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Experience with second-line trabectedin in daily clinical practice: case studies

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As a recommended second-line option for advanced soft tissue sarcoma, trabectedin can provide the necessary balance between long-term tumor control and preserved quality of life. Three case studies illustrate the long-lasting responses that patients can achieve with second-line trabectedin. A female patient with metastatic leiomyosarcoma maintained disease control for 2 years with trabectedin (× 41 cycles) with excellent tolerability and no relevant adverse events. At the time of writing, a male patient with a metastatic solitary fibrous tumor was asymptomatic after 30 cycles of trabectedin and treatment was ongoing. A young male patient with a recurrent, nonresectable, retroperitoneal myxoid/round cell liposarcoma was able to continue his sporting activities (triathlons) over 2 years with trabectedin (× 14 cycles) plus watchful waiting.

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Clinical practice guidelines for soft tissue and visceral sarcomas recommend trabectedin as a second-line option for patients with advanced soft tissue sarcoma (aSTS) [1]. Clinical trials and real-world studies show a trend toward an increasing duration of trabectedin therapy as clinical experience with its use accumulates [2], attributable at least in part to its acceptable and manageable safety profile [3]. This article presents three case studies that illustrate long-lasting responses that patients can achieve with trabectedin as second-line treatment.

Case 1: Long response to trabectedin in a patient with metastatic leiomyosarcoma

The case describes a 62-year-old woman with a previous ectopic pregnancy as her only relevant medical history. In August 2010 (at the age of 51 years), she complained of abdominal discomfort. An abdominal ultrasound performed at another center identified a mass of about 5 cm in its largest diameter. A computerized tomography (CT) scan showed the mass to arise from the right renal vein, in the retroperitoneal space. Unfortunately, no core biopsy was planned. A diagnostic surgery was scheduled and, in September 2010, the mass was resected with macroscopically complete margins. The histopathological examination revealed a grade 2 leiomyosarcoma. Margins were not specified in the original pathological report.

Periodic follow-up was initiated, involving CT scans every 3 months. A suspicious hepatic lesion (2 cm) was identified in April 2014. Resection confirmed the lesion as a metastasis from leiomyosarcoma. Periodic follow-up with CT scans was restarted. In December 2016, new hepatic lesions and subcentimetric pulmonary lesions were detected, consistent with disease progression.

Upon referral to the authors' center, the patient underwent initial evaluation in January 2017. In the presence of advanced unresectable leiomyosarcoma not previously treated with systemic therapy, the proposed first-line treatment was doxorubicin plus olaratumab, within a clinical trial. The patient completed six cycles of combination

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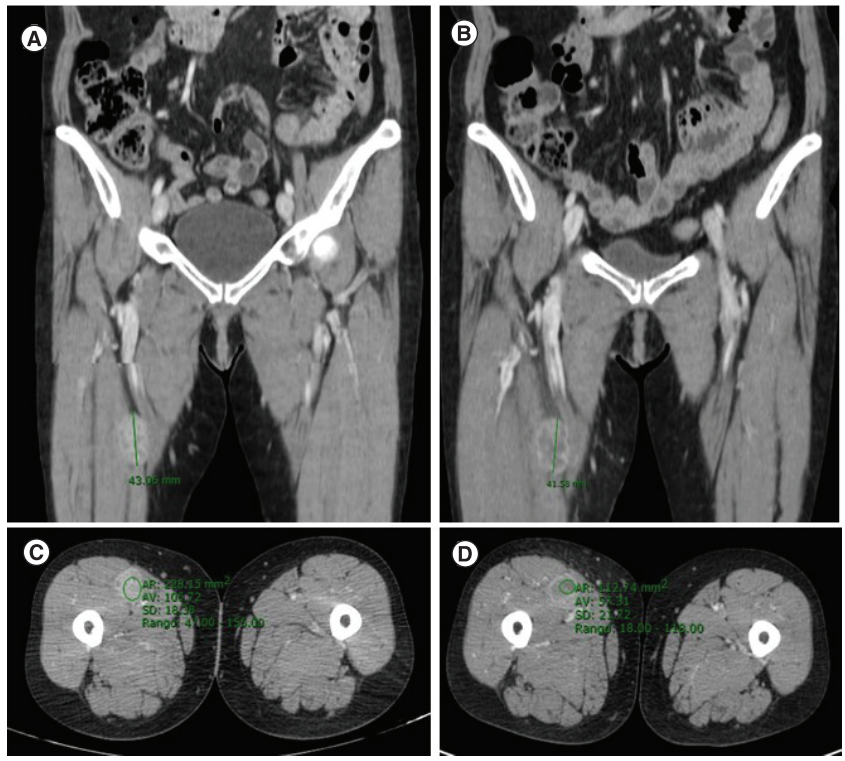

