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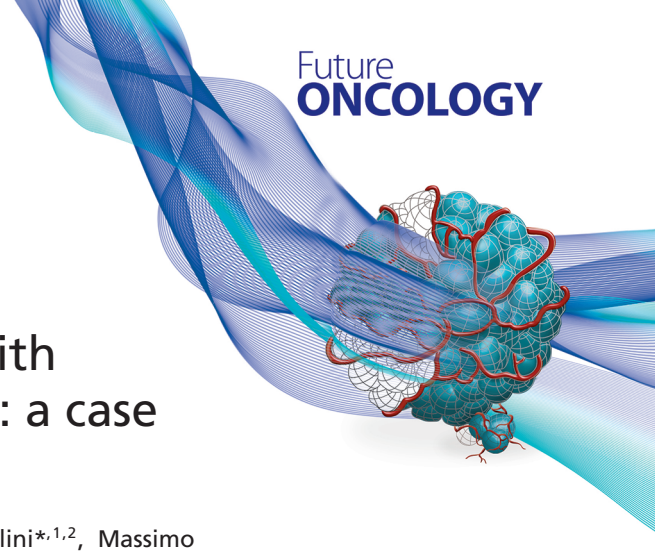

Response to Eribulin in a patient with metastatic uterine leiomyosarcoma: a case report

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We report the case of a 51 year-old patient affected by an advanced uterine leiomyosarcoma treated with eribulin as fourth-line therapy. The patient, with a previous history of leiomyomas of the myometrium, had undergone total hysterectomy for repeated metrorrhagias. After 7 years, metastases in the liver, bone and lung were documented. A fine needle liver biopsy demonstrated leiomyosarcoma metastasis. The patient was treated with first-line doxorubicin chemotherapy; after six cycles, disease progression was observed. A second-line trabectedin chemotherapy and a third-line gemcitabine chemotherapy were performed; no objective responses were seen after two cycles. The patient was then treated with eribulin on the basis of an EORTC Phase II trial showing preliminary activity in uterine leiomyosarcoma. After six cycles, CT scan showed partial remission of liver lesion. Disease progression was observed after nine cycles with eribulin, without severe side effects and preserving a good quality of life.

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The most common histological type of uterine sarcoma is leiomyosarcoma, but several other histotypes may affect this organ: endometrial sarcoma, adenosarcoma, undifferentiated sarcoma and other types.

Uterine leiomyosarcoma (uLMS) is a rare tumor among malignant gynecologic tumors; it arises from smooth muscle of the uterus, accounts for 1% of all uterine malignancies and is a disease with a very unfavorable prognosis independent of grading [1]. After surgical resection patients remain at high risk for local and distant recurrence. The highest prevalence of uLMS is in the pre and perimenopausal period and is often diagnosed incidentally following hysterectomy.

Total abdominal hysterectomy with or without bilateral salpingo-oophorectomy is the most important treatment for localized uLMS, with curative potential. Main prognostic factors for survival for all uterine sarcomas are tumor-free resection margins at primary surgery and disease stage [2,3].

Generally routine use of adjuvant chemotherapy or pelvic radiotherapy is not considered as standard therapy, due to no conclusive literature data.

First-line chemotherapy is standard treatment for advanced or recurrent disease, with a palliative role and with a median overall survival (OS) of about 12 months [4].

The most active first-line drug in uLMS remains doxorubicin, with or without ifosfamide [5].

Other cytotoxic agents with proven activity in uLMS are trabectedin, gemcitabine alone or in combination with docetaxel, dacarbazine and pazopanib [6-9].

Immunotherapy, targeted therapies and aromatase inhibitors are not of proven benefit in uLMS.

Eribulin is a marine sponge-derived analog of halichondrin B, with microtubule dynamics inhibitory action driving its cytotoxic mechanism. Eribulin is approved as a third-line therapy for metastatic breast cancer patients previously treated with an anthracycline.

