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Trabectedin in Advanced High-Grade Uterine Leiomyosarcoma: A Case Report Illustrating the Value of ^{18}FDG-PET-CT in Assessing Treatment Response

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Key Words
Sarcoma · Trabectedin · Delayed response · ^{18}FDG-PET-CT · Uterine leiomyosarcoma

Abstract
We report the case of a 60-year-old woman with metastatic high-grade uterine leiomyosarcoma who achieved a delayed response to second-line therapy with the marine-derived drug trabectedin (Yondelis®, PharmaMar). We used 2-deoxy-2-[^{18}F] fluorodeoxyglucose (FDG)-positron emission tomography (PET-CT) imaging as a tool for response monitoring in parallel with conventional re-staging according to Response Evaluation Criteria in Solid Tumours (RECIST) using computed tomography (CT). We illustrate the role of serial ^{18}FDG-PET-CT imaging in the functional assessment of tumour response. Three cycles after commencement of trabectedin treatment, a reduction of the maximum standardized uptake value (SUV_{max}) of the solid component of the pelvic mass was observed, indicating a cystic or necrotic response in the tumour to trabectedin. After 7 cycles of treatment, on ^{18}FDG-PET-CT there was clear evidence of ongoing disease improvement: the solid pelvic components were at worst stable, with an unchanged SUV_{max}, and possibly marginally reduced in size, while the pulmonary metastases had further reduced in size and become FDG negative; the bony metastases were stable. After a total of 13 cycles of treatment, administered over 13 months, the patient showed signs of progression on an ^{18}FDG-PET-CT scan. The safety profile of

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trabectedin remained manageable, showing no evidence of cumulative toxicity and being associated with a preserved quality of life. This report illustrates potential limitations of RECIST in response assessments and the critical role of serial ^{18}FDG-PET-CT imaging in assessing response to trabectedin treatment. Therefore, we propose that ^{18}FDG-PET-CT may improve the assessment of response to trabectedin in selected patients.

Introduction

Smooth muscle-derived uterine leiomyosarcomas are frequently aggressive tumours accounting for one third of all uterine sarcomas [1]. Even with early diagnosis, metastatic recurrence rates are high for leiomyosarcoma, with the lung, subcutaneous regions and abdominal cavity being the most frequent sites [2]. Prognosis is particularly poor when the primary tumour is large or already spread beyond the pelvis [3]. On diagnosis of relapsed disease, treatment is palliative in intent with a median survival of less than 1 year. Single-agent palliative chemotherapy has been shown to have some activity in locally advanced or metastatic uterine leiomyosarcoma, but the most encouraging results to date have been produced by the combination of gemcitabine and docetaxel, although even this regime was associated with a response rate of less than 40% in a phase II trial [4].

Trabectedin (Yondelis®, PharmaMar) is the first marine-derived antineoplastic drug approved by the European Medicines Agency in 2007, and by the National Institute for Health and Clinical Excellence (NICE) in 2010, for the treatment of patients with advanced soft tissue sarcoma (STS) after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. In addition, based on the results of a large phase III study (OVA-301) comparing pegylated liposomal doxorubicin alone with a combination of trabectedin and pegylated liposomal doxorubicin, in 2009 the European Commission granted the second marketing authorization for trabectedin combined with pegylated liposomal doxorubicin for patients with relapsed platinum-sensitive ovarian cancer. Trabectedin has a unique mechanism of action based on interaction with the minor groove of the DNA double helix; it affects gene transcription and DNA repair pathways, resulting in G2-M cell cycle arrest and ultimately apoptosis [5]. Trabectedin cytotoxicity is determined by the functional nucleotide excision repair and deficient homologous recombination repair machinery. In addition to direct growth arrest, trabectedin at therapeutic concentrations has selective anti-inflammatory and immunomodulatory properties due to the inhibition of factors that promote tumour growth, angiogenesis and metastasis [5, 6].

