radiological progression.

Diagnosis of myxoid liposarcoma was confirmed by a specialist soft-tissue pathologist at each of the five participating centres for all patients as part of their routine care, and was confirmed (by SP and PCo) by central review of

stained and unstained pathological slides in 33 patients in this retrospective analysis. In these 33 patients, the presence of t(12;16) was confirmed by fluorescence in-situ hybridisation (FISH) analysis using two Bac clones labelled directly by Spectrum Orange and Spectrum Green by nick translation. The Bac clone labelled by Spectrum Orange (by PCa and ET), called RP11-196G-11, contains an upstream region of *FUS* gene; the Bac clone (called RP11-181L23) was labelled by Spectrum Green (by PCa and ET) and spans the entire *DDIT3* gene. When frozen tissue was available, reverse-transcriptase-polymerase chain reaction (RT-PCR) was done (by PCa and ET) to sequence and characterise the fusion transcript.[23]

Statistical analyses

The primary endpoints were response rate and PFS, and the secondary endpoint was overall survival. PFS was defined as the date of inclusion in the compassionate-use programme to the date of documented disease progression. PFS curves, median PFS, and 95% CI were calculated by use of the Kaplan-Meier method with MedCalc (version 9.0.1.0).

See Online for webtable

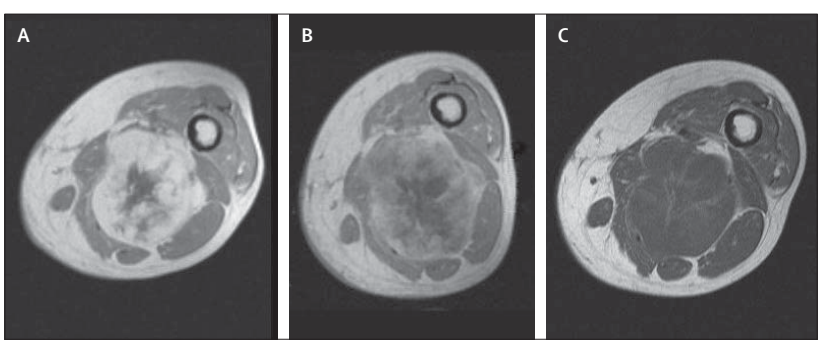

Figure 1: **MRI of left thigh showing progressive decrease of contrast enhancement without tumour shrinkage in patient 26**
Baseline MRI (A); after one course of trabectedin (B); and after four courses of trabectedin (C).

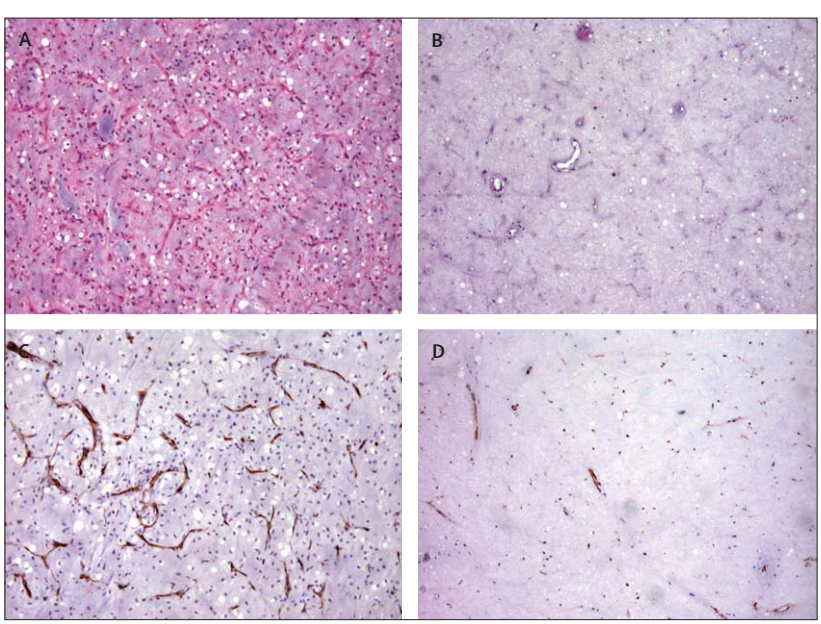

Figure 2: **Histological features of tumour tissue from left thigh before and after trabectedin treatment in patient 26**
Pretreatment (A) and post-treatment (B) stained with haematoxylin and eosin; pretreatment (C) and post-treatment (D) with immunostaining with CD31 highlighting the vascular network.