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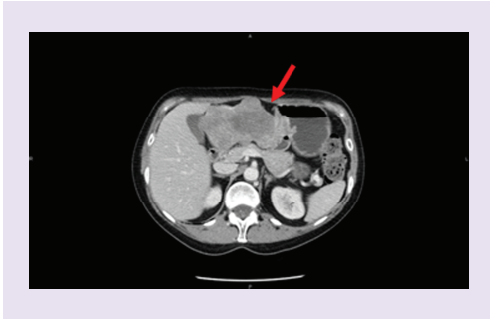

Figure 1. CT scan showing disease progression (January 2012).

In 2016, Eribulin has been approved for advanced liposarcoma, after an anthracycline-containing regimen, demonstrating an OS advantage in liposarcoma and leiomyosarcoma in a randomized Phase III clinical trial [10]. On the basis of this pivotal trial, both US FDA and EMA approved eribulin in liposarcoma histotype only, considering the efficacy and activity displayed in leiomyosarcoma insufficient. Here, we present a case of a progressing metastatic uLMS achieving a partial response after six cycles of eribulin.

Case presentation

We report the case of a 51-year-old woman, who was referred to our hospital in June 2010 for multiple metastasis from tumor of unknown origin.

Her medical history was unremarkable, but for a hysterectomy in 2003 for multiple leiomyomas of the myometrium. Despite the fact that we could not consult her previous documentation, she remembered significant bleeding was reported during her surgery.

In March 2010, the patient performed radiological exams for back pain. Magnetic resonance scan showed lumbar and sacral bone metastases. In April 2010, chest, abdominal and pelvic computed tomography (CT) scan showed four bilateral lung metastases, and an 8-cm large metastasis of left liver lobe. We performed a fine needle aspiration biopsy of the hepatic lesion showing a layer of spindle cells consistent with the diagnosis of a leiomyosarcoma (Ki67 40%, high-grade according to the FLNCC Classification).

We started a first-line treatment for advanced sarcoma in July 2010, using the schedule containing doxorubicin and obtaining a partial response; after six cycles, the CT scan showed partial response of liver and lung metastases and stable disease of bone metastases; during first-line chemotherapy many transfusions of red blood cells and platelets were needed. Subsequently, we started a follow-up program.

In October 2011, because of disease progression, we started a second-line treatment with trabectedin at the dose of 1.3 mg/m^2 given as a 24-h continuous infusion every three weeks (q3w). Unfortunately, the therapy did not have positive results after two cycles; therefore, for progression of liver metastasis we started a third-line chemotherapy with gemcitabine at the dose of 1000 mg/m^2 with schedule 1,8/21; many episodes of neutropenia occurred with this therapy.

The CT scan performed in January 2012 showed increase in size of liver and lung metastasis: the biggest diameter of liver metastases was 99 mm (Figure 1) and 25 mm for one target lung metastasis; the finding on bone disease was stable.

Subsequently, it was possible to start for this patient a clinical trial with the new drug eribulin. The patient was treated with eribulin at the dose of 1.4 mg/m^2 administered intravenously on Day 1 and Day 8 every 21 days until disease progression.

The first evaluation performed after two cycles of chemotherapy with eribulin showed shrinkage of the liver target lesion, with stable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) (Figure 2). In May 2012, (after four cycles with eribulin) a reduction of lung metastasis and further shrinkage of liver metastases was documented at the CT scan evaluation, with the biggest diameter of the liver metastasis being 82 mm large.

After six cycles (at the end of June 2012), the CT re-evaluation showed further reduction of the liver lesion, with a 76-mm diameter, and further reduction of the lung target lesion (11 mm) with stability of other lesions (Figures 3–5), achieving partial response (PR) according to RECIST v1.1. Therefore, eribulin treatment continued until the ninth cycle (September 2012), when tumor assessment was anticipated because of patient's symptoms. That CT scan showed tumor progression (progressive disease; PD) as per RECIST v1.1.

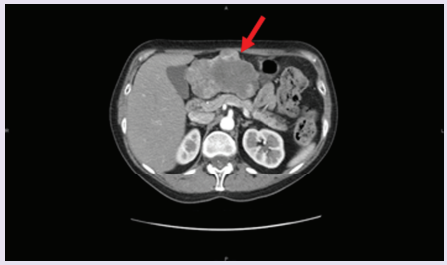

Figure 2. CT scan showing stable disease after two cycles (March 2012).

