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Doxorubicin and trabectedin for recurrent leiomyosarcoma – A case report

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ABSTRACT

Uterine leiomyosarcoma (LMS) represents a rare yet highly aggressive tumor, comprising approximately 1% of uterine malignancies. First-line regimens involving doxorubicin or gemcitabine and docetaxel demonstrate modest response rates. Notably, the combination of doxorubicin plus trabectedin has emerged as a preferred first-line option following the LMS-04 study, showing superior progression-free survival compared to doxorubicin alone. Second-line therapy for recurrent LMS poses greater challenges, with single-agent treatments exhibiting limited efficacy.

Herein, we present a case of a 65-year-old woman with stage 1B uterine leiomyosarcoma, previously treated with surgical resection and adjuvant gemcitabine/docetaxel, due to surgical morcellation. Despite initially achieving disease-free status, she experienced a first recurrence 5 years later, treated with surgery and radiation, and a second recurrence 4 years after, necessitating second-line therapy with doxorubicin and trabectedin. The patient exhibited a remarkable response to this regimen, achieving partial response after 6 cycles of doxorubicin and trabectedin chemotherapy. She maintained stable disease over 13 cycles of maintenance trabectedin and 6 months off treatment, for a total of 16 months of progression-free survival. This case underscores the potential efficacy of combination chemotherapy with doxorubicin and trabectedin as a second-line treatment option for recurrent uterine leiomyosarcoma.

1. Introduction

Uterine leiomyosarcoma (LMS) is an aggressive tumor that accounts for approximately 1 % of uterine malignancies (Mbatani et al., 2018). Although uncommon, it carries a poor prognosis and poses a management challenge for oncologists (Ricci et al., 2017). Gold standard surgical management consists of en bloc resection (Devaud et al., 2022). Stage I LMS does not typically receive adjuvant chemotherapy as it has not been shown to significantly improve survival (Hensley et al., 2018). Despite optimal surgical management, overall survival remains low, with five-year survival rates reported to be 55 % in stage 1 disease and 13 % in advanced-stage disease (Seagle et al., 2017).

Chemotherapy remains an important treatment option for advanced, recurrent, or inoperable LMS. First-line treatments with doxorubicin or gemcitabine/docetaxel yield a response rate of approximately 20 % (Seddon et al., 2017). Since the publication of the LMS-04 study, oncologists have adopted the combination of doxorubicin plus trabectedin in first-line treatment of metastatic or unresectable leiomyosarcoma, given its improved benefits on progression-free survival in patients with compared to doxorubicin alone, with a median progression free survival of 12.2 versus 6.2 months, in favor of the combination of doxorubicin plus trabectedin (HR 0.41, 95 % CI 0.29–0.58) (Pautier et al., 2022).

Second-line therapy in recurrent LMS is believed to be even less effective. In the second-line setting, single agent treatments have yielded low partial response rate for ifosfamide, gemcitabine, paclitaxel, cisplatin and pazopanib (Hawkins et al., 1990; Look et al., 2004; Rose et al., 1998; Gallup et al., 2003; Benson et al., 2016). Of note, single-agent doxorubicin in the second-line showed a response rate of 13 %-25 % (Omura et al., 1983; Muss et al., 1985). The efficacy of combination of doxorubicin and trabectedin for recurrent LMS in the second-line setting has yet to be described.

2. Case presentation

A 65-year-old woman with a history of recurrent lobular infiltrating breast carcinoma treated with epirubicin, cyclophosphamide and

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radiotherapy, was found to have a symptomatic 13 cm uterine fibroid-like mass when she was 53. At that time, the patient underwent a minimally invasive simple hysterectomy and bilateral salpingo-oopherectomy with morcellation. Final pathology reported a 13 cm uterine leiomyosarcoma. Lymphovascular invasion was negative, bilateral adnexa were free of tumor, as was her cervix. Estrogen and progesterone receptors were negative and mismatch repair status was proficient. Next-generation sequencing demonstrated a somatic BRCA2 mutation. The surgical pathologic stage was IB, but given the size and risk of metastatic disease associated with morcellation, the patient was treated with six cycles of Gemcitabine and Docetaxel. Five years later, the patient experienced abdominal pain and a PET scan showed a low 18-FDG avidity uptake mass close to the rectum. A CT scan showed another lesion in the left pelvis above the iliac muscle measuring 2.5 cm. The patient underwent a left parametrial resection, vaginectomy, and complete cytoreduction. The bladder, left parametrial, and vaginal nodules were confirmed to be recurrent LMS. Given the positive vaginal surgical margins, she was treated with adjuvant radiotherapy to the pelvis – 50.4 Gy delivered in 28 fractions using IMRT. After 4 years, MRI imaging suggested multiple metastatic implants with the largest deposits in the right adnexal region (2.9 cm by 2.3 cm) and left anterior pelvis ((Fig. 1**A, C**). The patient was discussed at tumor board – given oligometastatic disease, recommendation was made for surgical resection. However, on re-review of the case, the tumours were rapidly growing, and the decision was made to proceed with systemic treatment.