Figure 1. Coronal computerized tomography scan images of a soft-part nodule in the right thigh of a patient with metastatic leiomyosarcoma. (A) August 2018 at baseline. **(B)** January 2019 after 3 months' therapy with trabectedin. The lesion was stable according to Response Evaluation Criteria in Solid Tumors 1.1 (reduction of 3.4%), but a clear reduction in tumor density can be observed. Axial CT scan images of the same lesion with density measurements (HU) at **(C)** baseline (106 HU) and **(D)** after 3 months' therapy with trabectedin (57 HU). The 46% reduction in density corresponds to a partial response by Choi criteria.

therapy from January to June 2017 with a best response of stable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Disease progression was detected in August 2017. Although the hepatic lesions were stable, new pulmonary lesions emerged, as well as a soft-part nodule of almost 3 cm in the right thigh, which was clinically evident on physical exam and symptomatic.

At this time, the patient's Eastern Cooperative Oncology Group performance status was 0 and she was not experiencing any dyspnea or pain, apart from disturbances in the right thigh due to the soft-part nodule.

Taking into account factors such as histological subtype, disease extension, presence of a symptomatic lesion and previous doxorubicin-based chemotherapy, second-line treatment was proposed with trabectedin 1.5 mg/m^2 in a 24-h continuous infusion every 21 days. In September 2018, the patient received the first cycle of trabectedin through a central venous catheter, after proper premedication with dexamethasone (4 mg orally, 24 and 12 h before the infusion, and 20 mg intravenously 30 min before the infusion). The symptomatic soft-part nodule was treated with palliative radiotherapy (30 Gy in 10 fractions of 3 Gy each). Radiological reassessments indicated RECIST 1.1 stable disease, although the nodule showed density changes compatible with a Choi partial response to therapy (Figure 1). Treatment with trabectedin was maintained from September 2018 to February 2021 (× 41 cycles), with excellent tolerability and no relevant adverse events. Throughout more than 2 years of disease control, the patient was able to continue her daily activities (including intense physical activity related to an agricultural job).

In March 2021, disease progression was detected and third-line treatment was started with gemcitabine 1800 mg/m^2 plus dacarbazine 500 mg/m^2 every 2 weeks. At last follow-up (June 2021), the patient continued to receive this regimen with good tolerability and stable disease.

Clinical interpretation

Case 1 reports on a female patient with a metastatic retroperitoneal leiomyosarcoma who had progression-free survival of 7 months with first-line doxorubicin-based chemotherapy. In the histology-driven setting after doxorubicin failure [1], trabectedin is a suitable second-line choice, given its demonstrated activity in patients with leiomyosarcoma (and liposarcoma) [4,5]. The patient achieved prolonged disease control (more than 29 months) during trabectedin treatment, with excellent tolerability and quality of life. Prolonged disease control with second-line trabectedin is becoming increasingly common. A large, real-life series reported in 2018 of European patients found that 74% of those treated with second-line trabectedin received six or more cycles [6].

