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Case Report

Long-Term Progression-Free Survival in a Patient with Metastatic Leiomyosarcoma of the Inguinal Region Treated with Trabectedin

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Keywords
Trabectedin · Alkylating agent · Soft tissue sarcoma · Leiomyosarcoma · Metastatic disease · Partial response · Progression-free survival

Abstract
Presented here is the case of an elderly leiomyosarcoma patient with multiple comorbidities and relapses from prior lines of treatment, who experienced a long-lasting progression-free survival. After initial diagnosis, standard treatment protocols with surgery and subsequent adjuvant radiochemotherapy were administered, followed by a short course of oral pazopanib at the patient's request, which led to a rapid relapse. Afterwards, the patient received trabectedin for 22 months, achieving disease control with good quality of life over an extended period of time. After progression from trabectedin, the patient was switched to eribulin. Future clinical trials are needed to investigate the efficacy of trabectedin maintenance treatment and to identify predictive criteria for response to trabectedin among patients with advanced sarcoma.

Introduction

Sarcomas are rare malignant neoplasms arising from mesenchymal cells. They encompass numerous histological subtypes and can occur in virtually any anatomic site. Their total

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crude incidence in Europe is 5.6 per 100,000 persons per year [1]. Soft tissue sarcomas of the inguinal region represent a difficult problem because of misdiagnosis as groin hernia and are often difficult to treat as they develop in constrained anatomical areas where surgery may be complex [2]. Soft tissue sarcomas are diagnosed at a localized stage in 58% of patients. Surgery is the primary treatment for localized, clinically resectable sarcoma, optionally followed by adjuvant radiotherapy as recommended by the European Society for Medical Oncology (ESMO) and the European Sarcoma Network Working Group [3]. In localized, unresectable disease, chemotherapy with or without radiotherapy, or radiotherapy alone is recommended. For advanced and/or metastatic soft tissue sarcomas palliative treatment with various chemotherapeutic, antibody-based options and histology-driven therapies are available [3]. Overall, 5-year relative survival was reported to be 64%, but increased to 80% when the tumor was diagnosed at a localized stage [4].

Here we present the case of a patient with advanced metastatic leiomyosarcoma of the groin who had relapsed from surgery, radiochemotherapy and pazopanib, and subsequently achieved 22 months of progression-free survival (PFS) during treatment with trabectedin.

Case Presentation

We present the case of a 71-year-old female patient who presented to a radiologist because of increasing swelling in the right inguinal region. Figure 1 shows an overview of all diagnostic and therapeutic measures taken and their outcome over time. The patient had an abdominal sonography on 25 October 2013 where a tumorous mass of 3.5 × 2 cm was detected. The tumor was surgically removed on 7 November 2013, with re-excision because of an unclear resection margin on 13 December 2013. The tumor was histologically confirmed as a leiomyosarcoma of 4 cm in size, with a mitotic rate of between 30 and 40 mitoses per 10 high-power fields. Assessment of the medical history of the patient revealed arterial hypertension (treated with a β-blocker and an angiotensin-converting enzyme inhibitor), diastolic forms of heart failure with mild cardiac decompensation (treated with furosemide), hyperuricemia with intermittent gouty arthritis of the right large toe (treated with allopurinol), a struma resection in 1990, and diverticulosis of the colon. On 25 November 2013, a computed tomography (CT) of the thorax and abdomen was conducted to assess tumor staging and no metastases were identified. The case was brought to the tumor board and adjuvant radiotherapy combined with chemotherapy was recommended. Between 20 January 2014 and 28 February 2014, 60 Gy of adjuvant radiotherapy were administered, followed by 6 cycles of doxorubicin 75 mg/m^2 every 3 weeks between 19 March 2014 and 2 July 2014. Ten months after the end of chemotherapy, a follow-up CT revealed hepatic metastases (30 April 2015), which were confirmed as 6 liver metastases between 1 and 14 mm in size by magnetic resonance imaging on 11 May 2015. At the patient's request, oral therapy with pazopanib 800 mg once daily was administered for approximately 3.5 months between 29 May 2015 and 10 September 2015. Pazopanib was subsequently stopped due to disease progression (Fig. 2a). A CT of the abdomen confirmed increasing size and number of hepatic metastases. The patient's treatment was switched to trabectedin 1.5 mg/m^2 every 3 weeks and a total of 27 cycles were administered between 16 September 2015 and 6 June 2017. Trabectedin was well tolerated by the patient. Concomitant granulocyte-colony stimulating factor was given prophylactically due to the patient's age. Abdominal staging CT assessments were conducted every 4 months until progressive disease, diagnosed on 2 August 2017 (Fig. 1, 2b, c). Overall, a PFS of 22 months was achieved under trabectedin treatment. Upon progression, the pa-

tient was switched to eribulin 1.3 mg/m^2 on days 1 and 8 of a 21-day cycle on 3 August 2017.