Role of the funding source

This study was conceived by the investigators and did not receive any financial grants. PharmaMar Research and Development provided funding to support the shipment of the imaging material and tumour samples; they did not support any other activity to do with study design, data collection, data analysis, or writing of the report. FG, PGC, RS, and RLJ had access to the raw data. FG and PGC had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

51 patients (16 women and 35 men) were included in this retrospective analysis. Table 1 summarises the characteristics of the patients and the webtable shows additional details. All patients started treatment with trabectedin between April 4, 2001, and Sept 18, 2006. The median age at the start of trabectedin treatment was 50 years (IQR 42–58). ECOG performance status was 0 in 31 patients, 1 in 18 patients, and 2 in two patients. 33 patients were diagnosed with a pure myxoid liposarcoma, the other 18 patients had a round-cell component representing 5–90% of the total tumour. FISH analyses were done in 33 patients, all of whose tumours were found to have the t(12;16) chromosomal translocation. In 12 of these 33 patients, the availability of frozen tissue allowed us to do RT-PCR experiments. The obtained products were sequenced and characterised as: type II fusion transcript in eight patients; type I and IV in one patient; type II and IV in one patient; type III in one patient; and type II and III in one patient. Pathological samples of tumours from 18 patients could not be retrieved for the centralised review.

The most common primary tumour site was the thigh. 11 patients presented with metastatic disease at diagnosis. 27 patients had received adjuvant radiotherapy, and ten had received adjuvant chemotherapy after complete surgery. All but three patients had been treated with chemotherapy for advanced disease (ie, metastatic or inoperable disease). 46 received both anthracyclines and ifosfamide (of these, 31 patients received anthracyclines and ifosfamide in combination, and 15 patients received anthracyclines and ifosfamide in sequence) as first-line chemotherapeutic treatment, which is usual practice in some institutions according to individual patient data; two patients received anthracyclines only. The median number of previous chemotherapy regimens was two (IQR 1–3). Median time from initial diagnosis to start of trabectedin treatment was 46·3 months (31·4–120·1), and from relapse to start of trabectedin was 24·3 months (12·3–42·3). Four patients had locally advanced disease when they started trabectedin treatment, and 47 patients had metastatic disease, with a median of three sites involved (IQR 1–3). Sites of metastases

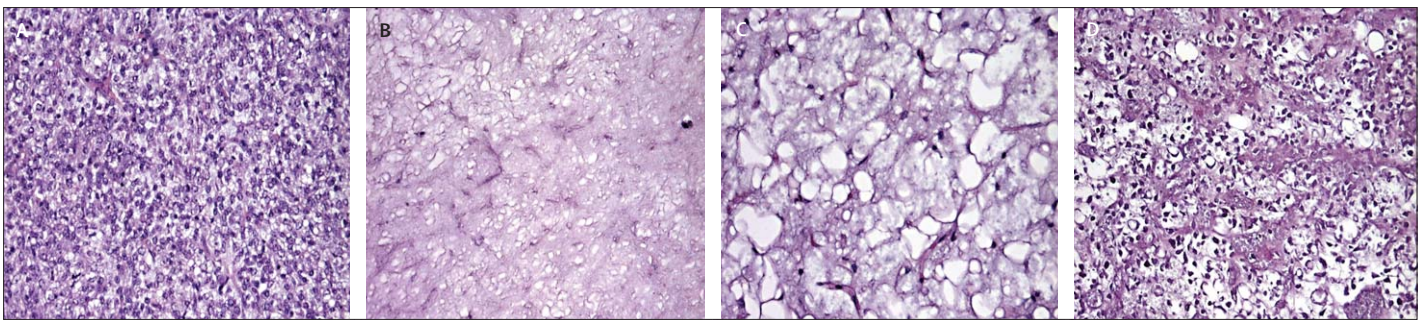

Figure 3: **Histological features of abdominal-tumour tissue before and after trabectedin treatment in patient 21**
Tumour tissue stained with haematoxylin and eosin before treatment (A) and after treatment (B–D): B, deposition of sclerohyaline material and cellular depletion; C, mature lipoblast-featuring cells; D, necrosis.

