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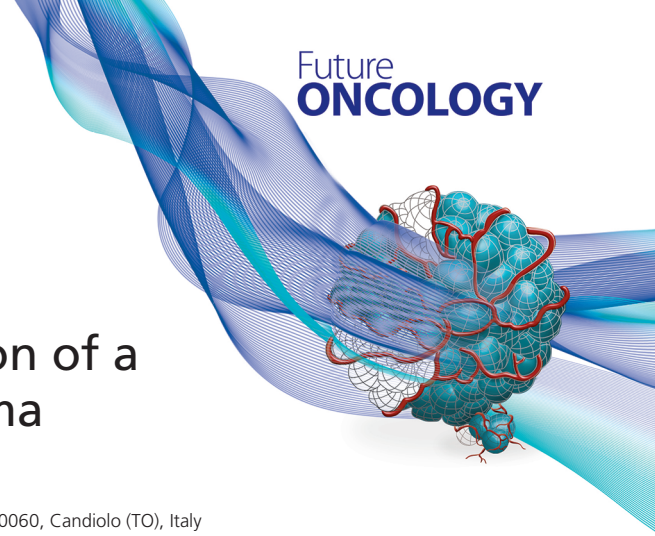

Being the ultimate travel companion of a patient with uterine leiomyosarcoma

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Uterine fibroids are difficult to distinguish from malignant masses using standard ultrasonography; and morcellation carries the risk of disseminating occult cancer in a small but relevant group of women with an undetected uterine malignancy. In this context, we follow the progress of a woman diagnosed with uterine leiomyosarcoma after suboptimal initial surgery for an assumed fibroid. Evidence is reviewed that guided multidisciplinary tumor board decisions about optimal management approaches after local seeding and development of distant metastases, and informed treatment selection at each line of therapy. As the case study illustrates, choice of treatment for advanced soft tissue sarcomas frequently involves finding an appropriate balance between the efficacy and toxicity of available options, aiming to allow patients to maintain their normal lives.

Tweetable abstract: Being the ultimate travel companion of a patient with uterine leiomyosarcoma

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The setting in which oncologists deal with uterine leiomyosarcomas (LMSs), which are relatively rare, differs from that of gynecologists, who regularly attend women with fibroids (uterine myomas). Fibroids occur in more than 40% of women. They vary in frequency according to age but are most common in women aged between 41 and 55 years. Most fibroids are small (<3 cm), with about 20% being ≥3–4 cm in size [1]. Pelvic ultrasound is the most common imaging modality used to investigate uterine masses but it cannot distinguish reliably between a benign and a malignant mass (Figure 1). This is the context for the case study presented below, which involves a woman with uterine LMS.

Case study

Case presentation

The patient was a 54-year-old woman (menopause aged 53 years) with an unremarkable medical history who had recently returned to Italy from Canada after retirement. She had bladder voiding symptoms caused by a 6-cm fibroid. Her gynecologist suggested a hysterectomy, and 'open' surgery was planned with a Pfannenstiel surgical incision.

Evidence review

There are no specific predictive factors to select patients at higher risk for uterine LMS relative to fibroids. In general, any growing mass up to the time of menopause is considered a higher risk for LMS. Age is also a factor. The overall risk of uterine LMS is 1.16 per 1000 (1 in 861) and increases with age from <1 case per 500 for patients aged <30 years to a peak of 10.1 cases per 1000 (1 in 98) for patients aged 75–79 years [2].

The morcellation debate between oncologists and gynecologists is ongoing. For women undergoing hysterectomy, morcellation is a minimally invasive procedure that improves postoperative pain, complications, quality of life, length of hospitalization and return to work; however, the procedure carries the risk of inadvertent morcellation of a uterine malignancy, with subsequent dissemination of occult cancer [3]. Although a review of large retrospective

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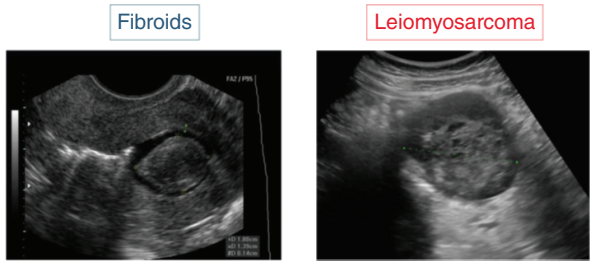

Figure 1. Ultrasound images of uterine fibroids and leiomyosarcoma.