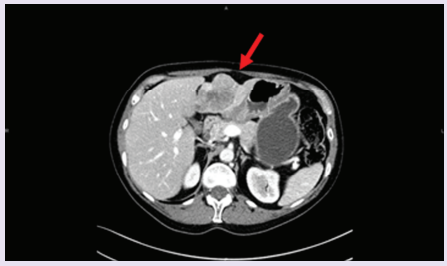

Figure 3. CT scan showing partial response of liver lesion (June 2012).

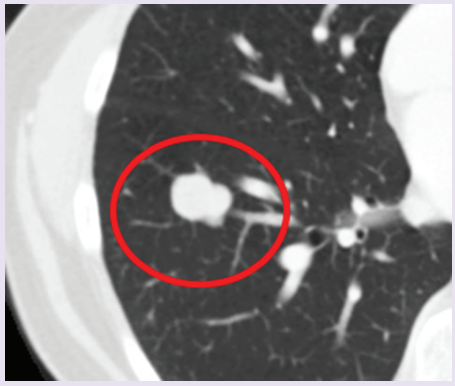

Figure 4. CT scan showing disease progression (January 2012).

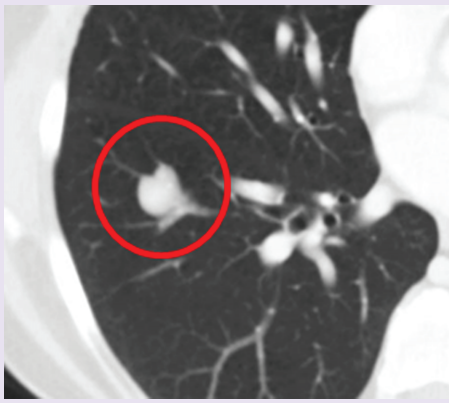

Figure 5. CT scan showing partial response of lung lesion (June 2012).

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Table 1. EMA-approved second-line regimens for advanced leiomyosarcoma.

Drug name	Indication
Pazopanib	Subtypes of advanced soft-tissue sarcoma that received prior chemotherapy for metastatic disease or that progressed within 12 months after (neo)adjuvant therapy
Trabectedin	Patients with advanced soft-tissue sarcoma, after failure of anthracyclines and ifosfamide, or unsuited to receive these agents
Dacarbazine	Patients with advanced soft-tissue sarcoma, after failure of anthracyclines and ifosfamide, or unsuited to receive these agents. Possible also in combination regimen with anthracyclines
Gemcitabine	Patients with advanced soft-tissue sarcoma, after failure of anthracyclines and ifosfamide, or unsuited to receive these agents

Toxicity was relatively mild, preserving a relatively good quality of life during treatment.
After PD with eribulin in September 2012, the patient was switched to pazopanib.

Discussion

Eribulin was approved by FDA on 28 January 2016, for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. EMA approved eribulin use in liposarcoma shortly after, on 1 April 2016, for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline-based regimens (unless unsuitable) for advanced or metastatic disease.

This case highlights that eribulin, despite its label, might display activity in advanced uLMS after failure of standard treatment options. In this case, eribulin showed initial disease stability achieving a partial response according RECIST 1.1 after the sixth cycle; furthermore, several nontarget lesions remained stable (bone lesions and lung lesions). Our patient PFS was 9 months, which is remarkably longer than the reported median PFS in the Phase III trial (2.6 months; 2.2 months in the LMS subgroup at the exploratory PFS analysis) [11,12]. Furthermore, eribulin treatment was performed without significant related toxicities and preserving a relatively good quality of life. Table 1 provides an overview of alternative treatment strategies for this patient.