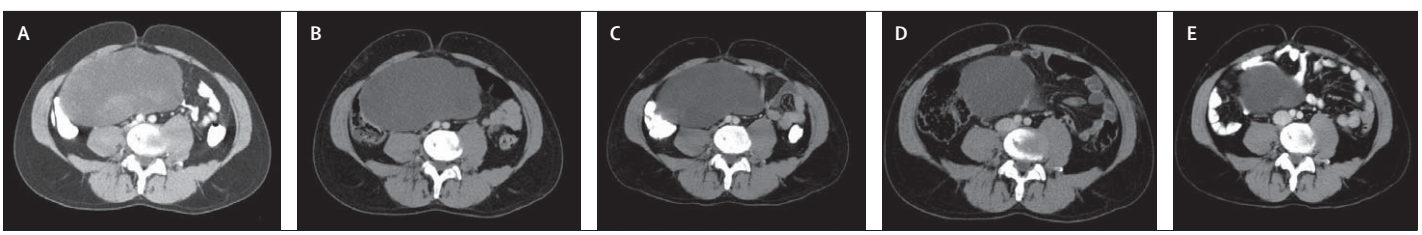

Figure 4: **Sequential CT scans of abdominal tumour displaying a decrease in tumour density followed by a decrease in tumour dimensions in patient 21**
Basal CT scan (A); after one course of trabectedin (B); after five courses of trabectedin (C); after eight courses of trabectedin (D); and after 11 courses of trabectedin (E).

at starting trabectedin treatment were: lung or pleura (or both), 34 patients; mediastinum, 24 patients; pericardium, 12 patients; abdominal cavity, 11 patients; bone, 11 patients; liver, one patient; and soft tissue, ten patients.

558 cycles of trabectedin were administered, with a median of ten cycles per patient (IQR 6–14; range 1–23). At the time of this analysis, 14 patients were still on treatment with trabectedin. 47 patients were treated with the 24-h continuous intravenous schedule at the following starting doses: 1·5 mg/m² in 16 patients, 1·3 mg/m² in 28 patients, and 1·2 mg/m² in three patients. Four patients were treated with the 3-h schedule at the following starting doses: 1·5 mg/m² in two patients, 1·3 mg/m² in one patient, and 1·1 mg/m² in one patient. Both schedules were repeated every 21 days. No treatment interruption due to toxicity and no unexpected toxic effects or severe adverse events of grade 4 were noted.

All patients were assessed for response. The first tumour assessment was done after a median time of 8 weeks (IQR 6–9) from start of trabectedin treatment. Median follow-up was 14·0 months (8·7–20·0). Overall, two CR and 24 PR were reported, which gave an overall objective response (ie, CR+PR) of 51% (95% CI 36–65) according to RECIST. Six patients had MR. 14 patients were reported as having SD as best response. Overall, tumour control (ie, patients who had CR, PR, MR, and SD) was achieved in 46 patients. Five patients had PD at their first tumour assessment.

In a subgroup of 41 patients, a centralised radiological review was done of available radiographical images from baseline to progression, to best response, and to treatment end; images from study centres in Milan, London, and Boston were used. Only six of the 23 patients in this subgroup with a confirmed CR or PR had achieved these responses by the first response assessment; out of the other 17 patients, eight patients had MR at first assessment, and nine had SD; median time to reach a dimensional decrease of the tumour that configured an objective response was 3·6 months (IQR 2·4–4·6). In these 17 patients who did not have a confirmed CR or PR by the first response assessment, early alterations in tumour appearance detected by CT scan or MRI were noted—the hallmark feature was a decrease in tumour density without substantial changes in tumour dimensions. The same early signs of decrease in tumour density were seen in 12 of the 15 patients with SD as their best response confirmed during central review. Median PFS for the three patients with SD but no radiologically detectable tissue changes were 2·2 months, 3·4 months, and 5·3 months.

One patient, who had a pericardial metastasis, received nine courses of trabectedin at a very low dose intensity (0·167 mg/wk) because of bone-marrow toxicity, and achieved a CR that was still maintained after 27 months from treatment initiation. Three patients achieved PR as their best response and continued to respond for up to 19, 20, and 23 cycles, respectively, at which point the patients and the treating clinicians shared the decision to stop treatment in view of the long treatment time. These three patients were then rechallenged with trabectedin on subsequent disease progression, and two of these had a second prolonged disease stabilisation, lasting 18 months and 22 months, respectively.

