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Case Report

Neoadjuvant Trabectedin plus Radiotherapy in High-Grade Sarcoma of the Leg: A Case Report

António José Loureiro da Silva[a, b] Carolina Carvalho[a] Miguel Jacobetty[a] João Freitas[b] Ruben Fonseca[b] Paulo F. Tavares[b] Helena Garcia[b, c] Margarida Borrego[a] José M. Casanova[b]

[a]Department of Radiotherapy, Coimbra University Hospital, Coimbra, Portugal; [b]Bone and Soft Tissue Tumor Unit, Coimbra University Hospital, Coimbra, Portugal; [c]Department of Anatomical Pathology, Coimbra University Hospital, Coimbra, Portugal

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Abstract
Here, we present the case of a 78-year-old male patient with undifferentiated spindle cell sarcoma on the posteromedial surface of the right leg who experienced a long-lasting progression-free survival. Due to an underlying cardiac disease, the patient was not suitable for anthracyclines. In September 2015, he received first-line chemotherapy with trabectedin (Yondelis®) at the approved dosage and regimen – concomitant with external radiotherapy (RT). After the first 9 cycles of trabectedin plus RT given in the neoadjuvant setting, the patient underwent surgical resection. At that stage, we observed a very good pathological response with 80% of necrotic area. The patient resumed the therapy with trabectedin; however, approximately 5 months later, we observed a new nodular heterogeneous lesion with ill-defined margins in the right leg and suggestive of tumor relapse. Subsequently an above-the-knee amputation was performed, and the patient resumed his trabectedin therapy with the same dosage and regimen. In January 2018, almost 2 1/2 years after the start of trabectedin treatment and 30+ cycles of trabectedin, the patient is locoregionally and distant metastatically disease-free. Currently, the treatment with trabectedin is maintained without any significant serious toxicity.

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António José Loureiro da Silva
Serviço de Radioterapia, Hospitais da Universidade de Coimbra
Praceta Prof. Mota Pinto
PT–3000-075 Coimbra (Portugal)
E-Mail aloureirosilva@hotmail.com

Future clinical trials are needed to gain additional insights into the role of trabectedin maintenance therapy until disease progression in the neoadjuvant setting and to identify predictive and prognostic criteria for response to trabectedin in patients with advanced sarcoma.

Introduction

Soft tissue sarcomas (STS) constitute a heterogeneous group, in terms of histology, molecular biology, and clinical presentations, of rare connective tissue cancers [1]. STS account for 1% of all human cancers and consist of at least 50 histologically different subtypes which have different clinical behavior [2]. In contrast to amputation, limb-sparing surgery has emerged as the treatment of choice allowing to preserve the affected limb while achieving equivalent survival. The integration of chemotherapy and radiotherapy in the management of large high-grade STS as well as the optimal timing of these adjunctive modalities with respect to surgery is still a matter of debate. Chemotherapy and radiotherapy have been combined to increase the chances of local response, decrease the extent of resection, and improve the rate of limb saving. Also, neoadjuvant chemotherapy can enhance the antitumor effect of radiation [3].

Here, we present the case of a patient with undifferentiated spindle cell sarcoma on the posteromedial surface of the right leg who achieved long-lasting disease stabilization under trabectedin treatment receiving a total of 30+ cycles of trabectedin both in the neoadjuvant (combined with radiotherapy) and the adjuvant setting.

Case Report

We present the case of a 78-year-old male patient with no relevant medical history who presented in February 2015 because of onset of pain associated with tumefaction of the right leg (Fig. 1). In March 2015, a contrast-enhanced MRI showed an ulcerated tumor lesion on the posteromedial surface of his right leg, measuring 46 × 30 × 18 mm (Fig. 2a). In June 2015, the lesion was biopsied, and the histological analysis revealed histomorphological features compatible with undifferentiated spindle cell sarcoma. Chest, abdominal, and pelvic CT scans did not show secondary metastatic lesions. We suggested radiochemotherapy treatment to the patient in a neoadjuvant setting. Due to an underlying cardiac disease, the patient was contraindicated to anthracycline therapy. Thus, concomitant external radiotherapy together with trabectedin chemotherapy was finally proposed to the patient. Treatment with trabectedin was started in September 2015 at the approved dosage and regimen: 1.5 mg/m^2 was given as a 24-h infusion on day 1 of every 3-week cycle. Between September 2015 and March 2016, the patient completed a total of 9 treatment cycles.