The patient started second-line doxorubicin 60 mg/m^2 and trabectedin 1.1 mg/m^2, through a special request for non-formulary drug (trabectedin) and completed 6 cycles, using dexrazoxane 600 mg/m^2 for cardiac protection in the last two cycles of doxorubicin. Cumulative doxorubicin dose reached 527 mg per square meter. Maintenance trabectedin 1.1 mg/m^2 was planned for 17 cycles as per LMS-04 trial, however the patient elected to stop after 13 cycles as she was experiencing depressive symptoms. The patient otherwise tolerated the treatment well, with only grade 1 fatigue and nausea reported as side effects. Given a somatic BRCA2 mutation found on tumour sequencing, the patient was then placed on Niraparib 200 mg daily, through a compassionate drug access program, after discontinuation of the trabectedin. Niraparib was well tolerated without side effects.

Overall, the patient's best overall response was a partial response noted on the imaging performed after 6 cycles of doxorubicin/trabectedin (Fig. 1**B,D**). The left pelvic implant decreased in size from 3.7 cm to 2 cm, and the right adnexal implant shrunk from 2.9 cm to 1.5 cm, with disappearance of some of the mesenteric nodules. Stable disease was then observed. After 16 months from the completion of the doxorubicin, or 6 months after the discontinuation of maintenance trabectedin, while on Niraparib, she was found to have progression in the size of the implants, without new documented implants, and trabectedin monotherapy was introduced. After 3 cycles of trabectedin, which were well tolerated, imaging showed rapid progression of her pelvic implants and palliative radiation was administered.

3. Discussion

We present a case of recurrent leiomyosarcoma treated by a second-line combination of doxorubicin/trabectedin. Patients tolerated this treatment without significant adverse events. This case provide insights into the safety and feasibility of administering the LMS-04 protocol in the second-line setting as well.

In the first line-setting, as described in the LMS-04 study, the combination of doxorubicin 60 mg/m^2 and trabectedin 1.1 mg/m^2 for 6 cycles, followed by maintenance trabectedin 1.1 mg/m^2 for 1 year (17 cycles of maintenance), demonstrated an objective response rate of 36 % (out of 74 patients, 3 had a complete response and 24 had a partial response). The disease control rate was 91.9 %, versus 78.9 % in the doxorubicin-arm ($p = 0.03$). It is important to note that patients in the LMS –04 trial were not allowed to have received prior systemic treatment for their LMS. Trabectedin was previously studied as a single agent in first-line and in pretreated patients. In first-line therapy for uterine LMS, it was found to show partial response in 10 % of patients and a clinical benefit rate, which includes the objective response rate and durable stable disease, of 60 % (Monk et al., 2012), with a median PFS of 5.8 months. In second-line for pretreated soft tissue sarcoma (Demetri et al., 2016), it also showed an objective response rate of 10 %. When compared with dacarbazine, it showed a 45 % reduction in the risk of