One patient (patient 26, webtable), who had a multifocal locoregional relapse of a pure-type myxoid liposarcoma of the thigh, received four preoperative courses of

Age, years	Sex	Location of myxoid liposarcoma	Myxoid liposarcoma grade	DDIT3-FUS transcript	Metastatic sites	Best response	PFS, months	Trabectedin treatment ongoing*	Status
42	Male	Thigh	High	II	Lung	CR	8·3	Yes	NED
45	Male	Thigh	High	II	Abdominal cavity	PR	16·3	No	NED†
65	Male	Leg	High	II	Mediastinum, pericardium	PR	20·5	No	AWD
34	Female	Thigh	High	II	Bone, liver, pleura, soft tissue	PR	11·1	Yes	AWD
47	Male	Thigh	Low	II	Pelvis, soft tissue	SD	15·2	No	NED†
60	Male	Thigh	High	II	Soft tissue	SD	12·1	Yes	AWD
48	Male	Leg	Low	II	Heart, pericardium	MR	14·5	No	AWD
50	Female	Thigh	High	II	Abdominal cavity	MR	6·7	Yes	AWD
55	Female	Thigh	Low	II and IV	Abdominal cavity	PR	7·3	Yes	AWD
52	Male	Leg	High	I and IV	Bone, pericardium, soft tissue	PR	18·0	No	AWD
58	Male	Groin	High	III	Pelvis, soft tissue	PD	1·3	No	AWD
53	Male	Thigh	High	II and III	Abdominal cavity, soft tissue	PD	1·3	No	DOD

NED=no evidence of disease. AWD=alive with disease. DOD=dead of disease. *At the time of the analysis. †NED after surgical removal of residual disease.

Table 2: **Characteristics of 12 patients who had molecular analysis**

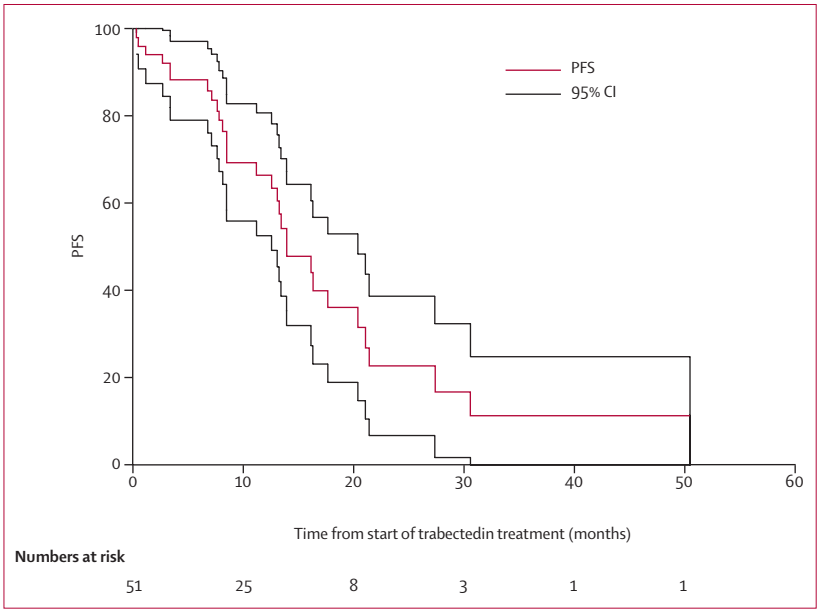

Figure 5: **Progression-free survival**

trabectedin. The MRI after four courses of trabectedin showed a marked decrease of contrast enhancement without any tumour shrinkage (figure 1). When this patient's post-surgery resection specimen was reviewed, both the typical plexiform vascular pattern and the immature spindle cell neoplastic component had disappeared and were replaced by sclerohyaline material in more than 70% of the sample; the remaining areas showed maturation represented by clear adipocytic differentiation (figure 2). A resection specimen from another patient (patient 21, webtable), who had a huge abdominal relapse of a myxoid liposarcoma with a cellular component up to 50% at diagnosis, and who was operated on after 17 courses of trabectedin, showed coagulative necrosis in almost half of the sample, sclerohyaline degeneration (20% of the areas), and areas of monovacuolated lipoblasts (figure 3). This patient had achieved an objective PR, which, like patient 26, was identified by the early appearance of tumour hypodensity on CT scans (figure 4).