Parallel to that, between November and December 2015, the patient underwent external radiotherapy with a total dose of 45 Gy in 25 fractions during 5 weeks, directed at the tumor lesion on the right leg. There were no significant toxicities during the whole period of neoadjuvant therapy. An MRI preoperative evaluation performed in April 2016 revealed the same tumor lesion in the subcutaneous tissue of the posteromedial face of the middle third of the right leg, whose dimensions were similar to those of the previous examination. In May 2016, surgical resection with flap was performed, and the tumor was histologically confirmed as a high-grade spindle cell sarcoma with skin ulceration reaching striated muscle tissue. The tumor showed a very good pathological response with 80% of necrotic area; the neoplasia was abutting one of

the circumferential resection margins. No postoperative radiotherapy boost was performed, due to the long healing period that surpassed the optimal period for that procedure.

The patient resumed his therapy with trabectedin in August 2016, following the same treatment regimen. In January 2017, a follow-up CT scan showed no secondary/metastatic lesions. An MRI of the right leg in February 2017 showed a nodular heterogeneous lesion with ill-defined margins, measuring 3 cm in the longitudinal axis and 3.7 × 1.8 cm in the transverse diameters (Fig. 2b). This lesion was suggestive of tumor relapse and had ill-defined margins with subcutaneous and muscular edema. In February 2017, the lesion was biopsied, and the histological analysis revealed a neoplasm on the right leg, compatible with a relapse of the clinically known undifferentiated spindle cell sarcoma.

After group discussion, we proposed above-the-knee amputation to the patient as well as continuation of trabectedin therapy. In March 2017, an above-the-knee amputation was performed, and the histological analysis revealed a local relapse of the undifferentiated spindle cell sarcoma in the medial surface of the right leg, occupying the full width of the soft tissues, causing cutaneous ulceration and involving vascular structures. The patient resumed his trabectedin therapy in April 2017 with the same dosage and regimen. In November 2017, a clinical and image re-evaluation revealed that the patient is locoregionally and distant metastatically disease-free (Fig. 3). Currently, trabectedin therapy is maintained. Up to January 2018, the patient has received a total of 30 cycles, without significant toxicity which mostly consisted of reversible neutropenia and transient transaminase increases.

Discussion

In large high-grade tumors, the rates of local and distant recurrence after surgery alone can be as high as 30 and 50%, respectively [4]. The incorporation of adjunct modalities, such as radiotherapy and systemic chemotherapy, has improved patients' outcomes lowering local recurrence to <10% and reducing distant recurrence hazard ratios by 21–29% when compared with surgery alone, respectively. In general, the preoperative setting is preferred when administering radiotherapy for several reasons: (i) the radiation field can be targeted more accurately due to the presence of the tumor; (ii) the tumor mass, displacing normal tissue, limits the radiotherapy-related toxicity; and (iii) the tumor's pseudo-capsule may thicken when treated with radiotherapy, facilitating subsequent surgical dissection and lowering the risk of intraoperative seeding.