While acknowledging that tumor biology can govern the time to progression, in this patient, progression-free survival with trabectedin was more than four-times that achieved with doxorubicin + olaratumab, corresponding to a growth modulation index (GMI) of >4. Although no externally validated prognostic/predictive factors for response to or benefit from systemic therapy have been identified in aSTS, some are suggested. A GMI of >1.33 relates to drug activity and better outcomes in patients treated with systemic therapy in general [7], and with trabectedin specifically [8,9]. The Spanish Group for Research in Sarcoma (GEIS) includes GMI in a prognostic score called GEISTRA [10], which, along with a metastasis-free interval <9.7 months, a Karnofsky score <80% and a histological subtype other than leiomyosarcoma or liposarcoma, aims to identify patients with better expected outcomes with trabectedin. The GEISTRA score ranges from 0 points (none of these factors, related to a better outcome) to 4 points (all these factors, related to a worse outcome). The GEISTRA score for this patient would be 0 (metastasis-free interval >9.7 months; Karnofsky score 100%, leiomyosarcoma; and GMI >1), which is consistent with the good outcome she achieved with trabectedin.

Another interesting aspect of Case 1 is the pattern of response to trabectedin. Although the disease was stable in terms of tumor dimensions, an important reduction in tumor density was observed, consistent with a partial response by Choi criteria [11]. While Choi criteria are not validated in STS, and are used mainly in gastrointestinal stromal sarcoma, it is not infrequent to observe density responses in patients with STS treated with antiangiogenics or even chemotherapy. As an example, in solitary fibrous tumor, Choi criteria appear superior to RECIST in evaluating the efficacy of antiangiogenics [12]. Although the expected RECIST response rate to trabectedin is less than 10%, density changes are often observed. A retrospective series suggested that Choi criteria may provide more information about trabectedin's efficacy than dimensional criteria alone in patients with aSTS [13]. Case 1 supports the concept that clinical factors known to be associated with a greater benefit from trabectedin should be factored into decision-making algorithms.

Case 1 also demonstrates the feasibility of combining trabectedin with radiotherapy to induce a response in the second-line treatment of aSTS, as shown in the phase I/II TRASTS study [14].

Case 2: long-lasting response to trabectedin in a patient with metastatic solitary fibrous tumor of the cervical region

The authors report the case of a 49-year-old man affected by a metastatic solitary fibrous tumor (SFT). His clinical history was unremarkable apart from arterial hypertension (diagnosed in 2010), which was treated with angiotensin-converting-enzyme inhibitors and diuretics (ramipril/hydrochlorothiazide 5 mg/25 mg, 1 tablet/day), and hypercholesterolemia (diagnosed in 2011), which was treated with atorvastatin 40 mg, 1 tablet/day. The patient was referred to the authors' center in October 2017, several years after tumor onset.

The patient had undergone surgical resection of an enlarging cervical mass in 1999. The diagnosis of hemangiopericytoma was subsequently reclassified as SFT. Surgical margins were negative and the mitotic figure count was 4/10 per high-power field (HPF). In October 2012, he experienced new cervical pain in the neck region. MRI showed a nodule 13.3 mm in diameter, consistent with tumor relapse (C2 level). Following neurosurgical resection in March 2013, the pathology report confirmed relapse of an SFT (negative surgical margins, Ki-67 10%, mitoses 7/10 HPF, $CD34^+$, CK AE1/AE3-, S100-, EMA-, p53-). MRI in June 2013 showed two new lesions at the level of the C2 and C4-C5 vertebrae. Stereotactic radiotherapy was delivered at both recurrence sites (total dose of 25 Gy/5 fractions).

CT scans and MRIs were repeated regularly and the disease remained stable for approximately 3 years. In March 2016, MRI showed a new cervical nodule at the vertebral body. After discussing the various options, the patient opted for watchful waiting, refusing therapeutic interventions. Under close follow-up, the three cervical localizations remained stable for more than 1 year.

