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Case Report

Long-Time Progression-Free Survival with Trabectedin in Chemorefractory Metastatic Leiomyosarcoma of the Retroperitoneum: A Case Report

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Trabectedin · Soft tissue sarcoma · Leiomyosarcoma · Chemorefractory · Case report

Abstract
We present the case of a 46-year-old mother of a young child who was diagnosed with metastatic leiomyosarcoma. At diagnosis, the tumor had already infiltrated the vena cava, infiltration of the pancreas was suspected, and pulmonary metastases had been histologically confirmed. The goal of treatment was to prolong survival and gain quality time for the family. When the patient had not responded to 4 cycles of doxorubicin, trabectedin was initiated. After an initial partial remission with a reduction in the size of the primary leiomyosarcoma as well as some pulmonary metastases, the disease remained stable for a total of 10 months. Upon progression, the patient did not further respond to subsequent treatment lines. The presented case shows that second-line trabectedin may represent a promising option for patients with chemotherapy-resistant leiomyosarcoma to prolong survival while preserving quality of life.

Introduction

Leiomyosarcoma (LMS) is a rare cancer but a common type of soft tissue sarcoma (STS) [1]. LMS consists of several subtypes of malignancies that predominantly occur in the soft tissues of the abdominopelvic organs and originate either directly from smooth muscle cells or from their precursor mesenchymal stem cells [2]. Due to their diverse origins, these subtypes of LMS differ in their biology, clinical picture, and response to treatment [3]. Due to

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its mostly asymptomatic course, retroperitoneal LMS is mainly identified by chance and diagnosed at an already advanced stage. Patients typically present with an unexplained enlarged abdomen with or without additional nonspecific symptoms pertaining to the tumor location [4]. Treating advanced and/or metastatic LMS is considered a major challenge. Patients with metastatic STS, even when treated in a reference center, were shown to have a median overall survival no longer than 24 months [5]. Treatment is therefore usually conducted with a goal of maintaining quality of life and prolonging survival [4]. In the metastatic setting, the standard first-line chemotherapy consists of doxorubicin (with or without dacarbazine) or gemcitabine plus docetaxel [6]. Trabectedin, an anticancer agent originally isolated from the Caribbean tunicate (*Ecteinascidia turbinate*), is approved in the STS setting in the European Union after failure of or in case of contraindication to anthracyclines and ifosfamide [7]. The European Society for Medical Oncology-European Reference Network for Rare Adult Solid Cancers-European Reference Network for Genetic Tumor Risk Syndromes (ESMO-EURACAN-GENTURIS) clinical practice guidelines recommend trabectedin as a second- or later-line option. Other options are pazopanib, eribulin, gemcitabine ± docetaxel, and dacarbazine [6]. Here, we present the case of a patient with chemotherapy-resistant LMS with initial infiltration into the inferior vena cava who attained progression-free survival over 10 months using trabectedin.

Case Presentation

The 46-year-old woman presented with persistent upper and mid-abdominal pain on the right with accompanying nausea over approximately 3 weeks. Computed tomography (CT) of the pancreas, upper abdomen, and small pelvis revealed a large retroperitoneal mass (5.8 × 5.5 × 5.2 cm) that displaced the pancreatic caput ventrally and infiltrated the inferior infrahepatic vena cava. Histologically, LMS was diagnosed. A thorax CT conducted in September 2021 showed multiple nodular and micronodular lesions in both lungs. Figure 1 shows a chronological overview of diagnostic and therapeutic measures and outcomes over time.

In a CT conducted in October 2021 (Fig. 2a) at our center, the known pulmonary lesions were shown to have progressed in size (from 1 mm to approximately 5 mm), but new pulmonary lesions could not be clearly demarcated. The primary LMS was stable in size but the previously cyst-like parts of the retroperitoneal mass appeared increasingly solid. The tumor stage had clearly progressed compared to the initial examination and the previously micronodular lung formations had to be re-staged as pulmonary metastases, which were histologically confirmed. The clinical tumor stage was determined as cT2, cN0, cM1 (pulmonary). The patient was initiated on intravenous (IV) doxorubicin monotherapy (75 mg/m^2 once every 21 days) as the first-line palliative chemotherapy. Monotherapy was preferred because no critical structures were affected. At the time of first diagnosis, the patient's daughter was still very young and the most important treatment goal was to prolong survival in the palliative setting while maintaining adequate quality of life in order for them to share some additional quality time together.