When compared with postoperative radiation therapy in STS of the limbs, the phase III trial of the National Cancer Institute of Canada demonstrated that preoperative radiotherapy to the extremities is associated with reduced late toxicities, such as grade 2 or higher subcutaneous fibrosis, joint stiffness, and edema [5]. Late radiation morbidity was reduced after preoperative radiotherapy at 2 years after treatment (preoperative vs. postoperative: 31.5 vs. 48.2% for fibrosis, 15.1 vs. 23.2% for edema, and 17.8 vs. 23.2% for joint stiffness). The decreased late toxicity in the preoperative arm likely results from a lower radiation dosage (50 vs. 66 Gy) and smaller radiotherapy volumes compared with the postoperative volumes that encompass all surgically manipulated tissues, incisions, and drain sites. In addition, preoperative radiotherapy uses fewer treatment fractions, which decreases costs and improves convenience for patients. Therefore, although preoperative radiotherapy doubles the risk of acute major wound complications, it is often favored for patients with STS. Moreover, historically, different chemotherapeutic agents were added to radiotherapy with the aim to improve tumor sensitivity to radiotherapy and to provide a systemic coverage as well [6].

Trabectedin is a tetrahydroisoquinoline, which was originally isolated from the Caribbean tunicate *Ecteinascidia turbinata* (ATC code: L01CX01) and is now produced synthetically. Trabectedin is unique in that it shares the mechanism of action of a cytotoxic agent and that of a targeted therapy [7]. The characteristic late and long-lasting responses reported with trabectedin, such as prolonged stabilization of tumor size, dormancy of metastases, and central tumor necrosis or tumor calcification, are now supported by the fact that trabectedin acts not only as a cytotoxic but also as an immunomodulating drug with high anti-inflammatory and anti-angiogenic activity [8]. Unfortunately, for STS, the percentage of treatment-induced necrosis is considered a marker of response, but an agreed threshold has not been established, and a correlation between pathological response and clinical outcome is still uncertain [9].

Trabectedin is the first marine-derived antineoplastic drug, approved in 2007 in the European Union and in over 70 countries across the world, for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide or of those who are not suitable to receive these agents. The most common adverse events to trabectedin are noncumulative neutropenia (50% grade ≥3), anorexia, nausea, vomiting, diarrhea or constipation, fatigue, asthenia, or hyperbilirubinemia (1% grade 3 each), and elevated alanine aminotransferase (ALT; 41% grade ≥3) and aspartate aminotransferase levels (AST; 51% grade ≥3) [10, 11]. Noteworthy, in agreement with the safety profile of trabectedin, the overall incidence and severity of those events decreased in frequency over time (cycles) [12]. Because of no cumulative toxicities, trabectedin could be administered for prolonged periods until progressive disease or intolerance (e.g., up to 59 cycles) [13]. This compares favorably with conventional treatments for STS, since cumulative cardiotoxicity induced by doxorubicin prevents protracted treatment and re-treatments with this drug in most cases [14], and renal toxicity and dose-limiting neutropenia have been largely associated with ifosfamide treatment [15].

In conclusion, this case report supports that the administration of trabectedin and radiotherapy is a therapeutic option with significant efficacy and minimal toxicity in the neoadjuvant setting for patients with undifferentiated spindle cell sarcoma. Our results additionally confirm the previously reported favorable toxicity profile of trabectedin, which can be administered for prolonged periods with no evidence of cumulative toxicity. A prospective phase I–II trial exploring the combination of trabectedin plus radiotherapy in patients with STS is currently ongoing (TRASTS study; NCT02275286). The study is testing the hypothesis that administering trabectedin plus radiotherapy shows synergic activity that favors tumor shrinkage.

Statement of Ethics

Informed consent for publishing the case was obtained from the patient. No personal identifiable information was utilized.

Disclosure Statement

The authors report no conflicts of interest.

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Fig. 1. Overview of diagnostic and therapeutic measurements and outcomes in our patient over time.