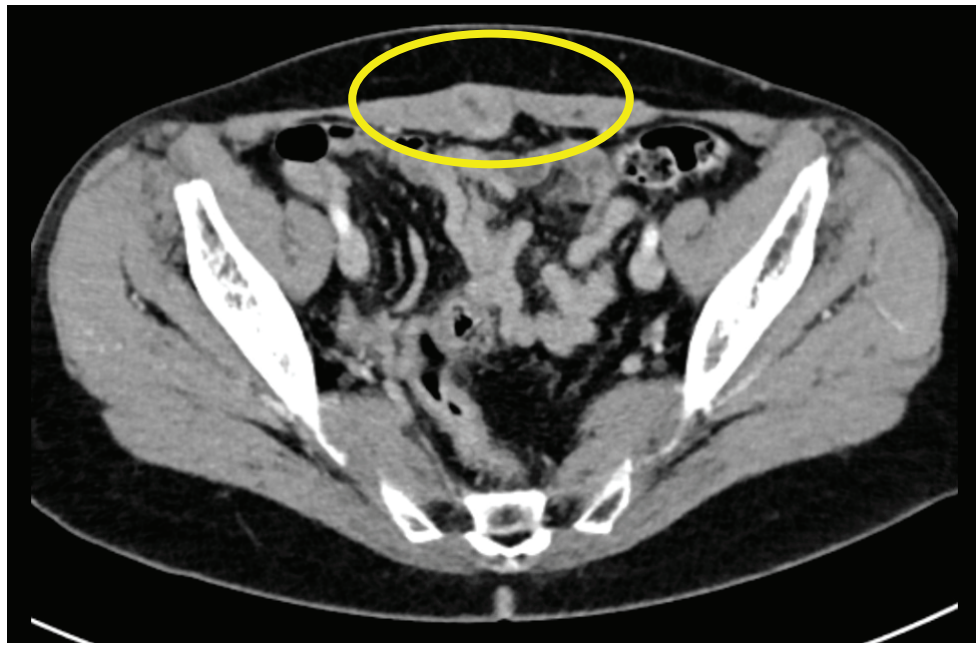

Figure 2. Recurrent abdominal wall nodule close to the surgical scar.

studies found a low incidence of occult uterine sarcoma following hysterectomy for fibroids using morcellation [4], ranging from 1/278 (0.36%) [5] to 1/157 (0.64%) [6], the risk remains nonetheless.

Case continuation

The patient underwent surgery in March 2017 outside our clinic. During surgery, tissue located in the patient's lower anterior uterine wall, which was tenaciously adhered to the bladder and assumed to be fibrotic, was lacerated. The patient was diagnosed with uterine LMS with necrotic areas and 15 mitoses per 10 high-powered fields.

Upon referral to our institute, the multidisciplinary tumor board considered three options: repeat surgery, adjuvant radiotherapy and adjuvant chemotherapy. In the setting of uterine LMS, evidence for the benefit of second surgery is lacking, as further surgery poses additional risk for the patient and increases medical costs. A randomized phase III trial failed to show any survival benefit of adjuvant pelvic radiotherapy for uterine LMS [7], and the role of adjuvant chemotherapy is not well established. The decision of the tumor board was to start follow-up.

In May 2017 the patient complained of a small nodule near the surgical scar (Figure 2), which was surgically removed the following month. Histological investigation indicated an LMS metastasis. A CT scan in July 2017 revealed lung metastases.