After 4 cycles of doxorubicin, a CT conducted in January 2022 showed disease progression. The retroperitoneal tumor mass had locally progressed in size from 5.5 × 4.7 to 6.7 × 5.6 cm axially. The known infiltration of the vena cava of approximately 180° of the vascular circumference had broken into the vessel and was now filling large sections of the lumen. There were no new pulmonary metastases but individual lesions had increased in size. Histological workup with next-generation sequencing using a 170 gene panel (Illumina TruSight) found monoallelic deletion of *TP53*, *RB1*, and *CDKN2A*, none of which currently represent druggable targets. The tumor was shown to be microsatellite stable. Homologous

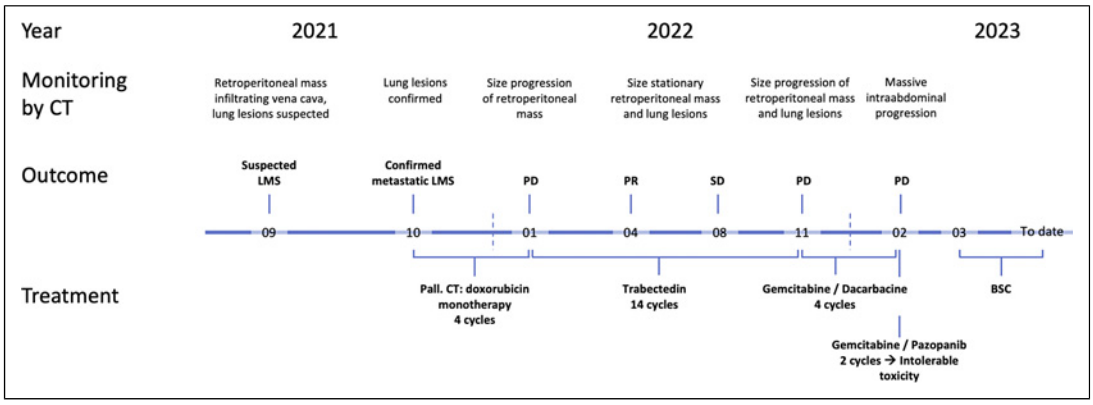

Fig. 1. Overview of diagnostic and therapeutic measures and outcomes over time. BSC, best supportive care; CT, chemotherapy; LMS, leiomyosarcoma; pall., palliative; PD, progressive disease; PR, partial remission; pul. Met., pulmonary metastasis; SD, stable disease; w, with.

recombination deficiency or genomic loss of heterozygosity was not tested at diagnosis as this was not a standard at our hospital in October 2021. As a second-line palliative treatment, trabectedin (1.5 mg/m^2 IV once every 21 days) was initiated.

After 4 cycles of trabectedin (April 2022), a CT of the trunk showed partial remission according to RECIST criteria (Fig. 2b). The size of the large retroperitoneal mass was stationary (approximately 7 × 6 cm). The infiltration in the vena cava measured approximately 100° of the circumference in the area of the vena mesenterica superior. Infiltration of the duodenum was suspected based on the observed duodenal displacement. There was no decrease in the number of pulmonary lesions but the size of a known lesion in the right upper lobe had decreased from 7 mm to below 3 mm. There was no evidence of pathological lymph nodes or other new metastatic lesions. Stable disease was subsequently confirmed in every follow-up CT for over 10 months.

In November 2022, after 14 cycles of trabectedin, progression of the retroperitoneal mass and the pulmonary lesions as well as new metastatic hepatic lesions were detected. As a palliative third-line treatment, gemcitabine (1,800 mg/m^2 IV once every 14 days, given first) and dacarbazine (500 mg/m^2 IV once every 14 days, given second) was initiated, from which the patient progressed after 4 cycles.