Discussion

This case is remarkable, because the patient achieved very long disease stabilization under trabectedin treatment, longer than the PFS obtained with previous treatments including radiotherapy and doxorubicin. Additionally, the fact that the patient was older than 70 years with multiple comorbidities and relapses from prior lines of treatment makes this case worth discussing. A randomized controlled trial showing superior efficacy when trabectedin was used until disease progression in comparison with treatment interruption after 6 cycles followed by rechallenge at relapse also supports the use of trabectedin until treatment intolerance or disease progression [5].

Standard treatment protocols with surgery and subsequent adjuvant radiochemotherapy were followed. Metastases were detected approximately 18 months after the first surgery. Oral pazopanib was started at the patient´s request and there was a relapse after approximately 3.5 months. In the PALETTE (PAzopanib expLorEd in sofT-Tissue sarcoma – a phasE III study) trial, the median PFS was 4.6 months in patients receiving pazopanib [6]. After relapse from pazopanib, the patient was initiated on trabectedin, where 2 visits with documented partial remissions as well as 3 control visits showing stable disease were achieved. After 22 months, progressive disease was diagnosed, upon which treatment was changed to eribulin.

The possibility of soft tissue sarcoma patients achieving long-lasting disease control under trabectedin treatment has been largely reported in different clinical trials [7, 8], real life studies [9, 10], and cases reports. Bongiovanni et al. [11] reported the case of a 53-year-old woman with metastatic well-differentiated uterine leiomyosarcoma refractory to multiple treatments. The patient underwent 22 cycles of trabectedin over 30 months with good tolerability. After obtaining a partial response, treatment was discontinued and the response was maintained for an additional 10 months without active treatment. Maruzzo et al. [12] reported a long-term response in a 66-year old patient with metastatic leiomyosarcoma unfit for standard therapy who received 25 cycles of trabectedin as first-line therapy. Disease stabilization was achieved and the patient survived 20 months after the diagnosis of metastatic disease. Galizia et al. [13] described a rare case of a 76-year-old patient with resected primary leiomyosarcoma of the thigh who achieved 17 months of disease stability with 22 cycles of trabectedin treatment in the third line after diagnosis of progressive metastatic lung lesions.

We can only speculate about the reasons of such a long PFS observed in these reports. Bongiovanni et al. [11] hypothesized that trabectedin may be capable of keeping tumor cell growth under control with an oncostatic rather than cytotoxic effect. Trabectedin (ET743, Yondelis®, PharmaMar, Madrid, Spain) is a synthetic alkaloid originally isolated from the Caribbean tunicate, *Ecteinascidia turbinata*. Trabectedin has a unique mechanism of action, as it binds to an atypical position of the DNA, the minor groove, thereby distorting the DNA double helix and generating double-strand DNA breaks. As a result, the transcription profile of cells is altered leading to cell cycle arrest and ultimately inducing tumor cell apoptosis. Trabectedin also interacts with DNA repair mechanisms, making cells with homologous recombination repair (HRR) deficiencies, such as *BRCA1* and *BRCA2* mutations, more sensitive to trabectedin [14, 15]. Finally, trabectedin influences the tumor microenvironment. By tar-

geting tumor inflammation and angiogenesis, trabectedin is able to downregulate the production of proinflammatory mediators by monocytes and tumor-associated macrophages [15]. This multi-target mode of action may explain the durable PFS observed in many patients. The question remains whether a long PFS ultimately translates into a longer overall survival. Noteworthy, the appropriate assessment of antitumoral activity of drugs in advanced soft tissue sarcomas is challenging [16]. For example, the significant improvement of PFS in patients treated with pazopanib [6] or trabectedin [7] did not translate into a significant improvement in overall survival. For pazopanib, median PFS was 4.6 months (95% CI 3.7–4.8) compared with 1.6 months (0.9–1.8) for placebo ($p < 0{\cdot}0001$) and overall survival was 12.5 months (10.6–14.8) versus 10.7 months (8.7–12.8) with placebo ($p = 0.25$) [6]. For trabectedin, median PFS versus dacarbazine was 4.2 versus 1.5 months ($p < 0.001$), and median overall survival for trabectedin versus dacarbazine was 12.4 versus 12.9 months ($p = 0.37$) [8]. Conversely, in the phase III trial assessing the activity of eribulin, a significant improvement of overall survival was observed without improvement of PFS [17]. The median overall survival of patients receiving eribulin was 13.5 months (95% CI 10.9–15.6) versus 11.5 months (9.6–13.0) with dacarbazine ($p = 0{\cdot}0169$), while median PFS was similar with 2.6 months (1.9–2.8) for eribulin and 2.6 months (1.8–2.7) for dacarbazine ($p = 0.23$) [17]. Thus, given the historical difficulty in demonstrating overall survival improvement, the clinical documentation of disease control, measured as PFS, has been proposed as a measure of clinically relevant efficacy in advanced sarcomas [18]. Finally, the convenient safety profile of trabectedin permitted long-term treatment of this elderly patient, who had relapsed from several previous lines of treatment.

