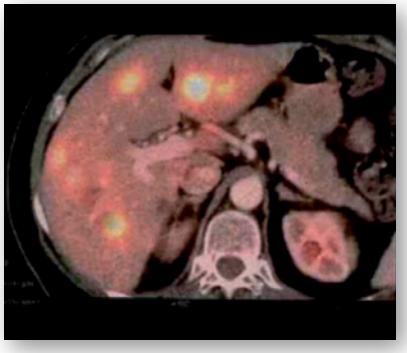

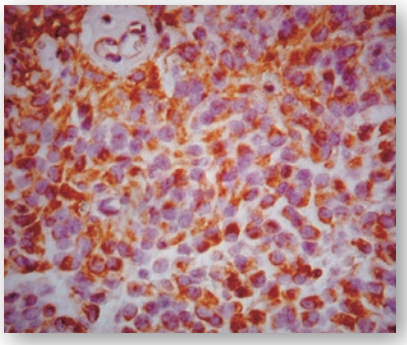

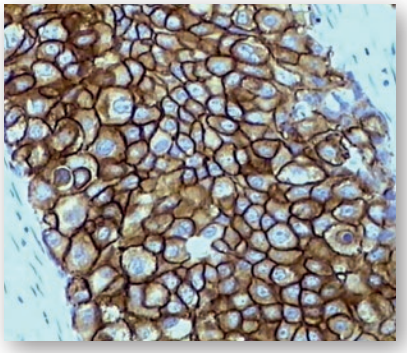

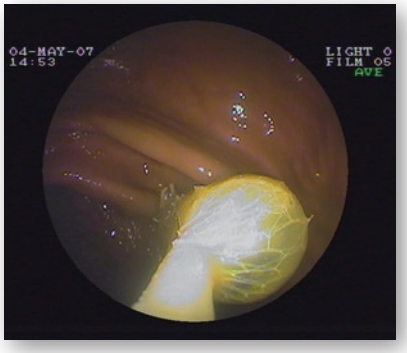

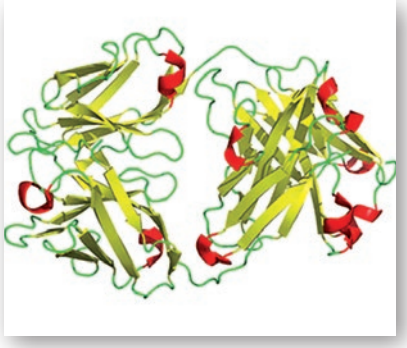

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Trabectedin in uterine sarcomas: Review of literature data and clinical experience

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Sarcomas: the most lethal type of uterine cancer

Uterine sarcomas represent 3% of all malignant tumors found in the uterus, being a relatively rare disease with 0.5-1 new cases for every 100,000 women per year[1]. They include uterine leiomyosarcomas (uLMSs, 63%), endometrial stromal sarcomas (ESSs, 21%), high-grade undifferentiated sarcomas (HG-USs, 5%), adenosarcomas (ASs, 6%), and other rare malignancies (5%; Fig. 1). Uterine sarcomas can collectively be considered the most lethal forms of malignant cancer affecting the uterus, with a 5-year life expectancy that ranges from 25 to 68% of cases, depending on the histological subgroup and the stage[1].

The management of uterine sarcomas is complex and presents numerous challenges during the different stages of the disease[1]:

- In the pre-operative setting, a distinction must be made between benign and potentially malignant lesions.
- Subsequently, an assessment of molecular characteristics is required to identify high-risk patients.
- Finally, it must be decided whether or not to administer adjuvant therapy and the sequence of the most appropriate therapeutic regimens in the different treatment lines.

The rarity of the disease, the varied nature of the histological variants, and the difficulty of conducting randomized clinical trials in specialized clinical settings (adjuvant therapy/early-stage radiotherapy) make the therapeutic approach difficult and often lead to heterogeneous management of patients in the clinical practice[1].

As it is clearly stated by ESMO guidelines on soft tissue sarcoma (STS), a multidisciplinary approach is mandatory in all sarcoma cases and its management should be carried out in reference centers and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually[2]. The best chance of cure is at primary presentation. An individualized management plan should be made, following a multidisciplinary sarcoma case discussion based on both imaging and pathological findings. The standard treatment of primary lesions is surgery, to be carried out by a surgeon with specific sarcoma expertise[2].

The Italian Society of Gynecology and Obstetrics (SIGO) has recently published a consensus on management of uterine sarcomas. When dealing with localized uterine sarcoma, the surgical approach recommended by the consensus is total hysterectomy with bilateral salpingo-ovariectomy (Table 1)[1]. Lymphadenectomy is not indicated in cases without macroscopic involvement of the lymph nodes.