The CT in February 2023 showed a massive intra-abdominal progression. The known retroperitoneal mass had progressed in size from 6 × 7.5 cm to 6 × 8.8 cm and had an extensive contact with the vena mesenterica superior, the portal vein, and the superior mesenteric artery. The known liver metastases had progressed in size. The suspected infiltration of the duodenum was confirmed. In fourth palliative therapy line, the patient received gemcitabine (1,000 mg/m^2 once every 14 days) in combination with pazopanib (400 mg/per day for 7 days), which was discontinued after 2 cycles due to intolerable adverse events and deterioration of the patient's general condition. Subsequently, the patient received best supportive care.

Discussion

The presented case shows a patient with advanced LMS failing to respond to chemotherapy who achieved a prolonged period of progression-free survival under trabectedin treatment. Already at initial diagnosis, the tumor was at a very advanced stage with a large retroperitoneal mass infiltrating the vena cava and multiple histologically confirmed, non-resectable metastatic lesions in the lung. In such a setting, palliative anthracycline-based

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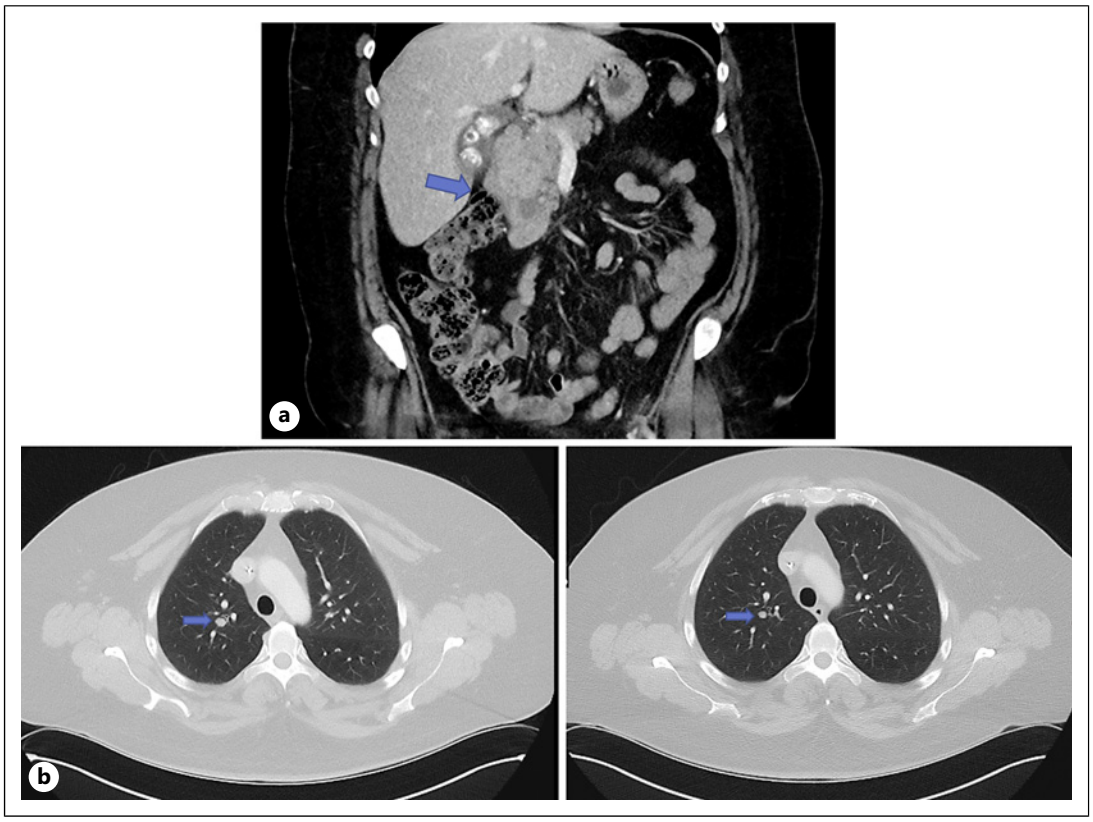