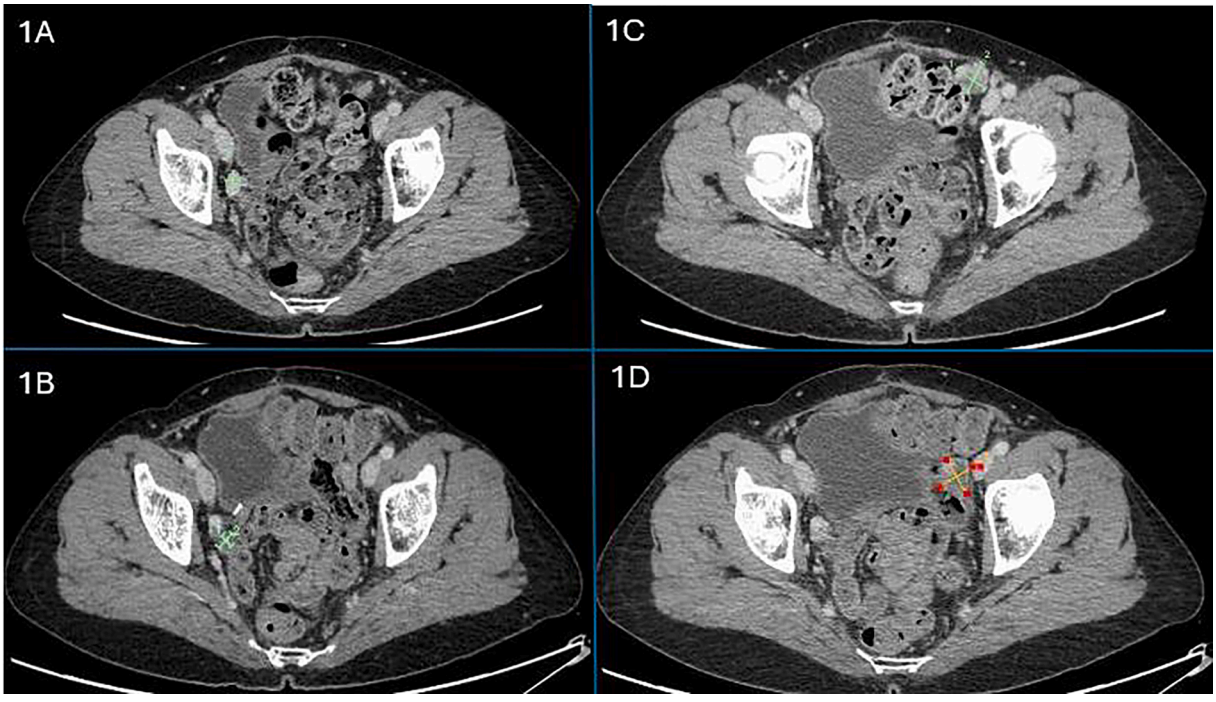

Fig. 1. A. Pretreatment recurrent lesion in right pelvis 2.9*2.3 cm. **B**. After treatment – decrease in size of lesion in right pelvis to 1.5*1 cm. **C**. Pretreatment recurrent lesion in anterior left pelvis 3.7*2.6 cm. **D**. After treatment – decrease in size of the lesion in left pelvis to 2*2 cm.

disease progression or death with median PFS of 4.2 months, versus 1.5 months ($p < 0.001$). Uterine leiomyosarcoma made up 41 % of the patients enrolled, and 88 % of the patients had previously received 2 or more lines of chemotherapy. Importantly, the most common grade 3 to 4 adverse effects noted in that trial were myelosuppression and transient elevation of transaminases in the trabectedin arm. These findings, in addition to preclinical data suggesting that trabectedin and doxorubicin resulted in synergistic pro-apoptotic effects in two soft-tissue sarcoma in vitro cell lines (Takahashi et al., 2001), led to the development of the LMS-02 study, a phase II trial studying the combination of doxorubicin and trabectedin in first-line uterine or soft tissue leiomyosarcoma (Pautier et al., 2015). The promising results of that trial, including a partial response rate of 60 % and disease control rate of 87 %, steered the development of the first-line, phase III trial, LMS-04. We are aware of only one study testing the combination of doxorubicin and trabectedin in previously treated soft tissue sarcoma, a phase I dose-finding study from Blay et al. (Blay et al., 2008), but the trial included only one patient with uterine LMS and her treatment history is unknown.

Given the paucity of data regarding the combination of doxorubicin and trabectedin in previously treated patients, it is difficult to ascertain the toxicity profile of the treatment. The LMS-04 regimen reported significant toxicities in previously untreated patients, with grade 3 to 4 adverse events reported in 96 % of patients receiving the combination therapy, notably haematological events such as neutropenia, anemia and thrombocytopenia (Pautier et al., 2022). Despite this number, only 9 % of patients had to discontinue the combination of doxorubicin and trabectedin due to toxicity, versus 4 % in the doxorubicin arm. In subsequent lines, the Blay et al. phase I trial included 41 patients with previously treated soft tissue sarcoma, and of those, only seven patients have had prior chemotherapy (Blay et al., 2008) ; and described common grade 3/4 toxicities such as neutropenia (71 %), ALT increase (46 %), and thrombocytopenia (37 %). Trabectedin as a single agent in subsequent lines is well tolerated, with 37 % risk of grade 3 to 4 neutropenia, and without cumulative toxicities (Demetri et al., 2016).

Despite a lack of data showing that the combination is superior to doxorubicin in the second-line, the promising results of LMS-04 in the first-line, coupled with the manageable side effect profile of trabectedin in second-line, makes a compelling hypothesis that the addition of trabectedin to doxorubicin could be beneficial and well tolerated, in second-line. Our case report gives the first example of a patient who has indeed done well with the combination.

Uterine leiomyosarcoma is rare, and most patients will have received the doxorubicin/trabectedin in first line as the new standard of care, therefore a phase II or III trial on second-line chemotherapy is unlikely to be designed. Currently used regimens for recurrent leiomyosarcoma showed a very low response rate, as pazopanib with an objective response rate of 6 % (van der Graaf et al., 2012) and Eribulin with a response rate of 4 %, while trabectedin alone showed a response rate of 10 % (Demetri et al., 2016). While widely explored, none of the different antitumor medications and molecular-targeted therapies have demonstrated significant tumor reduction in patients with recurrent leiomyosarcoma and a prior chemotherapy exposure, particularly those who have undergone multiple lines of treatment. It is of utmost importance to explore the durable response achieved in our patient by the doublet doxorubicin/trabectedin in more patients with recurrent, previously treated leiomyosarcoma.

4. Conclusion

Cumulative clinical experience with trabectedin may suggest that doxorubicin/trabectedin should be considered for second-line treatment in patient with a previously treated recurrent leiomyosarcoma. Further multi-centric, international rare-cancer databases should be established in order to augment clinical data of off-label use of this combination, until a high order level of evidence will inform us with the gold standard treatment for patients in this setting.

Informed consent statement

Consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Gabriel Levin: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Lucy Gilbert:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Shuk On Annie Leung:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Xing Zeng:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Victoria Mandilaras:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Laurence Bernard:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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