Although the numbers of patients in this study were too small to draw any definite conclusion, no relation between response, trabectedin concentration, infusion modalities, other patient characteristics (ie, patient sex, age, location, and grade of tumour), and previous interventions (ie, surgery, previous chemotherapy or radiotherapy) were apparent (webtable). In terms of molecular variants of the DDIT3-FUS fusion transcript, of the eight patients who carried the type II transcript, one achieved a CR, three had PR, and four had SD or MR with tissue changes (one of these patients was treated with four cycles of trabectedin and had a major pathological response after surgical excision). One patient carrying both the type II and type IV, and another carrying both type I and type IV transcripts achieved PR. By contrast, the two patients carrying the type III fusion transcript (alone or in combination with another subtype) had disease progression. These data are summarised in table 2.

The median PFS on trabectedin of the entire patient group was 14·0 months (95% CI 13·1–21·0). PFS of the entire patient group at 3 months was 92% (85–99), and at 6 months was 88% (79–95). Figure 5 shows the PFS curve of the entire patient group. According to RECIST, the median PFS of patients who attained a PR or CR was 20·3 months (14·0–30·6), and of patients who had SD or MR was 12·5 months (8·1–21·4), whereas PFS during previous chemotherapy (ie, before starting trabectedin treatment) for 34 patients for whom data were available was 8·4 months (3·1–11·1).

Discussion

In this multicentre, retrospectively studied series of 51 pretreated patients with advanced myxoid liposarcoma, trabectedin showed an objective response as measured by

RECIST of 51% (95% CI 36–65), with an additional 20 patients achieving MR or SD. The PFS was 88% at 6 months. Only five patients exhibited progressive disease. In the subgroup of 38 patients who did not have evidence of progression and with available radiographical images, 29 showed signs of a tissue response, with substantial radiological changes in the density of tumours, often before tumour shrinkage became evident.

Trabectedin has been studied as a possible treatment for advanced soft-tissue sarcoma since 1999.[24] This drug has been associated with a PFS exceeding 20% at 6 months, and rates of objective response according to RECIST in the 10% range.[9] If the results of this analysis are reproduced in ongoing prospective studies, myxoid liposarcoma would represent a uniquely sensitive subgroup to trabectedin treatment in the heterogeneous family of soft-tissue sarcoma.

This study was a retrospective analysis of patients who were given treatment compassionately. Other limitations of retrospective studies in general include: the use of non-stringent eligibility criteria and absence of a strict follow-up protocol, but in this study, the use of a protocol for compassionate use attenuated these limitations. Nonetheless, although this was not a prospective study, this series was collected on a multicentre basis by some of the world's major institutions with extensive experience with trabectedin. Findings, including PFS data, were consistent across these institutions.

In this series of patients with myxoid liposarcoma, the tumour objective response according to RECIST was 51%, whereas previously reported responses to other cytotoxics for pretreated advanced adult soft-tissue sarcoma generally do not exceed 20% (in patients for whom first-line conventional treatment failed).[16,17] A further 12 of 15 patients in the subgroup who had radiological images available for central revision had SD with a tissue response—ie, obvious changes in the radiographical density of tumours, mainly hypodensity on CT scan (or consistent alterations on MRI). Indeed, of the 29 patients with radiographical density changes at first tumour assessment, an objective response was documented in 17 patients after additional trabectedin treatment, and in the others an MR or a prolonged stabilisation of disease was noted. Moreover, in two patients of this series whose disease was resected after preoperative trabectedin, these radiological findings were consistent with a major pathological response, marked by cellular depletion, disappearance of the plexiform vascular structure, deposition of sclerohyaline material, and increase of monovacuolated lipoblasts. These features were especially relevant in myxoid liposarcoma with a cellular component which exhibited very little evidence of lipid accumulation at baseline. The same histological changes had been described in myxoid liposarcoma specimens of patients treated with troglitazone, which stimulates peroxisome proliferator activated receptor-gamma, a nuclear receptor that has an important role in the last phases of adipocyte differentiation.[25] All these observations suggest that trabectedin-induced hypodensity in tumours might be a biologically and clinically relevant tumour response to the drug.