In premenopausal patients suffering from leiomyosarcoma with apparently normal ovaries, bilateral salpingo-ovariectomy and lymphadenectomy can be avoided. In fact, as confirmed by two extensive data collections, avoiding these two procedures in ≤ 51-year-old women does not affect survival[1].

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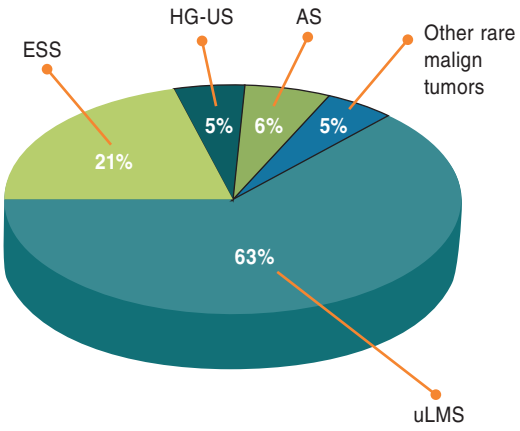

Figure 1. *Subtypes of uterine sarcoma and their frequency. uLMS: uterine leiomyosarcomas; ESS: endometrial stromal sarcomas; HG-US: high-grade undifferentiated sarcomas; AS: adenosarcomas* (adapted from Ferrandina et al., 2020)[1].

According to some authors, in young premenopausal women with low-grade ESSs, ovarian preservation should be considered on an individual basis, given the uncertain benefits of bilateral salpingo-ovariectomy and the side effects of hormonal castration; in these circumstances, estrogen replacement therapy appears to be unfavorable for women who have previously undergone hysterectomy for the same diagnosis.

There is no evidence to support fertility-preserving surgery and it should not be regarded as a standard procedure, although it can be considered in highly selected cases. In high-grade ESSs, HS-US, and AS presenting with sarcomatous overgrowth, fertility-preserving surgery is not advisable due to poor clinical outcomes[1].

Focus on leiomyosarcoma, the most common uterine sarcoma

Leiomyosarcoma accounts for approximately 15-20% of all STS[3] and can be classified as non-uterine or uterine (each one representing 50% of all leiomyosarcoma cases). As with many sarcoma subtypes, patients may have non-specific symptoms. Leiomyosarcoma can be a particularly aggressive phenotype, with approximately half of patients developing long-term metastases despite optimal treatment of localized disease[3].

Doxorubicin-based chemotherapy is the standard first-line treatment for leiomyosarcoma[3]. In this setting, the prospective randomized Phase III GeDDiS trial showed that gemcitabine plus docetaxel had no advantage over doxorubicin alone in the overall population of patients with advanced or metastatic STS nor in the subgroup with uterine or non-uterine leiomyosarcoma[4]. Importantly, gemcitabine and docetaxel combination was more difficult to deliver (more treatment interruptions, more dose reductions, and a lower dosage rate) and was associated with greater toxicity and a worse global health status than doxorubicin[4].

In leiomyosarcoma, the activity of ifosfamide is unconvincing based on the available retrospective evidence, with a significantly reduced overall survival (OS) compared with doxorubicin ($p = 0.0247$)[5].

Recently, an extensive retrospective analysis of the first-line treatment of patients with advanced leiomyosarcoma has been published[6]. The study involved 303 leiomyosarcoma patients treated at 18 reference institutions within the EORTC-STBSG from nine European countries: 39% of the patients were treated with doxorubicin plus dacarbazine, 23% with doxorubicin plus ifosfamide, and 38% with doxorubicin monotherapy.

Treatment with doxorubicin in combination with dacarbazine resulted in a median progression-free survival (PFS) of 9.2 months, with respect to 8.2 months with doxorubicin plus ifosfamide, and 4.8 months with doxorubicin alone (Fig. 2). Data on the overall response rate (ORR) also favored the doxorubicin plus dacarbazine regimen (30.9%), compared with doxorubicin alone (25.6%) and doxorubicin plus ifosfamide (19.5%).

As emphasized by the authors of the study, doxorubicin and dacarbazine showed favorable activity in terms of both ORR and PFS and warrant further investigation in prospective studies[6].