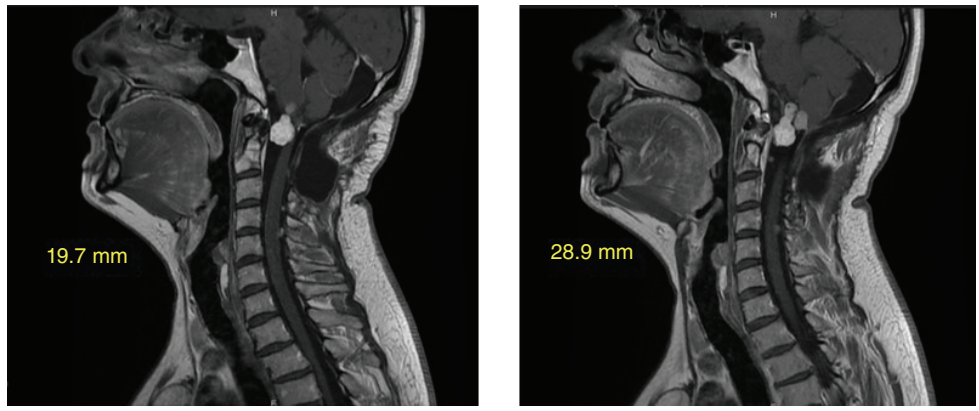

Figure 2. November 2018: adjacent slices from T1 MRI sequences showing progressive cervical disease.

In June 2017, neck pain reappeared along with novel symptoms of tongue and bilateral hand paresthesias. Progressive disease was confirmed consisting of dimensional increases in pre-existing cervical deposits and extension to the occipital foramen, in the form of multiple nodular lesions on the C1 vertebrae and two tiny, nodular lesions on the C2 and C4-C5 vertebrae. In August 2017, the more critical and symptomatic lesion localized near the foramen magnum was resected (SFT, G3, mitosis 6/10 HPF, STAT6+, $CD34^+$, Ki-67 7%).

A follow-up chest CT scan in August 2017 revealed a new pulmonary nodule. The patient underwent video-assisted thoracic surgery with left lower lobectomy and lymphadenectomy, again with a diagnosis of SFT localization (negative margins, mitosis 11/10 HPF, anti-$CD34^+$, STAT6+, TTF-1, actin-, HBM45-, chromogranin A-, EMA-, Ki-67 15%).

Upon referral of the patient to the authors' center in October 2017, the case was discussed by the sarcoma multidisciplinary tumor board. Due to multiple sites of inoperable, progressive disease, first-line chemotherapy was indicated. From November 2017 to February 2018, the patient received six cycles of doxorubicin 25 mg/m^2/day on days 1, 2 and 3 in 21-day cycles and concomitant dacarbazine 250 mg/m^2/day on days 1, 2 and 3 in 21-day cycles, with no significant toxicities apart from neutropenia (G2), nausea (G3) and diarrhea (G1). The disease remained stable for approximately 1 year.

A CT scan in June 2018 showed a minimal increase of existing lung and cervical lesions. The patient was asymptomatic and chose to delay second-line treatment until November 2018, when he began to experience worsening cervical pain. Adjacent slices from T1 MRI sequences showed progressive cervical disease (Figure 2A & B). Available therapeutic options were discussed within the multidisciplinary tumor board and with the patient – in particular, the possibility of using either antiangiogenic agents (pazopanib) or trabectedin (authorized in Italy as second- or further-line treatment for any STS histology). After careful discussion, trabectedin was chosen and started at the dose of 1.5 mg/m^2 in a 24-h continuous infusion every 21 days, tapered to 2.6 mg. MRI and CT scans after two doses of trabectedin showed stable disease.

From November 2018 to September 2020, the patient received 20 cycles of trabectedin. Tolerability was good without relevant side effects apart from spontaneously reversible G2-3 liver enzyme (transaminase and alkaline phosphatase) elevation. CT scans in October 2019 and March 2020 indicated a partial but steady response of cervical lesions and stable lung lesions. An MRI in August 2020 showed a marked reduction of cervical nodules (Figure 3A & B).

In October 2020, at the patient's request, longer (4- or 5-week) intervals between trabectedin doses were established and the dose was reduced (1.1 mg/m^2). At the time of writing, treatment had reached 30 cycles and was ongoing. The patient was asymptomatic. Other clinical benefits were pain reduction (no use of analgesics after the first ten cycles of trabectedin) and improved quality of life.

Clinical interpretation

SFT is a rare mesenchymal tumor characterized by a NAB2–STAT6 gene fusion (inv[12][q13;q13]). It can occur anywhere in the body and exhibits a wide spectrum of histological features [15].