Indeed, the results from the randomized, open label, multicenter, Phase III trial of eribulin in previously treated patient with advanced liposarcoma or leiomyosarcoma reported that eribulin is a promising regimen for patients affected by advanced soft-tissue sarcoma, if compared with the standard drug dacarbazine [11]. In this study, patients with intermediate- or high-grade leiomyosarcoma and liposarcoma, who had received two previous lines of therapy were randomized to eribulin or dacarbazine in a 1:1 fashion. OS, was significantly better in patients assigned to eribulin (n = 228) compared with those assigned to dacarbazine (n = 224; median 13·5 months vs 11·5 months; hazard ratio 0.77 [95% confidence interval (CI): 0.62–0.95]; p = 0.0169). Since this trial was not powered to detect the efficacy of eribulin in leiomyosarcoma or liposarcoma, we cannot rule out the efficacy of eribulin in leiomyosarcoma just on the basis of subgroup analysis and further trials need to explore this.

The conclusion of the subgroup analysis from a Phase III, open-label, randomized study in patients with leiomyosarcoma demonstrated that efficacy of eribulin in these patients is comparable to that of dacarbazine [12]. Given these premises, our patient's history is rather stirring if compared with data of eribulin activity in LMS reported in the literature. Dacarbazine is known to be specifically active in LMS. Therefore, dacarbazine choice in the Phase III control arm might at least partially explain why the differential benefit in this histotype had been less evident than in liposarcoma. Moreover, data recently presented at ESMO 2019 [13] by Takahashi *et al.* compel the scientific community to further look into eribulin activity in other sarcoma histotypes, which might have been overlooked. Indeed, in a prospective, observational study, they enrolled 255 patients treated with eribulin as first-line (18 patients), second-line (81 patients) or further-line treatment and affected by six major histotypes (LMS, liposarcoma, undifferentiated pleomorphic sarcoma, angiosarcoma, synovial sarcoma and rhabdomyosarcoma) with an overall median OS of 328 days (95% CI: 259–400); by subtype: 386 (LMS, 95% CI: 259–585), 635 (liposarcoma, 95% CI: 271–not reached), 246 (undifferentiated pleomorphic sarcoma, 95% CI: 121–497), 386 (angiosarcoma, 95% CI: 104–516), 356 (synovial sarcoma, 95% CI: 136–not reached) and 136.5 (rhabdomyosarcoma, 95% CI: 25–296), respectively. These data are in line with our case report suggesting hints of efficacy in this specific histotype as well. However, in these rare tumors, it is almost impossible to foresee another trial testing the activity of eribulin specifically in LMS. It is also worth mentioning that the 'LMS label' encompasses a heterogeneous family of tumors with potentially different sensitivity to the same chemotherapy according to anatomic sites of origin. Indeed, in

the aforementioned 2019 subgroup analysis [12], HRs in terms of OS and PFS seem to favor eribulin in nonuterine LMS, while the opposite was observed in uLMS.

In conclusion, since in the last years LMS treatments have failed to show major improvements in the advanced setting, eribulin critical reappraisal may enrich our clinical armamentarium in the interest of our patients.

Summary points

- Leiomyosarcoma (LMS) is a rare cancer with poor prognosis in the advanced/metastatic stage.
- In this setting, the treatment options for LMS remain scarce and mainly with a palliative intent in the advanced stage.
- Doxorubicin-containing regimens are the most widely used, yet burdened by significant toxicity.
- Eribulin is a novel, marine organism-derived chemotherapeutic agent active in a few cancer types.
- Eribulin is approved by US FDA and EMA for use in advanced liposarcoma on the basis of a Phase III study investigating its activity in liposarcoma and leiomyosarcoma patients.
- In our case report, we highlight a case of pretreated uLMS patient who had shown a remarkable response with further-line eribulin treatment.
- We discuss the results of previous trials and compare the reported mPFS with our patient PFS and the possible mechanisms underlying this observation.
- Finally, we report state-of-the-art clinical research concerning eribulin use in soft tissue sarcomas and advocate further translational investigations trying to delve into this complex conundrum of differential response among these rare cancer types.

Author contributions

All authors were involved in the writing and revision of this manuscript and have provided final approval to submit.

Financial & competing interests disclosure

G Grignani has received fees for consulting and advisory board roles from Eisai. All other authors declare no competing interests. The authors have no relevant affiliations or financial involvements with any organization or entity with a financial interest in or a financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.