Evidence review

The tumor board considered surgery after taking into account the 5-year survival rate of 25% for soft tissue sarcoma (STS) patients undergoing pulmonary metastasectomy [8]. The board's eventual decision to administer neoadjuvant chemotherapy followed by surgery was based on several factors: the short interval between appearance of the scar

metastasis and distant metastases; the ability to test tumor chemosensitivity using preoperative chemotherapy; the benefit of an early CT scan to minimize risk of losing the 'window' for further surgery due to a sudden increase in the dimension of lung metastases; and recognition that a complete response with nodule disappearance is a rare event.

Separately, the board considered whether to initiate chemotherapy with a single agent or a combination of agents. In general, in advanced STS, it is reasonable to accept the higher toxicity of doublet chemotherapy when the aim is to render a tumor resectable or to control symptoms. Doublet toxicity is less acceptable when the aim is to slow progression of advanced STS. To determine which doublet to use, the results of relevant studies were reviewed.

The phase III GeDDiS trial of first-line doxorubicin versus gemcitabine plus docetaxel for locally advanced or metastatic STS showed comparable median progression-free survival (PFS) with each regimen (23.3 vs 23.7 weeks) [9]. The toxicity profiles of doxorubicin alone and gemcitabine plus docetaxel showed some similarity, with the most frequent serious adverse events being febrile neutropenia (17 vs 12%), fever (12 vs 15%) and neutropenia (14 vs 8%), although this may have reflected a pragmatic decision by investigators to use lower doses and fewer treatment cycles of gemcitabine plus docetaxel based on previous reports of unacceptable toxicity. Despite dosing modifications, the gemcitabine plus docetaxel combination was more difficult to deliver (lower dose intensity, more treatment delays, more patients discontinuing treatment early due to toxicity) and was associated with a numerically lower global health status than doxorubicin [9]. The investigators concluded that doxorubicin remains the standard of care as first-line treatment for locally advanced or metastatic STS, and that gemcitabine plus docetaxel is not recommended as routine first-line treatment, neither for STS patients in general nor for any specific subgroup of patients [9].

The phase III European Organisation for Research and Treatment of Cancer 62012 trial of first-line doxorubicin versus doxorubicin plus ifosfamide for advanced or metastatic STS showed that doublet chemotherapy significantly prolonged PFS with a hazard ratio (HR) of 0.74 (95% CI: 0.60–0.90; p = 0.003). However, toxicity of the doublet was higher, as indicated by discontinuation rates due to toxic effects (including toxic death) of 18 and 3% in the combination arm and monotherapy arm, respectively [10].

In a retrospective study evaluating doxorubicin plus dacarbazine, doxorubicin plus ifosfamide and doxorubicin monotherapy as first-line treatments for advanced/metastatic LMS, median PFS was significantly longer with doxorubicin plus dacarbazine compared with doxorubicin monotherapy (HR: 0.72; 95% CI: 0.52–0.99) [11]. This study also confirmed the limited role of ifosfamide in LMS, because patients who received the drug reported the lowest response rate and the lowest median overall survival among the three treatment arms [11].

Collectively, these data informed the board's decision to initiate treatment with doxorubicin plus dacarbazine.

Case continuation

From July to November 2017, the patient received doxorubicin 75 mg/m^2 plus dacarbazine 750 mg/m^2 per cycle, administered intravenously every 3 weeks. Relevant toxicities (according to Common Terminology Criteria for Adverse Events v.5.0) were grade 4 neutropenia, grade 2 anemia, grade 2 thrombocytopenia and grade 2 creatinine increase. No dose reduction was necessary, as she recovered fully before each subsequent treatment cycle. Her functional ability was good, with an Eastern Cooperative Oncology Group performance status of 0, and she consistently recorded good quality of life and patient-reported outcome measure scores. She achieved a near partial response after four cycles and, after five cycles, underwent lung metastasectomy (March 2018). Of the five completely resected pulmonary nodules, pathological analysis indicated four LMS metastases with pathological partial response and one fibrotic nodule. A decision was taken to restart follow-up.