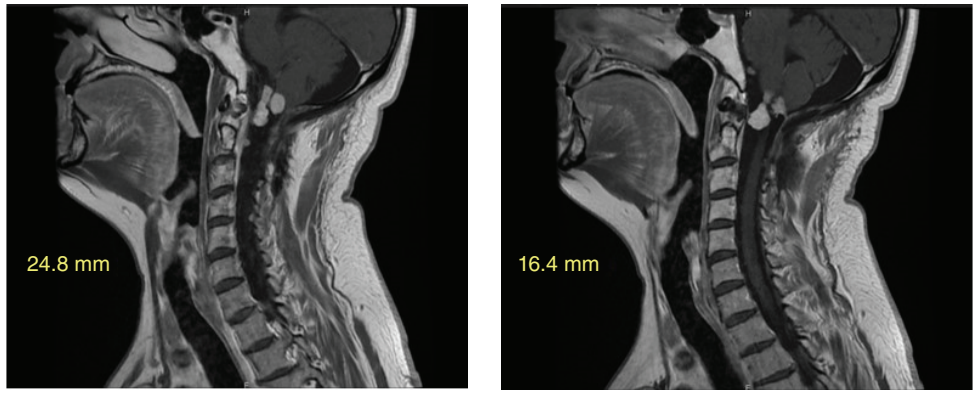

Figure 3. August 2020: adjacent slices from T1 MRI sequences showing response of cervical lesions to trabectedin (× 19 cycles).

Table 1. Comparison of outcomes from a retrospective analysis of patients with advanced soft tissue sarcoma treated with trabectedin and a *post hoc* analysis of those with rare or ultra-rare advanced sarcomas.

	Objective response rate (%)	Stable disease (%)	Disease control rate (%)	Ref.
Advanced soft tissue sarcoma (n = 512)	13.7	33.0	46.7	[18]
Rare or ultra-rare advanced sarcomas (n = 36)	11.4	34.3	45.7	[19]
Advanced solitary fibrous tumor (n = 11)	18.2	36.4	54.5	[19]

Systemic agents with activity in locally advanced or metastatic SFT are mainly cytotoxics and antiangiogenics [16]. Three retrospective analyses have reported promising activity with trabectedin. Sixty-eight patients with SFT of the pleura were followed from initial surgical resection through to chemotherapy for advanced disease [17]. Beyond first-intent chemotherapy with mainly doxorubicin-based regimens in 11 patients, 12 different second- and third-line regimens were administered. Of these, trabectedin (as second-line [n = 1] or third-line therapy [n = 8]) produced the highest disease control rate (78%). The median time to progression of 3.4 months was comparable to that reported for other STS histologies [18]. The French Sarcoma Group identified 11 patients with advanced SFT, mainly from the RetrospectYon database, who had received trabectedin as second-line (n = 8) or at least third-line (n = 3) therapy. One patient (9.1%) had a RECIST partial response and eight patients (72.7%) had stable disease, for a disease control rate of 81.8%. After a median follow-up of 29.2 months, median progression-free survival was 11.6 months and median overall survival was 22.3 months [19]. More recently, the Italian Sarcoma Group retrospectively analyzed 512 patients with advanced STS who were treated with trabectedin after the failure of ≥1 anthracycline-based regimen [20]. Patients received a median of four trabectedin cycles (range: 1–40), mostly as a second-line treatment (~60% of patients). A *post hoc* analysis conducted to evaluate outcomes in patients (n = 36) with rare or ultra-rare sarcomas found that outcomes for the subgroup with SFT (n = 11) compared favorably with those for all patients with advanced STS and with those for all patients with rare or ultra-rare sarcomas (Table 1) [21].