Indeed, such patterns of tumour response have been reported with molecularly targeted treatments—eg, in patients with gastrointestinal stromal tumours who receive KIT-kinase inhibition with imatinib or sunitinib, and in those with other solid tumours (eg, chordoma) who are undergoing molecular targeted treatments.[26–29] In this sense, trabectedin might target a molecular mechanism with crucial transforming activity in myxoid liposarcoma, therefore, accounting for the unexpectedly high response rates in this subtype. *DDIT3* fusion oncogenes are found in virtually all myxoid liposarcomas, and preclinical studies have shown that trabectedin has transcriptional regulatory functions.[30] In our study, in 12 patients with the type of fusion transcript characterised, the two who had early progression had the much less common type III transcript, thus further suggesting a molecular specificity of action, preliminary and scant though these observations might be. These fusion transcript types contain a variable number of exons of fusion (involved in t(12;16) in malignant liposarcoma [*FUS*]) and *DDIT3*. Type III is the longest fusion transcript, containing the first eight exons of *FUS* fused to exons 2 to 4 of *DDIT3*. Compared with type III, in type II and I, *FUS* contributes less to the fusion protein (exons 1–5 and 1–7 respectively), while type IV is the shortest transcript, comprising exons 1–5 of *FUS* and exons 3–4 of *DDIT3*.[12] Translational studies investigating this potential selective mode of action are currently ongoing.

Although the clinical findings from this retrospective analysis of a global compassionate-use programme need to be confirmed, one can speculate how to best exploit the high activity of trabectedin in this histological type. Myxoid liposarcoma seems to have a better prognosis compared with other soft-tissue sarcoma subtypes, but as many as 40% of patients relapse despite optimum initial treatment. From time of metastasis, the course of disease might last longer than other metastatic soft-tissue sarcomas, but eventually metastatic myxoid liposarcoma leads to death. Thus, an effective medical treatment is important to improve the outcome of patients with advanced myxoid liposarcoma. Also, trabectedin is a generally well-tolerated treatment with predictable and manageable side-effects.[9] The most prevalent drug-related event is a moderate to severe, reversible, acute increase of transaminases. Severe neutropenia and thrombocytopenia are in the 15% range; the drug does not induce alopecia, mucositis, or diarrhoea.[31] Of note, the absence of cumulative toxicities makes trabectedin suitable for prolonged treatment, as confirmed also in this cohort, in which some patients received many courses of trabectedin. As a result of this study, a phase II trial of trabectedin in advanced pretreated myxoid liposarcoma patients by the Italian Sarcoma Group is currently ongoing, and a phase II international multicentre trial in the preoperative setting is underway for patients with localised, operable disease

who might benefit from cytoreduction. These various efforts should help clarify the best ways to exploit trabectedin in patients with myxoid liposarcoma.

Contributors

FG and PGC took part in the study concept and design. FG, RLJ, GDD, IRJ, JYB, ALC, RS, PCa, PD, PCo, SS, JAF, and SP participated in data acquisition. CS collected data for the central radiological review. CS, PCo, PCa, ET, and SP did the centralised radiological and pathological reviews. ET collected data for the cytogenetic and molecular analysis. JAF contributed to the cytogenetic analysis. PCa did the cytogenetic analysis. SP contributed to the analysis and interpretation of the pathological, cytogenetic, and molecular data. FG, RLJ, AG, and PGC analysis and interpretation of the data. JCT and JJ contributed to the discussion on the data analysis. FG and RLJ drafted the manuscript. GDD, IRJ, JYB, ALC, ET, MDI, JAF, SP, and PGC took part in critical revision of the manuscript. All authors approved the final version of the report. JCT and JJ participated in administrative, technical, and material support. FG, RLJ, GDD, JYB, AL, RS, PD, and SS read the patients' medical records.

Conflicts of interest

FG, RLJ, RS, PCa, PCo, PD, CS, SS, ET, AG, JAF, and SP declared no conflicts of interest. GDD is a consultant for, has an advisory role, has received research funding from, and has paid expert testimony for PharmaMar and Johnson & Johnson; IRJ is a consultant and has an advisory role for PharmaMar; has received honoraria and research funding from PharmaMar; and has paid expert testimony for PharmaMar. JYB, ALC, and PGC are consultants and have advisory roles for PharmaMar, Novartis, and Pfizer, and have received honoraria and research funding from Novartis and Pfizer. JCT and JJ are employed by PharmaMar. JJ owns stocks in Zeltia, PharmaMar's holding corporation. MDI is a consultant for, and has an advisory role for, PharmaMar, and has received research funding from PharmaMar.

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