Table 1. *SIGO consensus on the surgical approach to early-stage uterine sarcomas*

Summary of recommendations for early disease	LoE	GoR	Consensus (%)
The preferred surgical treatment for uterine leiomyosarcoma is total hysterectomy + bilateral salpingo-oophorectomy	C	Positive strong	100
Lymphadenectomy is not indicated in patients without macroscopically involved lymph nodes	D	Negative strong	100
Morcellation must be avoided	B	Negative strong	100
Bilateral ovary salpingectomy can be avoided in premenopausal women with apparently normal ovaries in uterine leiomyosarcoma	D	Positive weak	100
Conservative surgery (uterine preservation after tumorectomy) can be considered in highly selected women with Stage IA disease who desire to preserve childbearing potential managed at referral centers in leiomyosarcoma, low-grade endometrial stromal sarcoma, or adenosarcoma without sarcomatous overgrowth	D	Positive weak	100
Conservative surgery is not considered in high-grade endometrial stromal sarcoma or high-grade undifferentiated sarcoma or adenosarcoma with sarcomatous overgrowth	D	Positive strong	100

LoE: level of evidence (A: based on one systematic review or at least two independently conducted research projects; B: based on at least independently conducted research projects within concordance; C: based on one independently conducted research project or at least two trials within concordance; D: based on one trial or multiple expert opinions). GoR: grade of recommendation.
Adapted from Ferrandina et al., 2020[1].

After failure of anthracyclines, agents commonly used to treat advanced leiomyosarcoma are trabectedin-, pazopanib-, and gemcitabine-based regimens.

One Phase II study showed that gemcitabine/docetaxel was more effective than gemcitabine alone in patients with advanced STS (30% of leiomyosarcoma patients), showing improved both median PFS (6.2 vs. 3.0 months) and median OS (17.9 vs. 11.5 months), but at the expense of a significant increase in toxicity (40% of discontinuations due to adverse events associated with the combination)[7]. The results of the previous study pointed to a possible superiority of the combination in patients with leiomyosarcoma (together with positive results of a single-arm Phase II study performed with gemcitabine-docetaxel in uterine leiomyosarcoma)[8], however, this superiority was not confirmed in a later randomized trial conducted in leiomyosarcoma only[2]. Results of this study[9] showed no advantage of gemcitabine plus docetaxel over gemcitabine alone: median PFS was 3.4 months versus 6.3 months in extrauterine patients and 5.5 months versus 4.7 months in uterine patients, respectively[3,9]. As expected, toxicity was higher with the combination of gemcitabine and docetaxel in both trials[2]. According to the conclusions of a pooled analysis carried out from both studies[10], gemcitabine and docetaxel combination does not significant improve response rate or PFS in metastatic leiomyosarcoma[3].

Pazopanib was compared to placebo in a randomized Phase III study performed in advanced STS[11]. In the subgroup of 168 leiomyosarcoma patients, active treatment prolonged median PFS (4.9 vs. 1.9 months) but had no significant impact on survival (median OS 16.7 vs. 14.1 months, respectively)[3,11]. The lack of efficacy in terms of survival can be attributed to a "rebound effect" that accelerates disease progression when treatment with pazopanib is discontinued[3]. A Kaplan–Meier estimate of post-progression survival suggested shorter median OS in the pazopanib versus placebo arm[3,12]. This possibility of rapid tumor growth after treatment discontinuation, along with the frequent resistance by patients to receive intravenous therapy after receiving oral therapy, tends to position pazopanib as a treatment choice for later lines[13].

Trabectedin as second-line treatment of leiomyosarcoma

Trabectedin is indicated for the treatment of adult patients with advanced STS, after failure of anthracyclines and ifosfamide, or as frontline therapy for patients who are unsuited to receive these agents. The ESMO-EURACAN Clinical Practice Guidelines for the management of STS recommend trabectedin as second-line treatment of STS[2].

Specifically in leiomyosarcoma, the efficacy and safety profile of trabectedin have been assessed in numerous clinical trials and real-life studies:

– In a randomized Phase III trial comparing trabectedin with dacarbazine, the median PFS in the leiomyosarcoma patient group (423