Given the rarity of SFT, patient-derived SFT mouse xenograft models have been used to predict tumor sensitivity to potentially effective monotherapy or combination regimens. In a study that compared the activities of doxorubicin, dacarbazine and ifosfamide (administered singly or in combinations), trabectedin and eribulin in two models of dedifferentiated SFT, the doxorubicin + dacarbazine combination proved most effective, producing >80% tumor volume inhibition in both models. Trabectedin and eribulin also showed a high level of activity [22]. A prospective phase II clinical study is currently in progress comparing doxorubicin + dacarbazine with trabectedin in patients with advanced SFT (ClinicalTrials.gov identifier: NCT03023124) [23].

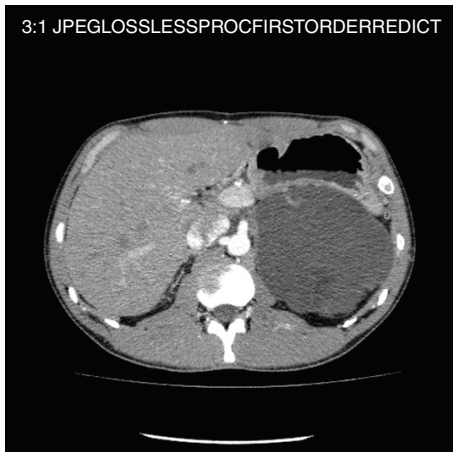

Figure 4. March 2007: Computerized tomography scan showing unresectable recurrence of a retroperitoneal myxoid/round cell liposarcoma in a young, male patient, which had doubled in size (from 5 cm to 11 cm) over 5 months.

Case 3: long-term stable disease in a young, active patient with recurrent, nonresectable, retroperitoneal grade 3 myxoid/round cell liposarcoma treated with trabectedin & watchful waiting

A 19-year-old male triathlete without comorbidities was diagnosed in December 2005 with retroperitoneal grade 3 myxoid/round cell liposarcoma measuring 15 cm at the largest diameter. He received doxorubicin-ifosfamide neoadjuvant chemotherapy followed by R1 surgery.

In November 2006, he had an unresectable retroperitoneal recurrence. As the 5 cm tumor was asymptomatic, with no signs of local compression or risk of complication, the chosen strategy was watchful waiting. By March 2007, the tumor had doubled in size to 11 cm (Figure 4).

The patient received trabectedin (× 14 cycles) from March 2007 to March 2008. PET of the tumor after nine, 11 and 13 cycles of treatment showed stable disease (Figure 5). Trabectedin was well tolerated with only two postponements (cycle 10 and cycle 12) due to grade 2 adverse events (nonsymptomatic increase in liver enzymes × 5 normal, increase in creatine phosphokinase × 3 normal). However, due to the recurrence of grade 2 hepatitis and in consultation with the patient, it was decided to stop trabectedin and administer consolidative radiotherapy. The patient refused surgery for residual lesions because of his sporting activity.

Definitive radiotherapy (54 Gy) was administered from April to June 2008, followed by watchful waiting until July 2009. PET after radiotherapy showed maintained stable disease. A CT scan of the thorax, abdomen and pelvis 3 months later (September 2009) showed a slight increase in tissue mass compared with the previous PET scan.

Over the 2-year time frame (1 year of trabectedin and 1 year of watchful waiting), the patient maintained an excellent Eastern Cooperative Oncology Group performance status and was able to continue his sporting activities, participating in national and international triathlon competitions.

A CT scan in February 2010 showed overall volumetric stability of the left retroperitoneal mass; however, a left median mesenteric formation of 38 mm in diameter was detected. A CT scan 4 months later (July 2010) indicated progression of the mesenteric lesion. In August 2010, the patient's tumor progressed rapidly and was resistant to sorafenib. He received palliative care and died in March 2011 at the age of 25.

Clinical interpretation

Chromosomal translocations occur in about 20% of sarcoma cases [24]. Myxoid-round cell liposarcoma is characterized by a t(12;16)(q13;p11) translocation or, less commonly, a t(12;22)(q13;q12) translocation, which results in expression of *FUS-DDIT3* and *EWS-DDIT3* fusion genes, respectively [24]. The activity of trabectedin in myxoid liposarcoma appears to derive from its ability to counteract the biological activity of the chimeric *FUS-DDIT3* oncoprotein [24].