Fig. 2. Abdominal CT images at diagnosis and during trabectedin treatment. **a** CT 10/21 at initial diagnosis. The arrow depicts the tumor with extensive contact with the vena cava. **b** Partial response in the reference pulmonary lesion (blue arrow) during trabectedin therapy. CT left: 01/22, CT right: 04/22.

treatment is the primary therapeutic strategy [6]. Monotherapy with doxorubicin was chosen in view of the expected lower toxicity compared to combination with ifosfamide [8] and because no critical structures were affected, which would have mandated more aggressive treatment. The tumor, however, was completely unresponsive to doxorubicin and had already progressed at the first control visit after 4 cycles of doxorubicin (approximately 3 months). The median progression-free survival with doxorubicin monotherapy was reported to be 4.6 months (95% CI: 2.9–5.6) in a phase III randomized controlled trial in patients with advanced or metastatic STS [8]. Our patient can therefore be considered a nonresponder to standard chemotherapy. At this point, it is important to highlight the need to establish predictive markers of response to systemic therapies, especially for patients who do not respond to standard chemotherapy. Research is being conducted into genomic profiling of uterine and non-uterine LMS [9–11] which will support the identification of targeted therapies for patients who currently have no adequate treatment options.

The patient was subsequently initiated on trabectedin. Chemotherapy refractory LMS was shown in clinical trials to be especially sensitivity to trabectedin. In a phase III randomized controlled trial in patients receiving trabectedin after failure of one or more lines of conventional chemotherapy, patients with non-uterine LMS had a median progression-free survival of 4.9 months, which was significantly longer than in patients receiving dacarbazine in the comparator arm (HR = 0.58, 95% CI: 0.37–0.92) [12]. Under trabectedin treatment, our patient showed a short period of partial remission followed by disease stabilization which lasted over a total of 10 months. Importantly, these additional months of disease stabilization

represented a gain in quality time for the patient and her young child and family. Trabectedin was shown to have direct effects on tumor growth through transcription regulation, as well as effects on the tumor microenvironment through its selective activity on tumor-associated macrophages, inhibition of angiogenesis, reduction of inflammation, and modulation of stroma-mediated resistance to therapy [13]. There is evidence from patient case reports in LMS that disease control well beyond the progression-free survival found in clinical trials can be achieved in selected patients. Skandera reported 19 months of disease control in a patient with advanced non-uterine LMS [14], and Haslbauer reported 22 months of disease stabilization in a patient with metastatic LMS of the inguinal region [15].

Upon progression from trabectedin, the patient received two more lines of palliative therapy, both using gemcitabine as a backbone as recommended by guidelines [6]. However, the benefit of gemcitabine-based regimens has not yet been fully confirmed by comprehensive phase III trials [16]. In a phase II study of gemcitabine plus dacarbazine, the median progression-free survival among patients receiving the combination was 4.2 months [17]. Our patient progressed after 4 cycles (approximately 3 months) from gemcitabine plus dacarbazine. A phase II study of gemcitabine in combination with pazopanib showed a median progression-free survival of 4.1 months [18]. Our patient discontinued this regimen due to intolerable toxicity. Thereafter, no further antineoplastic therapy was attempted and the patient received best supportive care.

Conclusions

This is a case of a chemorefractory patient who showed a response only to trabectedin. The presented patient was treated according to the guideline recommendations under consideration of the unresectable nature of the primary tumor as well as the metastases. In this palliative setting, the treatment strategy was to alleviate the tumor burden and prolong survival while preserving the best possible quality of life. Despite a rapid progression from docetaxel, the disease was stabilized for a prolonged period of 10 months using trabectedin. Trabectedin may thus represent a good second-line option for LMS especially in cases with clear non-response to the first-line chemotherapy and no druggable genetic profile for targeted therapy. Thereafter, the disease could not be further stabilized and the patient ultimately received best supportive care after a total of four lines of palliative treatment. This patient case adds to the growing number of reports indicating that in certain cases trabectedin may allow long-term disease control well beyond that shown in clinical trials.