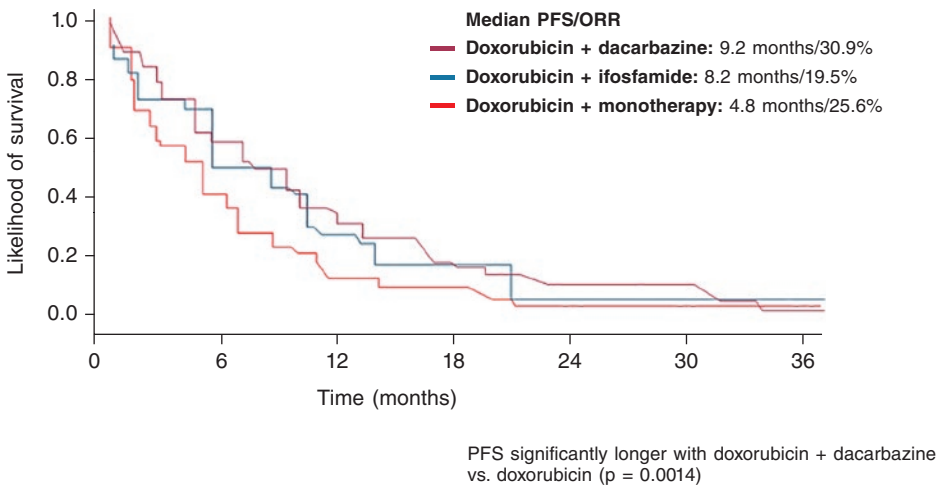

Figure 2. *First-line treatment of leiomyosarcoma: recent retrospective data. PFS: progression-free survival; ORR: overall response* (adapted from D'Ambrosio et al., 2020)[6].

cases) was 4.3 and 1.6 months, respectively, showing a statistically significant superiority in favor of trabectedin ($p < 0.001$)[14].

- Large "real-life" studies have reported specific efficacy data with trabectedin in advanced leiomyosarcoma:
  - A retrospective analysis performed by the French Sarcoma Group revealed a median PFS of 5.5 months, with a 3-month PFS rate of 69% and a median OS of 15.1 months in 321 leiomyosarcoma patients treated with trabectedin[15].
  - In the trabectedin worldwide expanded access program study, a median OS of 16.2 months was observed in 318 leiomyosarcoma patients[16].

Regarding uterine leiomyosarcoma in particular, the efficacy of trabectedin has also been extensively evaluated:

- In the subgroup of 232 uterine leiomyosarcoma patients included in the previously described randomized Phase III study[14], trabectedin treatment was beneficial in terms of median PFS (4.0 vs. 1.5 months; $p = 0.0012$; Fig. 3) and clinical benefit rate (complete responses + partial responses + stable disease for at least 18 weeks: 31% vs. 18%; $p = 0.05$)[17].
- In a recent Phase II study, a median PFS of 4.1 months and a median OS of 20.6 months were achieved in 115 uterine leiomyosarcoma patients treated with trabectedin[18].
- A retrospective case series analysis from two reference centers showed activity with trabectedin treatment in 66 uterine leiomyosarcoma patients who had failed a median of three previous cytotoxic lines. All patients had received prior treatment with anthracycline ± ifosfamide and gem ± docetaxel was also previously administered in 87% of cases. Trabectedin treatment resulted in a median PFS of 3.3 months and a median OS of 14.4 months. Tolerability to trabectedin was good, without cumulative toxicities[19].
- A recent retrospective multicenter study analyzed 36 women with metastatic uterine leiomyosarcoma treated with trabectedin in 11 Spanish centers following administration of anthracyclines[20]. This analysis conducted by the Spanish Ovarian Cancer Research Group (GEICO) reflects the results obtained using trabectedin according to the marketing authorization in the real-life setting.

The use of trabectedin resulted in a median PFS (primary endpoint) of 5.4 months and a median OS of 18.5 months. The ORR (27.8%) and the disease control rate (77.8%), exceeded expectations according to the authors, being highly significant, even compared with the results reported in the previously described randomized Phase III[17] (Median PFS: 4 months, median OS 13,4 months, and ORR: 11%)[20].

The efficacy outcomes of this real-life analysis are the most recent available data with trabectedin in uterine leiomyosarcoma and are largely comparable to results shown in previous clinical studies (Table 2), confirming the ability of trabectedin to provide long-term tumor stabilization with a good tolerability profile[20].

The importance of using trabectedin as second-line therapy (or as first line in patients unsuited to standard treatment), rather than