The activity of trabectedin in myxoid/round cell liposarcoma is well reported and formed the basis for treatment selection in this patient. Retrospective analyses in patients with advanced pretreated myxoid liposarcoma reported tumor control rates of up to 90% and prolonged survival (Table 2) [25–29]. The patient in this case achieved durable stable disease with trabectedin, which was maintained after consolidative radiotherapy. In this case, the recurrence of hepatitis was a reason to stop trabectedin as per the approved label.

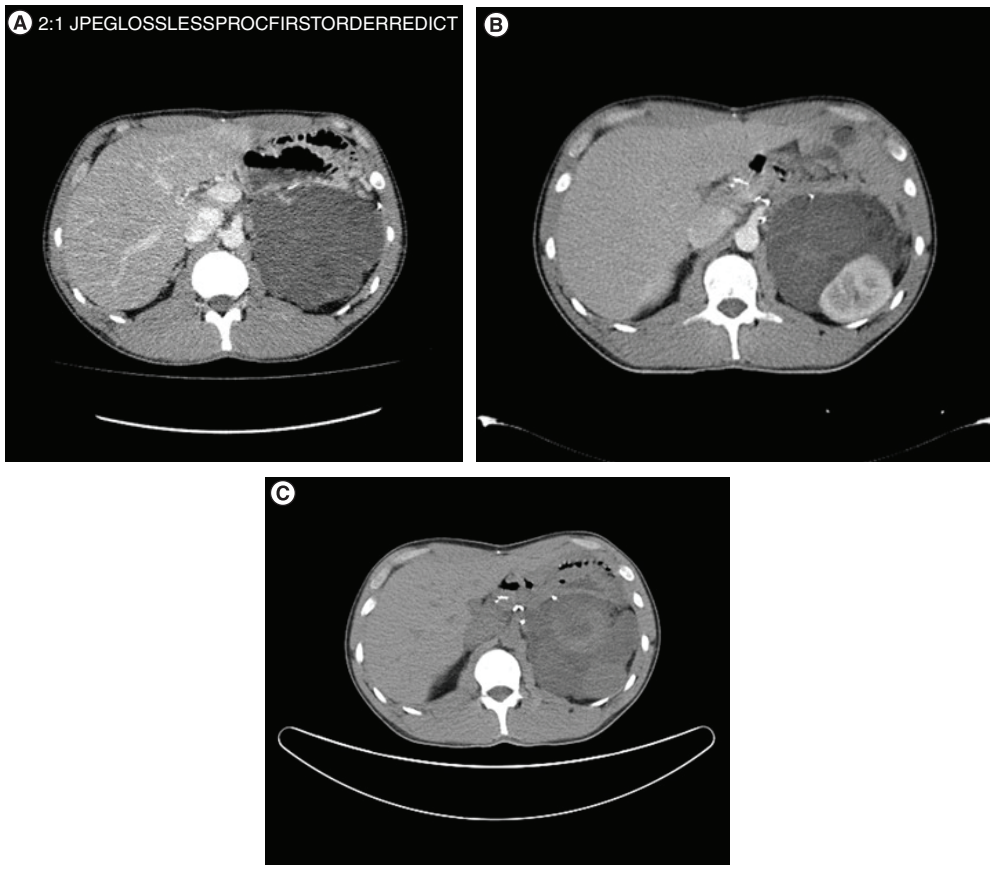

Figure 5. PET scans during treatment with trabectedin. (A) August 2007: after nine cycles of trabectedin. Single focus of pathological fixation in a nodular formation in contact with the diaphragm. Standardized uptake value (SUV) max = 8.8. Absence of fluorodeoxyglucose (FDG) uptake in the large pre- and suprarenal abdominal mass of 10.5–11 cm in diameter. **(B)** October 2007: after 11 cycles of trabectedin. The voluminous left prerenal tumor mass (10 cm in diameter) hardly fixes FDG. SUV max = 1.7. Only a nodular component immediately subdiaphragmatic left significantly fixes FDG. Estimated SUV max = 2.7, similar to previous scan (August 2007), taking into account the lack of correction for respiratory movements. **(C)** January 2008: after 13 cycles of trabectedin. Persistence of voluminous left prerenal tumor mass (11.3 cm on cross section vs 10 cm), with low FDG uptake. SUV max = 2 (vs 1.7). Uptake is heterogeneous, with centrolesional necrosis. Persistent fixation focus of the nodular component of the upper part of this mass (immediately left subdiaphragmatic): SUV max = 3.6 (vs 2.7). On uncorrected images, this nodule does not appear to be significantly changed.