Conclusions

Clearly, disease stabilization in combination with good quality of life over an extended period of time is the goal of treatment for most soft tissue sarcoma patients in the advanced setting. Future clinical trials should aim at investigating the efficacy of trabectedin maintenance treatment. In addition, increased efforts are warranted to identify predictive criteria for response to trabectedin for the identification of sarcoma patients with major benefit from trabectedin treatment in the routine clinical setting.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure Statement

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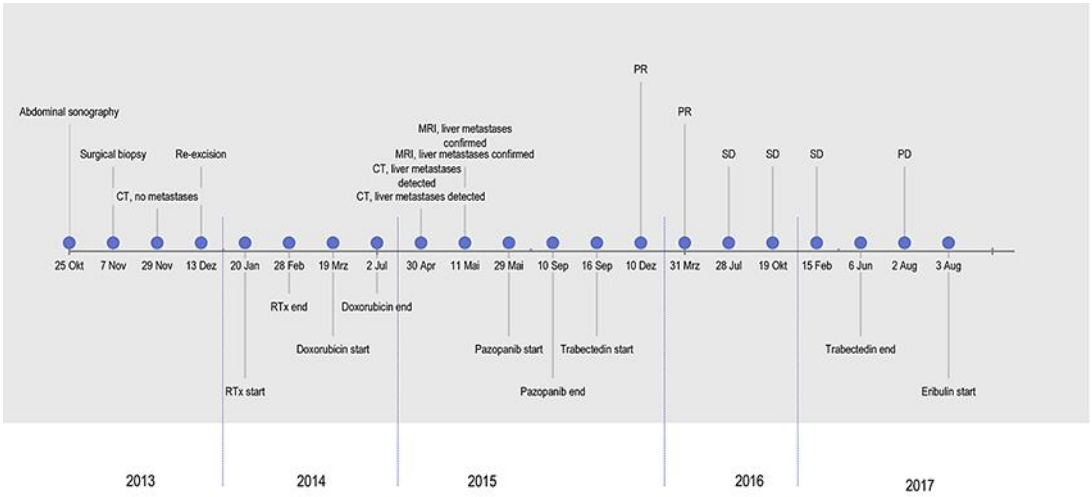

Fig. 1. Overview of diagnostic and therapeutic measures and outcomes over time. CT, computed tomography; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial remission; RTx, radiotherapy; SD, stable disease.

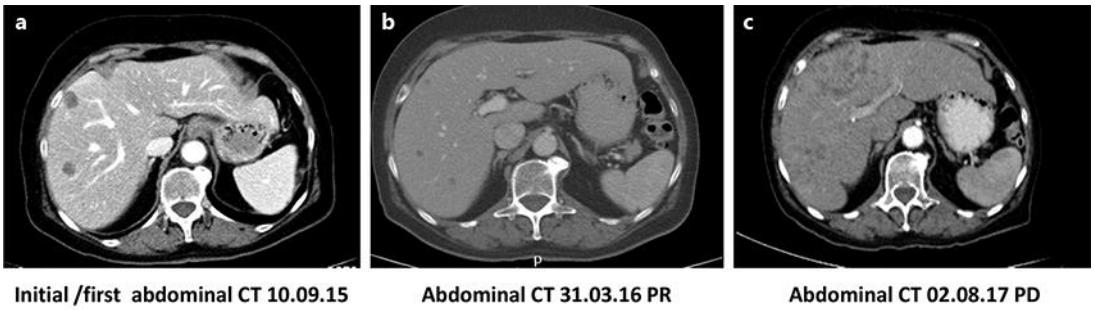

Fig. 2. Abdominal CT images during trabectedin treatment. **a** Disease progression after pazopanib treatment. **b** Second diagnosis of partial remission after 6.5 months of trabectedin treatment (first partial remission observed after 3 months of trabectedin). **c** Disease progression after 22 months of trabectedin treatment. CT, computed tomography; PD, progressive disease; PR, partial remission.