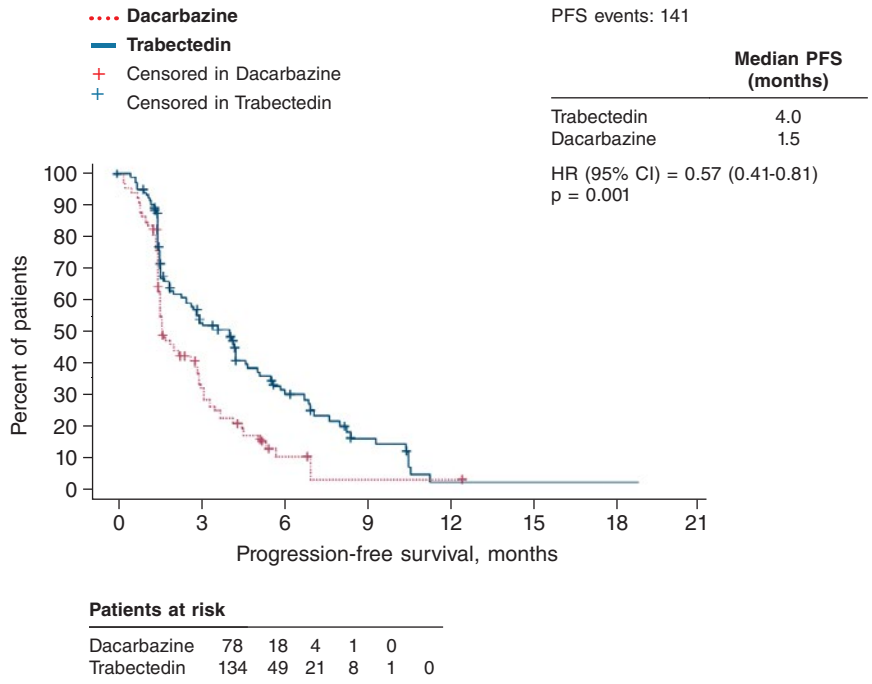

Figure 3. *Uterine leiomyosarcoma: progression-free survival with trabectedin versus dacarbazine* (adapted from Hensley et al., 2017)[17].

more advanced lines, was reflected in the significantly higher OS observed with an early administration of trabectedin in the advanced disease (Fig. 4)[20].

Along with the administration of trabectedin in the initial lines, a good ECOG PS at trabectedin administration and localized disease at initial diagnosis was also indicators of better results (Table 3)[2].

Based on the results described, the authors concluded that trabectedin provides clinical benefit with a manageable safety profile to patients with recurrent/metastatic uterine leiomyosarcoma, after anthracycline failure and especially when administered in early lines[20].

To better illustrate the effects of trabectedin on the reality of uterine leiomyosarcoma management, a clinical case is described below.

Clinical case: prolonged treatment with trabectedin as 2nd line therapy of elderly patient with uterine leiomyosarcoma

Clinical scenario

In August 2014, a 68-year-old woman was subjected to instrumental tests to determine the cause of painful abdominal discomfort and the appearance of hacking cough.

A thoracoabdominal-pelvic computed tomography (CT TAP) showed a 12 mm nodule in the anterior segment of the right lung, two solid formations of 45 mm and 78 mm at the base of the right lower lobe, two formations of 10 mm and 7 mm in liver segment VI, and a solid 34 mm neoformation in the right adrenal gland (Fig. 5). The adnexa appeared enlarged.

The uterus appears enlarged due to the presence of myomatous nodules, the largest being 5 cm.

Hysterectomy and bilateral adnexectomy were performed in October 2014.

Histological examination

Uterine leiomyosarcoma with vascular invasion and extension to the bilateral periadnexal and right paracervical soft tissues. Diffuse atypical features of moderate to severe degree, areas of tumor necrosis. Average mitotic index of 9/10 HPF (high-power fields), infiltrative margins.

Immunophenotypic profile

Positive for smooth muscle actin, desmin, caldesmon, ER, P16, CD 10 (weak and focal). Negative for PgR. Ki67:34%.

Table 2. *GEICO real-life study in context with prospective clinical data with trabectedin in uterine leiomyosarcoma*[20]

Studies	Number of patients (n)	Median age years (range)	ECOG PS score 1/2 (%)	CR (%)	PR (%)	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)
Phase II study Gadducci et al., 2018	115*	57 (34-76)	100.0	7.0	16.5	23.4	60.8	4.1	20.6
Phase III study Hensley et al., 2017	232	54 (27-81)	100.0	0.0	11.0	11.0	31.0	4.0	13.4
Real-world outcomes Rubio et al.	36	54 (29-68)	92.9	2.8	25.0	27.8	77.8	5.4	18.5

CR: complete response; DCR: disease control rate; ECOG: Eastern Cooperative Oncology Group; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; PS: performance status.
*Population per protocol.
Adapted from Rubio et al., 2020[20].