In December 2018, 9 months later, the patient developed multiple new lung metastases, which were deemed unresectable. Second-line options for LMS are trabectedin, gemcitabine, pazopanib, dacarbazine, gemcitabine–dacarbazine and gemcitabine–docetaxel [12–16]. As the patient expressed a clear wish to receive a treatment allowing her to continue her daily activities, trabectedin was selected.

Evidence review

In a phase III trial of trabectedin or dacarbazine for metastatic LMS or liposarcoma following failure of conventional chemotherapy, trabectedin was associated with a 45% reduction in the risk of disease progression or death compared with dacarbazine (median PFS: 4.2 vs 1.5 months; HR: 0.55; p < 0.001) [12]. In the subset of patients with uterine LMS, trabectedin significantly prolonged PFS compared with dacarbazine (4.0 vs 1.5 months; HR: 0.57; p = 0.0012) [17].

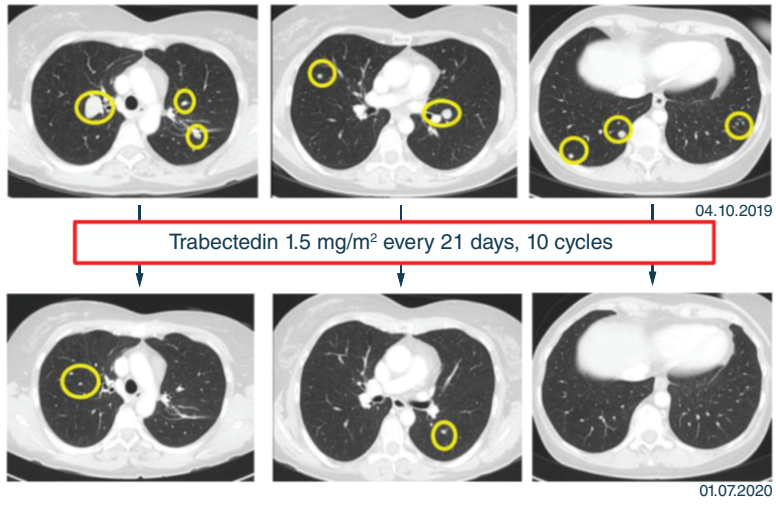

Figure 3. Response to trabectedin during the first ten cycles (of 18 in total).

Case continuation

The patient received trabectedin at the standard dose (1.5 mg/m^2 every 3 weeks) from January 2019 to December 2020 and achieved a near partial response (Figure 3). After the tenth treatment cycle, standard monitoring indicated signs of liver toxicity, with grade 2 elevation of total bilirubin, alanine transaminase, aspartate aminotransferase and alkaline phosphatase persisting more than 21 days after the latest trabectedin administration. Trabectedin was withheld until her liver function recovered. From the 11th cycle onwards, the trabectedin dose was reduced to 1.2 mg/m^2. Notwithstanding the liver toxicity, the patient continued to report good maintenance of her quality of life, and her Eastern Cooperative Oncology Group performance status was 0. After 18 cycles, progressive disease was detected with the appearance of new lung metastases.

Evidence review

Options for third-line therapy after trabectedin in the setting of advanced LMS are single-agent (gemcitabine, pazopanib, dacarbazine) or doublet (gemcitabine–dacarbazine, gemcitabine–docetaxel) chemotherapy; however, it is necessary to determine whether the higher toxicity of a doublet is justified. A phase II study from the French Sarcoma Group showed that the efficacy of gemcitabine plus docetaxel was not superior to that of gemcitabine alone in patients with metastatic or relapsed uterine LMS (median PFS: 5.5 vs 4.7 months) and that patients receiving single-agent gemcitabine experienced less toxicity [18]. Another study reported superior median PFS (6.2 vs 3.0 months) and median overall survival (17.9 vs 11.5 months) with gemcitabine plus docetaxel compared with gemcitabine alone in patients with advanced STS (30% with LMS); however, 40% of patients receiving the combination discontinued treatment within 6 months due to toxicities, despite dose reductions [16]. Taken together, the evidence excluded gemcitabine plus docetaxel for our patient. Gemcitabine plus dacarbazine was also ruled out due to doublet toxicity, and pazopanib was rejected at this time due to the potential for tumor vascular rebound following cessation of antiangiogenic treatment [19,20]. The literature review informed the decision to initiate treatment with gemcitabine monotherapy.