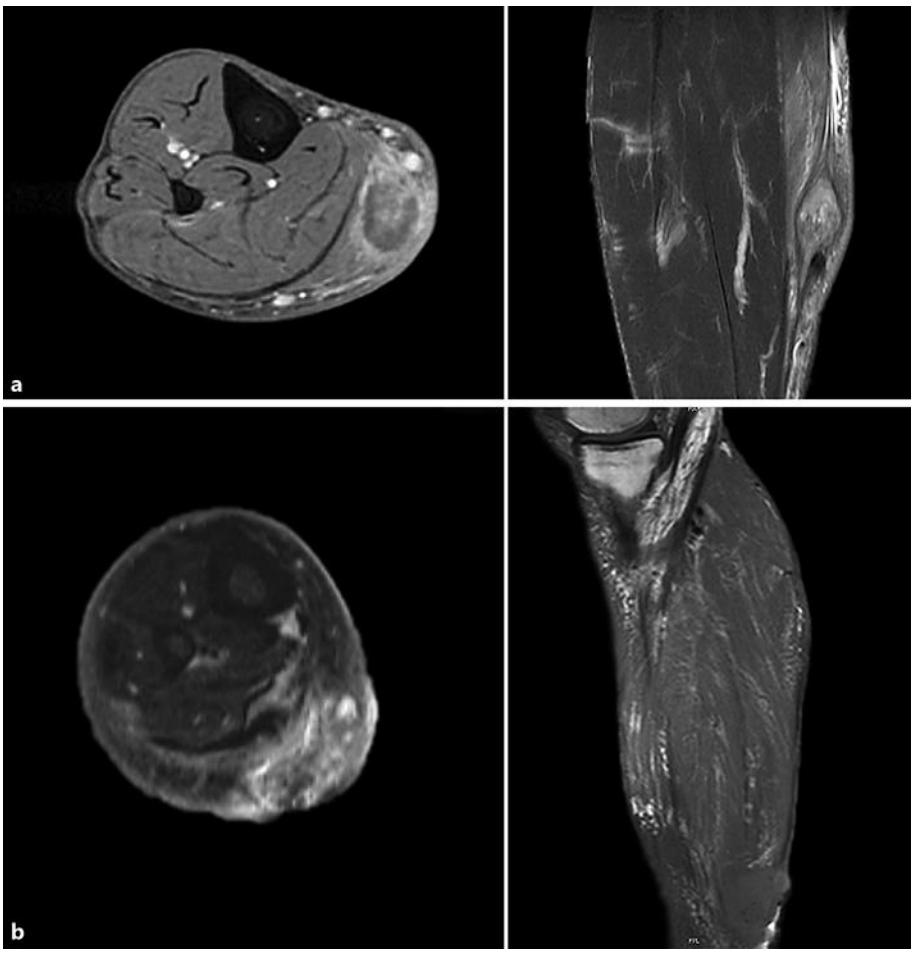

Fig. 2. MRI scans of the patient's right leg.

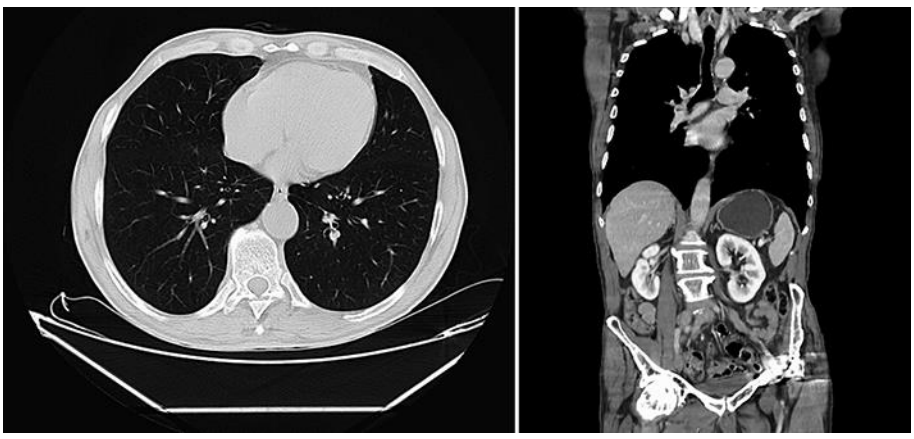

Fig. 3. A chest, abdominal, and pelvic CT confirming stable disease without metastases (November 2017).