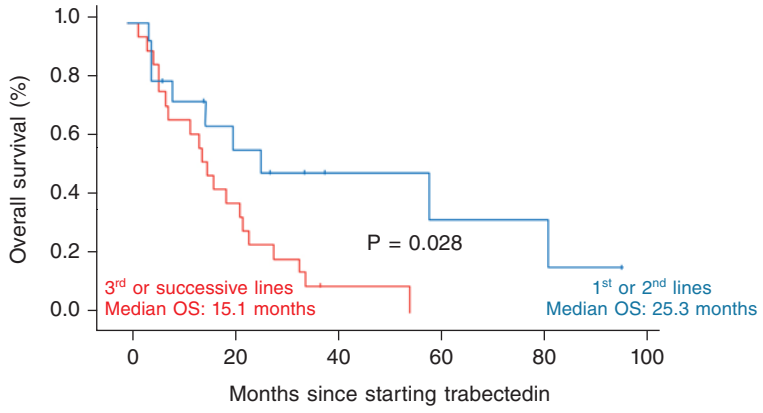

Figure 4. *Overall survival since starting trabectedin treatment in uterine leiomyosarcoma patients considering treatment line* (adapted from Rubio et al., 2020)[20].

Diagnosis

Uterine leiomyosarcoma with pulmonary, hepatic, and adrenal sites (Stage IV).

First-line chemotherapy

Anthracycline-based chemotherapy for a total of 7 cycles from November 2014 to May 2015.

Imaging

In May 2015, CT TAP showed an increase in the target lesions.

Chest

Increase in the pulmonary nodule in the anterior segment of the left upper lobe (15 × 14 mm vs. 10 × 11 mm); enlarged nodule in the posterior basal segment of the right lower lobe (7.8 × 6.8 cm vs. 7.1 × 5.8 cm).

Abdomen

The small 7 mm hypodense formation in liver segment VI and the nodular lesion in the right adrenal gland remained unchanged. Minimal enlargement of some lymphadenopathies at the root of the

Table 3. *Survival analysis considering key characteristics of patients or treatments (data from GEICO real-life study)*[20]

	Since trabectedin treatment			Since diagnosis		
	Progression-free survival	p	Overall survival	p	Overall survival	p
Median line of trabectedin treatment of advanced disease						
1st-2nd (n = 15)	5.4 (0.0-11.1)	0.470	25.3 (0.0-66.7)	0.028	87.4 (22.6-152.1)	0.310
3rd or successive (n = 21)	5.7 (3.8-7.7)		15.1 (10.9-19.2)		44.7 (42.4-47.0)	
ECOG at trabectedin start*						
0-1 (n = 28)	5.4 (3.7-7.0)	0.260	19.8 (12.9-26.7)	0.013	46.0 (32.7-59.9)	0.930
2-3 (n = 4)	3.1 (1.7-4.5)		6.0 (2.4-9.6)		30.0 (28.1-31.9)	
Disease at diagnosis						
Localized (n = 19)	3.1 (0.0-6.9)	0.410	21.1 (11.1-31.2)	0.130	87.4 (28.2-146.5)	0.041
Locally advanced (n = 4)	3.0 (1.4-4.6)		4.1 (0.4-7.9)		30.0 (0.0-68.8)	
Metastatic (n = 13)	6.8 (3.9-9.8)		18.5 (8.0-29.1)		44.0 (19.4-68.6)	

Adapted from Rubio et al., 2020[20].

mesentery (particularly one in the mesogastrium and one in the left para-aortic site). Minimal fluid layer in pouch of Douglas.

Second-line chemotherapy

Treatment with trabectedin for a total of 29 cycles from July 2015 to June 2017. The treatment, administered with adequate corticosteroid premedication, was well tolerated and the patient's quality of life was good. A dose adjustment was required due to Grade 2 neutropenia. No hepatotoxicity was detected. During the first few cycles, the patient needed additional antiemetic therapy during 2-3 days following the infusion (Table 4).

Imaging

In June 2017, the patient underwent a chest CT TAP that revealed the appearance of small pulmonary parenchymal nodules, minimal increase in nodular formation with arteriovenous malformations (AVM) in the lower right lung lobe, and solid tissue in the left para-aortic site compatible with lymph node aggregates.

Third-line chemotherapy

Gemcitabine and docetaxel chemotherapy for a total of 7 cycles from August 2017 to February 2018.

Imaging

The patient underwent a new CT TAP in February 2018.

Chest

Increase in size of the lesion containing AVM in the posterior basal segment of the right lower lobe (57 × 30 mm vs. 43 × 24 mm). No change in the size of the mass in the lateral segment of the lower right lobe, in which the vascular lesion could no longer be recognized. The lymph node conglomerate in the left para-aortic site was reduced.

Fourth-line chemotherapy

The patient was treated with anastrazole from March 2018 to January 2019.