Case continuation

Gemcitabine was initiated in December 2020 and slowed disease progression for 5 months. Following progression, and with choices limited to pazopanib and dacarbazine, pazopanib was selected due to the patient's previous exposure to dacarbazine. Pazopanib was started in the fourth line but was discontinued shortly thereafter due to a pneumothorax. The patient began palliative care and died 6 weeks later.

Evidence review

There are multiple reports associating pazopanib treatment with the development of pneumothorax in patients with STS and lung metastases [21–25]. Others have argued that the presence of cavitary lung and/or pleural-based nodules and masses is the primary risk factor for developing pneumothorax [26] and that pazopanib, as an antiangiogenic agent, accelerates the necrosis of lung lesions, leading to pneumothorax [27]. Irrespective of cause, in patients with

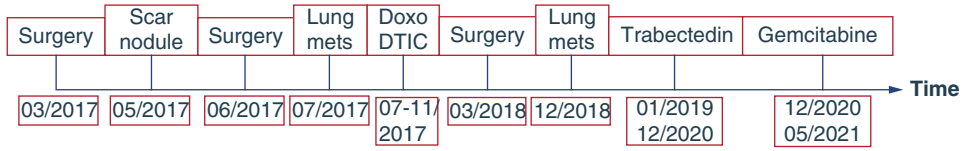

Figure 4. Treatment timeline in a woman with uterine leiomyosarcoma.
Doxo: Doxorubicin; DTIC: Dacarbazine; Mets: Metastases.

lung metastases, pneumothorax worsens respiratory status and further reduces the chances of survival [27]. We considered pneumothorax in our patient a contraindication for further use of pazopanib.

Conclusion

The timeline of treatment for this patient is summarized in Figure 4. The case highlights the importance of differentiating between uterine fibroids and LMS prior to initial surgery to avoid compromising the surgical outcome. As repeat surgery, adjuvant radiotherapy and adjuvant chemotherapy were all ruled out for the patient, our only option was follow-up. The appearance of a metastatic nodule soon after the patient was referred to our center promptly shifted the focus to management of advanced disease. Although many patients with metastatic STS do not achieve such prolonged survival as observed in our patient, the fact that some patients do [28] is sufficient reason to explore all treatment options. As illustrated by the case study, selecting treatment in patients with advanced STS involves finding an appropriate balance between the efficacy and toxicity of available options at each successive treatment line with the aim of allowing patients to maintain their normal lives for as long as possible.

Executive summary

- As benign uterine fibroids are much more common than uterine leiomyosarcoma (LMS), there is risk of compromising a patient's outcome unless great care is taken to distinguish between the conditions prior to surgery.
- This case study follows the progress of a woman diagnosed with uterine LMS after suboptimal initial surgery for an assumed fibroid.
- As the patient presented a metastatic nodule soon after referral to our reference center, the focus shifted immediately to the management of advanced disease.
- Each line of therapy was informed by evidence review, taking into account the expected benefits and risks of the available options and the patient's wishes and functional status.
- Treatment consisted of: neoadjuvant chemotherapy followed by surgery for pulmonary metastases; first-line doxorubicin plus dacarbazine because of the greater activity of dacarbazine versus ifosfamide in LMS; second-line trabectedin because of the patient's desire to live 'as normal a life as possible'; third-line gemcitabine monotherapy because of the greater (and likely unacceptable) toxicity of doublet therapy; fourth-line pazopanib because of its activity in LMS.
- Using this approach, the patient was able to maintain a relatively normal life for approximately 4 years after presenting with metastatic disease, an exceptional result in this setting.

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Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patient for inclusion of her medical and treatment history within this case report.

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