Trabectedin represents a novel approach to the management of STS. Although objective response rates are rather low, unexpectedly durable responses have been reported. For instance, in 1 phase II trial the duration of response was up to 20 months (median 9 months) [7], and 6-month progression-free survival rates of over 20% have been reported [8, 9]. Noteworthy, recent data have demonstrated that trabectedin selectively targets mononuclear phagocytes, including tumour-associated macrophages, and downregulates the production of proinflammatory mediators, which induces changes in the tumour microenvironment contributing to its antitumour activity [6]. Recently, a retrospective analysis of 66 patients pretreated for metastatic uterine leiomyosarcoma reported that 11 patients achieved a radiological partial response according to Response Evaluation Criteria in Solid Tumours (RECIST), whilst a further 23 demonstrated stable disease following treatment with trabectedin [10]. Moreover, 2 patients achieved a delayed response to treatment, 1 showing a response after 10 cycles and another, who had already demonstrated a decrease in tumour

density, finally achieved a reduction in tumour size after 14 cycles of trabectedin. Hence, there is hope that trabectedin may achieve clinically useful disease control despite little initial radiological evidence of response.

Herein, we evaluated the use of 2-deoxy-2-[^{18}F] fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) imaging as a tool for response monitoring in the treatment of a 60-year-old woman with metastatic high-grade uterine leiomyosarcoma undergoing therapy with trabectedin.

Case Report

A 60-year-old woman presented following 2 episodes of postmenopausal bleeding, several months apart. The patient had no significant medical, surgical or family history, was on no medication and with all previous screening investigations reported as normal. Initial trans-abdominal and trans-vaginal ultrasound scans demonstrated appearances which were felt to be consistent with uterine fibroids. A subsequent CT scan confirmed a large (80 × 60 mm) heterogeneously enhancing but predominantly hypo-dense mass within the uterus, extending deeply, with only a very thin layer of normal myometrium. There were no enlarged lymph nodes and no evidence of local or distant disease spread. Endometrial chippings obtained by Pipelle biopsy demonstrated a high-grade sarcoma, with a mitotic count of 15 per 10 high-powered fields. Cells were positive for vimentin, strongly positive for oestrogen receptors and moderately positive for progesterone receptors. Staining for cytokeratin, actin, myoD1 and CD10 was negative. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed, following which histology confirmed a high-grade, undifferentiated sarcoma of the uterine corpus extending deeply into the myometrium and reaching up to the serosa.

Lymphovascular invasion was present and the mitotic count was high, at 42 per 10 high-powered fields. There was no evidence of malignancy affecting the fallopian tubes, ovaries, cervix or the single pelvic lymph node removed. Peritoneal washings were negative for malignancy. This was reported as an International Federation of Gynaecology and Obstetrics (FIGO) stage 3a high-grade uterine sarcoma [11]. Following surgery, the patient commenced a course of adjuvant chemotherapy, receiving five 3-weekly cycles of the combination of doxorubicin (50 mg/m^2) and ifosfamide 5 g/m^2 (1,700 mg/m^2 on days 1, 2 and 3). Repeat CT imaging of the chest, abdomen and pelvis was performed on completion of adjuvant chemotherapy and, again, 26 months after surgery. On neither scan was there any evidence of metastatic disease. At a routine review 31 months after surgery, the patient described a short history of new pelvic discomfort although she remained well, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Magnetic resonance imaging (MRI) of the pelvis confirmed a large (7.5 × 5 cm) heterogeneous mass in the anterior pelvis, indenting the bladder, with 2 soft tissues nodules (3 × 2.3 and 1.6 × 1.4 cm) in the pelvis. A subsequent CT scan demonstrated new pulmonary metastases and a bone metastasis in the T7 pedicle.

On confirmation of metastatic disease, and in view of the strongly positive staining for oestrogen receptors on the original histology, the treatment selected was a trial of the aromatase inhibitor letrozole (2.5 mg). However, CT reassessment after 8 weeks of therapy demonstrated a marked increase in the size of the pelvic masses, along with minor increases in the sizes of both the pulmonary and T7 metastases. There was new metastatic involvement of the L3 pedicle. An ^{18}FDG-PET-CT scan confirmed the disease was moderately FDG avid and revealed multiple additional sites of skeletal involvement, including the right

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scapula, left sixth rib and right acetabulum. The multiple pelvic masses were described as being confluent and part solid, part cystic, with a maximum axial dimension of 13 cm. The cystic components were FDG negative, whilst the most FDG-avid soft tissue component was located medial to the right external iliac vessels, with a maximum standardized uptake value (SUV_{max}) of 9.4.