Imaging

A CT TAP in September 2018 showed a radiological picture of slow disease progression.

The patient died in March 2019 from a cerebral hemorrhage.

Case conclusions

Trabectedin proved to be an appropriate second-line therapy for this elderly patient with advanced

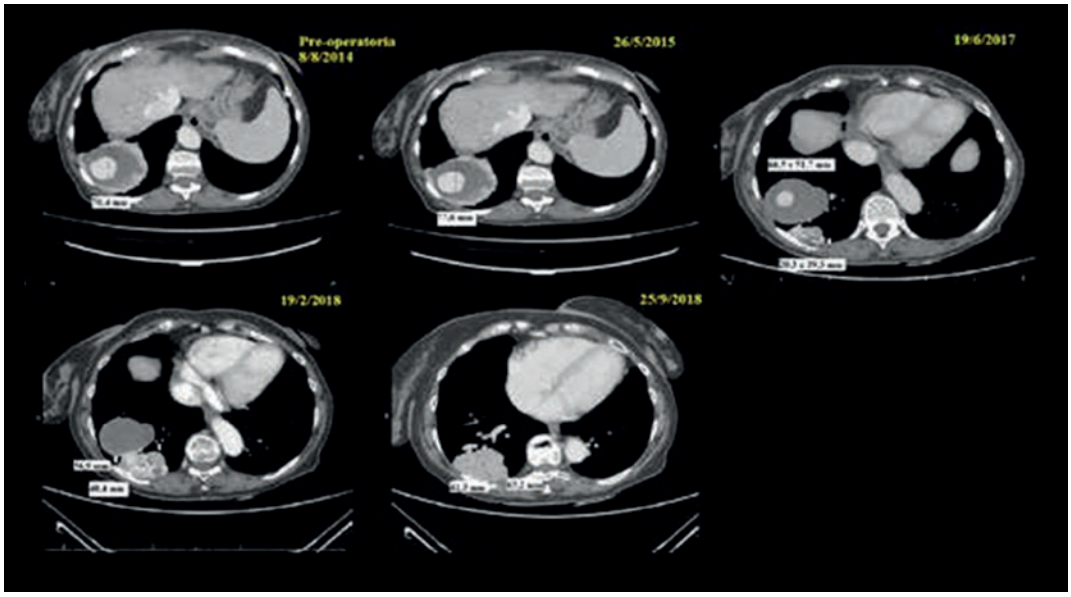

Figure 5. *Sequence of thoracoabdominal-pelvic computed tomography scans from August 2014 to September 2018.*

Table 4. *Trabectedin administration schedule used*

Premedication with dexamethasone 4 mg PO 2 times/day on day -1
Trabectedin: 1.5 mg/m^2 24 h IV infusion q3w by CVC
Premedication with dexamethasone 20 mg IV, 30 min before infusion
Growth factor supplement (pegfilgrastim) on day 2 post-chemotherapy
Dexamethasone 4 mg PO 1 time/day on days 2 and 3 and antiemetic prophylaxis

uterine leiomyosarcoma, providing prolonged tumor control for over 2 years with a good safety profile combined with a preserved quality of life.

Prolonged tumor control and preserved quality of life associated with trabectedin treatment in uterine leiomyosarcoma

The long-term benefit provided by trabectedin in the previous case (29 cycles) has also been observed in other two uterine leiomyosarcoma patients treated at the same hospital (Spedali Civili in Brescia), who achieved 8 years of survival from primary diagnosis and over 3 years after discontinuation of trabectedin (Table 5). Moreover, Table 6 summarizes several significant clinical cases found in the literature in which long-term tumor control is also observed with trabectedin treatment in uterine leiomyosarcoma patients.[21]

The prolonged disease control that is frequently observed indicates that trabectedin is capable of controlling tumor cell growth due to its ability to produce an oncostatic effect rather than the purely cytotoxic effect previously associated with this drug.