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Statement of Ethics

Ethics approval is not required for this report of a patient treated in clinical practice according with national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The CARE Checklist has been completed by the author for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533827).

Conflicts of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

The author complies with the ICMJE criteria of authorship, has substantially contributed the acquisition and interpretation of data for the work; reviewed the work critically for important intellectual content; and provided final approval of the version to be published. The author agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

This is a report of a patient treated in routine clinical practice and data not included in this article are protected by physician-patient privilege and subject to the patient's consent to making it available. Further inquiries can be directed to the corresponding author.

References

1 Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer. 2013;49(3):684–95.
2 Mangla A, Yadav U. StatPearls: Leiomyosarcoma. Treasure island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551667/ (accessed 22 May 2023).
3 Martin-Liberal J. Leiomyosarcoma: Principles of management. Intractable Rare Dis Res. 2013;2(4):127–9.
4 Kasper B, Achee A, Schuster K, Wilson R, van Oortmerssen G, Gladdy RA, et al. Unmet medical needs and future perspectives for leiomyosarcoma patients — a position paper from the national LeioMyoSarcoma foundation (NLMSF) and sarcoma patients EuroNet (SPAEN). Cancers. 2021;13(4):886.
5 Lochner J, Menge F, Vassos N, Hohenberger P, Kasper B. Prognosis of patients with metastatic soft tissue sarcoma: advances in recent years. Oncol Res Treat. 2020;43(11):613–9.
6 Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). Ann Oncol. 2021;32(11):1348–65.
7 European Medicines Agency. Yondelis: summary of product characteristics. European Medicines Agency; 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/yondelis-epar-product-information_en.pdf (accessed June 05, 2023).
8 Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014;15(4):415–23.
9 Astolfi A, Nannini M, Indio V, Schipani A, Rizzo A, Perrone AM, et al. Genomic database analysis of uterine leiomyosarcoma mutational profile. Cancers. 2020;12(8):2126.
10 Seligson ND, Tang J, Jin DX, Bennett MP, Elvin JA, Graim K, et al. Drivers of genomic loss of heterozygosity in leiomyosarcoma are distinct from carcinomas. NPJ Precis Oncol. 2022;6(1):29.
11 Lamm W, Natter C, Schur S, Köstler WJ, Reinthaller A, Krainer M, et al. Distinctive outcome in patients with non-uterine and uterine leiomyosarcoma. BMC Cancer. 2014;14(1):981.

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DOI: 10.1159/000533827

12 Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol. 2016;34(8):786–93.
13 D'Incalci M, Badri N, Galmarini CM, Allavena P. Trabectedin, a drug acting on both cancer cells and the tumour microenvironment. Br J Cancer. 2014;111(4):646–50.
14 Szkandera J. Keeping up the "race pace" in a patient with nonuterine leiomyosarcoma. Future Oncol. 2022;18(29s):12–6.
15 Haslbauer F. Long-term progression-free survival in a patient with metastatic leiomyosarcoma of the inguinal region treated with trabectedin. Case Rep Oncol. 2018;11(1):246–51.
16 Ducoulombier A, Cousin S, Kotecki N, Penel N. Gemcitabine-based chemotherapy in sarcomas: a systematic review of published trials. Crit Rev Oncol Hematol. 2016;98:73–80.
17 García-Del-Muro X, López-Pousa A, Maurel J, Martín J, Martínez-Trufero J, Casado A, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol. 2011;29(18):2528–33.
18 Somaiah N, Van Tine BA, Wahlquist AE, Milhem MM, Hill EG, Garrett-Mayer E, et al. A randomized, open-label, phase 2, multicenter trial of gemcitabine with pazopanib or gemcitabine with docetaxel in patients with advanced soft-tissue sarcoma. Cancer. 2021;127(6):894–904.