Considering disease progression with letrozole, trabectedin was commenced at an initial dose of 1.5 mg/m^2 administered as a 24-hour intravenous infusion every 3 weeks. Each infusion was preceded by 500 ml 0.9% sodium chloride and 20 mg dexamethasone intravenously. Treatment was tolerated well with grade 2 fatigue and grade 1 nausea, responding to oral cyclizine, being the worst trabectedin-related adverse events. The patient's ECOG performance status continued to be 0 for at least half of every cycle and was never greater than 1. After 3 cycles of trabectedin, a further ^{18}FDG-PET-CT scan was performed to assess initial response to therapy (fig. 1, right panel). The pulmonary disease was stable and the skeletal deposits had marginally increased in avidity. There was a marked increase in the size of the pelvic mass, with expansion of the cystic component, such that the maximum diameter was now 20.1 cm. However, there was an associated reduction in the SUV_{max} of the solid component of the pelvic mass, indicating a cystic or necrotic response in the tumour to trabectedin, with the site of most active disease displaying reduced FDG uptake. No new lesions were identified. Taking into consideration the response detected by PET-CT, treatment continued with trabectedin.

Following 3 cycles, the frequency of administration was reduced to 4-weekly, and after 6 cycles the dose was reduced to 1.3 mg/m^2. Each change was made in response to escalating fatigue (>grade 2). A pelvic ultrasound scan after the sixth cycle of trabectedin suggested a subjective interval decrease in the solid peripheral component of the pelvic tumour. Yet, before the patient could proceed to cycle 7 she was admitted for acute abdominal pain and vomiting. At this stage a repeat pelvic ultrasound scan revealed that the complex pelvic mass had collapsed, with crenation of the peripheral margin and new moderate-volume generalized ascites. A total of 3.7 litres of sero-sanguinous fluid was drained with marked symptomatic relief, and the patient was discharged home after 48 h with no treatment delays. A further 2 cycles of trabectedin 1.3 mg/m^2 were administered at 4-weekly intervals, following which reassessment of the extent of disease was made. Interpretation was complicated by the pelvic cystic collapse and subsequent drainage, altering tumour size and by implication any response measure as per RECIST. However, on ^{18}FDG-PET-CT there was clear evidence of ongoing disease improvement after 7 months of treatment with trabectedin (fig. 1). The lingular pulmonary metastasis had reduced in size and become FDG negative, and there was further reduction in the size of a second left upper lobe pulmonary metastasis. The bony metastases were stable. The solid pelvic components were at worst stable, with an unchanged SUV_{max}, and possibly marginally reduced in size. The patient continued on trabectedin 1.3 mg/m^2, 4-weekly, finally showing signs of progression on an ^{18}FDG-PET-CT scan performed after a total of 13 cycles of treatment, administered over 13 months. The safety profile of trabectedin remained manageable, showing no evidence of cumulative toxicity, maintaining quality of life. Fatigue resulted in an ECOG performance status that fluctuated between 0 and 1 during the treatment.

All procedures were conducted in accordance with the Declaration of Helsinki, guidelines for good clinical practice and local regulations, and were approved by the institutional review board. Signed informed consent was obtained from the patient.

Discussion

This report describes a patient with metastatic high-grade uterine leiomyosarcoma who demonstrated a delayed response to second-line therapy with trabectedin. It also illustrates potential limitations of RECIST in assessing response to trabectedin treatment, and the critical role of serial ^{18}FDG-PET-CT imaging in assessing response to treatment with trabectedin.

Our patient demonstrated a radiological reduction in tumour size only after 6 cycles of trabectedin. A delayed response to treatment with trabectedin has been reported previously [10, 12, 13]. Whilst the anti-proliferative effects of trabectedin may be mediated primarily via effects on the nucleotide excision repair pathway [5], it has been proposed that more diffuse stromal effects may also contribute to the delayed tumour responses which have been reported [5, 6]. The characteristic late and long-lasting responses, such as prolonged stabilization of tumour growth and dormancy of metastases reported with trabectedin, 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 antiangiogenic activity [6]. Thus, the potential for tumour response to occur several months after commencing trabectedin means that careful assessment of each patient, at each stage in their treatment, is imperative.