Trabectedin presents a complex mechanism of action affecting key cell biology processes in tumor cells as well as in the tumor microenvironment[22]. Trabectedin binds to the minor groove of the DNA, inducing DNA damage that triggers the nucleotide excision repair (NER) pathway. Bound trabectedin protrudes from the DNA helix and blocks several DNA-binding molecules, including transcription factors and proteins involved in the NER pathway. This prevents the trabectedin-induced DNA damage from being repaired and results in the formation of double-strand breaks, which subsequently lead to cell death[23]. In the tumor environment, trabectedin

Table 5. *Summary of the treatment pathways of three uterine leiomyosarcoma patients treated at the Spedali Civili in Brescia*

No.	Age	Diagnosis	Start of therapy	Stage	1st line	2nd line	Trabectedin cycles	3rd line	OS (months)
1	68	uLMS	11/2014	IV	Ifo/ epi	TRAB 26/6/17	29	Gem/ doc	55
2	46	uLMS	03/2012	I	Ifo/ epi	TRAB 30/1/18	18	Gem/ doc	105
3	40	uLMS	05/2012	I	Ifo/ epi	TRAB 28/3/18	13	Pazo	103

uLMS: uterine leiomyosarcoma; Ifo: ifosfamide; epi: epirubicin; TRAB: trabectedin; Gem: gemcitabine; doc: docetaxel; Pazo: pazopanib. Author's records data.

Table 6. *Case reports in the literature considering the results of trabectedin therapy in metastatic uterine leiomyosarcoma*[21]

Authors year	Sarcoma type	Patients n	Cycles of trabectedin	Response
Tavella et al., 2017	Metastatic uLMS	1	30 cycles	Very good partial response, especially at the pulmonary and pancreatic levels, stable disease at the rest of metastatic sites
Bongiovanni et al., 2015	Metastatic uLMS	1	22 cycles	Partial response with good tolerability, maintenance of the response for 10 months after trabectedin withdrawal
Corrado et al., 2011	Metastatic uLMS	1	6 cycles	Prolonged clinical response in a heavily pretreated patient with lung metastases of uLMS, improvement of dyspnea symptoms, and acceptable toxicity profile
Amant et al., 2009	Three patients with uLMS, one with uterine adenosarcoma, one with endometrial stromal sarcoma	5	25 cycles were administered (mean = 5; range: 2-12)	Partial response with clinical benefit was noted during 9 months in one patient (partial response in an epigastric mass and lung metastasis), whereas stable disease after 3 months was noted in 1 patient and progressive disease in 3 patients Taken together, the response rate was 1 out of 5 for all patients, and one out of three uLMS responded
Tewari et al., 2006	Metastatic uLMS	1	12 cycles	A 38-year-old patient with and advanced, recurrent, and refractory uLMS (lung metastasis, pelvic progression) responded to trabectedin after failing four prior regimens (doxorubicin, gemcitabine, docetaxel, and ifosfamide) with a durable objective response lasting at least 8 months

Adapted from Nteli et al., 2018[21].

induces rapid apoptosis exclusively in mononuclear phagocytes, causing a selective depletion of monocytes/macrophages, including tumor-associated macrophages (TAMs). Besides this direct effect, trabectedin also inhibits the production of pro-inflammatory mediators such as CCL2 and interleukin (IL)-6 by monocytes, macrophages, and TAMs that are relevant for tumor growth and progression. The modulation of cytokines and chemokines takes place at the transcriptional level[22].

This immunomodulating effect of trabectedin, with high anti-inflammatory and anti-angiogenic activity, may explain the long-lasting response experienced by patients. In fact, clinical evidence has demonstrated that trabectedin treatment should be maintained until disease progression to obtain maximum benefit. In a randomized Phase II study, patients who were free from progressive disease after 6 trabectedin cycles were randomly assigned to continuous treatment or therapy interruption. PFS

at 6 months was 51.9% in the continuation group versus 23.1% in the interruption group (p = 0.0200), with similar occurrence of treatment-related Grade 3/4 adverse events in both groups[24].

The safety profile of trabectedin is key to allow long-term administrations. It is characterized by a lack of cumulative toxicities overtime, a low incidence of life-threatening toxicities (such as cardio or pulmonary toxicity)[25], and by comparing favorably with other active drugs used in uterine leiomyosarcoma[26].

Conclusions

Uterine sarcomas can be considered collectively as the most lethal forms of malignant cancer affecting the uterus[1]. Its management entails numerous challenges and requires a mandatory multidisciplinary approach carried out in reference centers[2].

Patients with uterine leiomyosarcoma, the most common type of uterine sarcomas[1], are generally treated in first-line with standard anthracycline-based chemotherapy[3], being doxorubicin and dacarbazine combination, the regimen that has recently shown the most promising efficacy[6].

Trabectedin, gemcitabine-based regimens, and pazopanib are commonly used treatments after anthracyclines failure in uterine leiomyosarcoma patients. Available data demonstrate the ability of trabectedin to provide prolonged disease control with a preserved QoL, making it the preferred second-line therapy for most patients with advanced uterine leiomyosarcoma[17,26,27]. To maximize its efficacy, trabectedin should be administered early in the course of uLMS and until disease progression[20].

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