Table 2. Outcomes of retrospective analyses investigating the efficacy of trabectedin in patients with advanced pretreated myxoid liposarcomas.

Author	Patients (n)	Median follow-up	Objective response rate (%)	Disease control rate (%)	Median progression-free survival (months)	Progression-free survival at 6 months (%)	Median overall survival (months)	Ref.
Grosso *et al.* 2007	51	14.0 months	51	90	14.0	88	–	[25]
Grosso *et al.* 2007	32[†]	24.8 months	50	90	17	90	Not reached	[26]
Le Cesne *et al.* 2012	27	–	15	67	9	64	18	[27]
Blay *et al.* 2013	28	6 years	21	75	10.5	–	33.4	[28]
Kobayashi *et al.* 2019	22		31.8	–	17.4	–	27.6	[29]

[†]Includes 31 patients reported originally in Grosso *et al.* 2007 [25].

Conclusion

Cumulative clinical experience with trabectedin has informed its better use within the treatment sequence in patients with aSTS. Although no externally validated prognostic/predictive factors (e.g., age, sex) of long-term response

to trabectedin have been identified, superior outcomes have been recorded in certain histotypes (e.g., myxoid liposarcoma), with second- versus later-line use and with continuous versus interrupted treatment until disease progression, unacceptable toxicity or impairment in any organ function. Indeed, in patients with histologies sensitive to trabectedin, second-line use offers the possibility of prolonged stable disease and even partial or complete responses in certain cases. The manageable safety profile of trabectedin can allow patients to maintain their daily activities, including intense physical activity, and preserves the excellent performance status that many patients continue to exhibit in the second-line setting. Looking forward, a new prognostic tool, which combines several objective parameters to predict response to systemic therapy, may have value in identifying patients with better expected outcomes with trabectedin.

Summary points

- Clinical practice guidelines recommend trabectedin as a second-line option for patients with advanced soft tissue sarcoma (aSTS).
- As clinical experience with the use of trabectedin accumulates, a trend is apparent for an increasing proportion of patients to receive six or more continuous cycles.
- This article describes three patients with aSTS who achieved long-lasting responses with second-line trabectedin.
- A woman with unresectable metastatic leiomyosarcoma involving extension to the liver, lung and thigh (Case 1) achieved disease control for more than 2 years with trabectedin (× 41 cycles) and was able to continue with her daily activities (including intensive job-related physical activity). Time to progression with trabectedin was more than four-times that achieved with first-line doxorubicin-based chemotherapy.
- A male patient with metastatic solitary fibrous tumor of the cervical region and lung lesions (Case 2) achieved stable disease (including marked reduction of cervical lesions) and improved quality of life with trabectedin. At the time of writing, he had received 30 cycles and treatment was ongoing.
- Over a 2-year period that involved trabectedin (× 14 cycles), radiotherapy and 1 year of watchful waiting, a young man with a recurrent, unresectable, retroperitoneal grade 3 myxoid/round cell liposarcoma (Case 3) maintained an excellent performance status and was able to participate in national and international triathlon competitions.
- Trabectedin has been shown to reduce tumor density, suggesting that Choi criteria may provide more information about trabectedin efficacy than dimensional criteria measured by Response Evaluation Criteria in Solid Tumors in patients with aSTS.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patients for inclusion of their medical and treatment histories within these case reports. Case 1: the patient provided written informed consent for anonymized use of clinical data and radiological imaging. Case 2: the patient provided written informed consent for anonymized use of clinical data and radiological imaging. Case 3: the patient provided written informed consent for anonymized use of clinical data and radiological imaging.

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