In this patient, ^{18}FDG-PET-CT metabolic imaging was crucial for patient monitoring and treatment. A reduction in FDG avidity indicated disease response, but was associated with an increase in the overall volume of the recurrent pelvic disease. Response assessment with MRI or CT alone, according to RECIST, would have been inadequate and misleading and would have required CT Choi criteria of changes in contrast enhancement as part of the comprehensive reporting of response. ^{18}FDG-PET with CT has revolutionized oncological imaging by providing metabolic and anatomical imaging combined in a single examination and offers an alternative quantitative assessment of response. ^{18}FDG-PET as a modality to monitor treatment response in patients with high-grade STS has been shown to correlate well with histological response, which often precedes anatomical changes [14]. It is therefore crucial to consider that this imaging modality has an integral role in response assessment in tumours, where disease response cannot be assessed on the basis of a reduction in tumoural size alone. Our results confirm those reported by Kasper et al. [15], who examined patients with metastatic STS treated with trabectedin using ^{18}FDG-PET and, in parallel, conventional imaging of the same target lesion using CT and/or MRI to determine the response according to RECIST. Taken together, this group deemed that ^{18}FDG-PET imaging may complement radiological tomography and histological grading, thus improving the assessment of STS and influencing therapeutic decisions in the future.

This case report also provides evidence in support of stable disease as an acceptable endpoint in the treatment of metastatic leiomyosarcoma with trabectedin. This patient exceeded 12 months of maintenance therapy with trabectedin, at reduced dose intensity. Symptomatically, clinically and radiologically her disease remained stable over a long period. Treatment was associated with a preserved quality of life, which was acceptable to the patient, allowing her to pursue normal activities for much of the treatment cycle. Trabectedin therefore offers the realistic prospect of a well-tolerated maintenance regime in this aggressive disease.

Disclosure Statement

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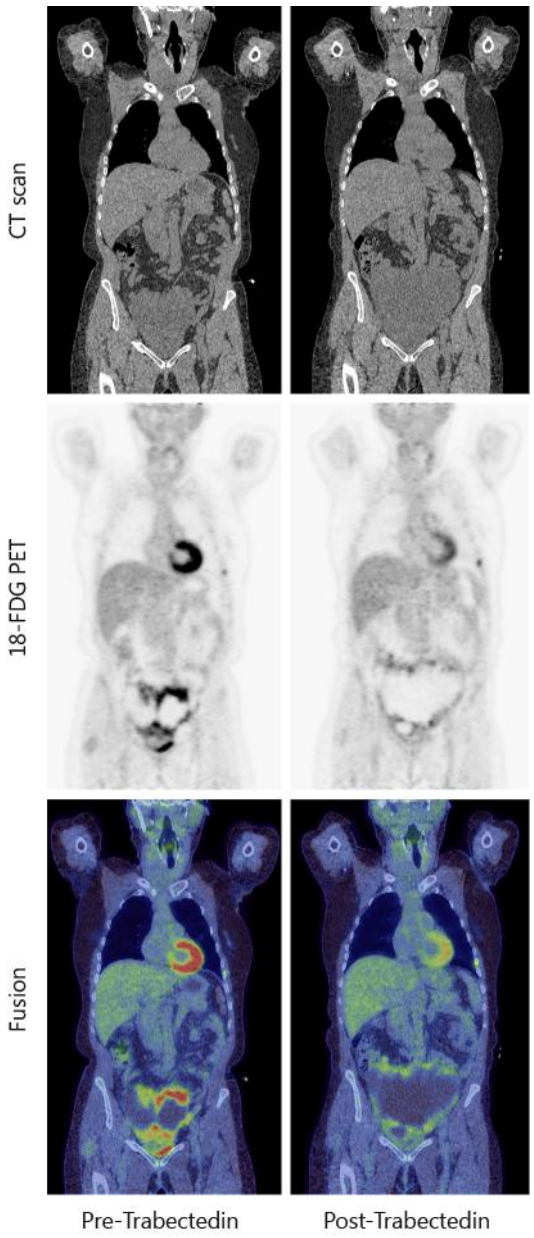

Fig. 1. Comparison of ^{18}FDG-PET-CT images before and 3 months after treatment with 3 cycles of trabectedin. There is expansion of the mass in the pelvis, with reduced ^{18}FDG uptake and formation of a larger cystic/necrotic cavity within the mass. Note the left rib lesion. The PET images and fused PET-CT images are on an identical SUV 0–6 scale.