Case 1 – Treatment of uterine sarcoma with 3-hour trabectedin intravenous infusion

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Abstract
We report a case of advanced uterine leiomyosarcoma treated with trabectedin first-line, in a patient unfit for standard chemotherapy treatment, with off-label schedule of 3 hours infusion.
The patient had a progressive disease by RECIST after 3 cycles of trabectedin, with improvement of Eastern Cooperative Oncology Group (ECOG) perfomance status and early signs of tissue response; after 6 cycles we got a partial response by RECIST that has been confirmed after 13 cycles of trabectedin with no relevant toxicity.
We showed that trabectedin administered in first-line and with an off-label schedule could be effective in advanced uterine leiomyosarcoma; the response could appear later and RECIST criteria for the evaluation of response may be not effective with this drug.

Key words: soft tissue sarcoma, trabectedin, uterine leiomyosarcoma

Introduction

Trabectedin is a marine-derived antineoplastic agent. It is indicated in Europe in patients with advanced soft-tissue sarcoma who have progressed despite receiving previous treatment with anthracyclines and ifosfamide or in those who are unable to receive these agents [1].
To investigate the efficacy of trabectedin in uterine leiomyosarcoma, a retrospective case series analysis was conducted of patients treated with trabectedin at two reference sarcoma centers in Europe between 2000 and 2010 [2]. In all, 66 patients with metastatic uterine leiomyosarcoma were identified. The overall tumor control rate was 51% (16% partial responses; and 35% stable disease). Progression-free survival of the entire cohort was 3.3 months, and the progression-free rate at 3 and 6 months was 53% and 33%, respectively. At present, a prospective study, ongoing in Italy, is investigating the use of trabectedin as second line treatment in advanced uterine leiomyosarcoma.
We report a case of a 47-year-old female with a diagnosis of advanced uterine leiomyosarcoma and treated with trabectedin in first-line with off-label schedule of 3-hours intravenous infusion.

Case report

In June 2010, the patient presented with recurrent metrorrhagia, intense fatigue and dyspnoea.
On admission at our hospital, she had severe anaemia (haemoglobin 6.3 g/dL) and a voluminous mass in the pelvic abdominal region. She was treated with a transfusion of red blood cells and plasma to restore volume and reduce weakness.
A computed tomography (CT) scan showed the presence of a bulky pelvic mass (maximum diameter 25 cm) arising from the uterine body, with mediastinal and abdominal lymphadenopathy and bilateral lung metastases. Bilateral pleural effusion, bilateral pulmonary embolism and deep vein thrombosis of the external iliac, femoral and right saphenous vessels were also present.
Positron emission tomography (PET scan) confirm the CT scan results.
The patient was given anticoagulation therapy with subcutaneous (s.c.) eparin at therapeutic dosage and placed infrarenal inferior vena cava filter.
In July 2010, the patient underwent exploratory laparotomy, hysterectomy and bilateral annessiectomy and removal of an enlarged external iliac lymph node. On intraoperative palpation and inspection there were no other suspects in the abdominopelvic lymph nodes and in the peritoneum.
An intraoperative histological examination indicated the presence of a pleomorphic mesenchymal malignancy and

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the definitive histological examination showed a high-grade uterine leiomyosarcoma with myxoid and pleomorphic pattern. The tumour infiltrated the myometrium and extended to the cervical canal, with a high mitotic rate (75/10 HPF) and peritumoral vascular invasion.

The postoperative course was uneventful and the patient was followed in the intensive care unit and then in the gynaecological oncology department as per protocol.

In August 2010, the patient underwent a brain CT scan to complete the staging and no secondary lesions or vascular complications were found. A CT scan of the chest and abdomen repeated postoperatively showed recanalization of the inferior vena cava and pulmonary vein, persistence of reactive abdominal lymphadenopathy and bilateral lungs lesions, the major one in the right lung of 3.2 cm diameter.

The patient was discharged 17 days after surgery in good general condition and refused any medical treatment.

In October 2010, the patient had intense pelvic pain and severe asthenia; a PET scan showed progressive disease in the lungs and in the abdomen, with a lesion in the right abdominal quadrant.

The patient refused medical treatment that caused alopecia (e.g. anthracyline-based chemotherapy or docetaxel and gemcitabine), and we proposed trabectedin as first-line treatment, but the patient decided to delay it.

In early December 2010, we observed a deterioration in general condition with worsening abdominal pain; trabectedin treatment was re-proposed and the patient agreed to start it at a dose of 1.5 mg/m^2, but not at the continuous 24-hour infusion rate schedule approved for soft tissue sarcomas, but over 3 hours, for personal reasons. The radiological evaluation was unchanged from October 2010 and a central venous line was placed for drug infusion.

On 28 December 2010, the patient started treatment with a 3-hour infusion of trabectedin 1.5 mg/m^2 monotherapy every 21 days. After 3 cycles an improvement in Eastern Cooperative Oncology Group (ECOG) performance status was seen, but a CT scan showed a slight progression of lung lesions. We found progressive disease according to RECIST criteria in the abdominal lesion, with extensive areas of necrosis within it. We also found suspicious secondary lesions in the liver and peritoneum.

Regardless of the progression, we decided to continue trabectedin treatment for another 3 months using the same schedule.

Clinical evaluation in May 2011 found better performance status and a total regression of pelvic pain by visual analog scale (VAS). A CT scan showed stable disease according to RECIST criteria in the lung, peritoneum and omentum; a partial response according to RECIST criteria was seen in the liver and in the abdomino-pelvic lesion with more extensive areas of necrosis within it.

The patient continued trabectedin at the same dose and schedule and, on CT re-evaluation after 13 cycles in October 2010, we found progressive disease according to RECIST criteria in the lung with a colliquative necrotic component and stable disease according to RECIST criteria in the other disease sites.

During treatment there was no severe toxicity (transaminitis, asthenia or haematological toxicity), except for grade 2 anaemia after 6 cycles treated with erythropoietin.

Conclusion

We showed that trabectedin administered as first-line, in a patient unfit for standard first-line treatment, and using a 3-hour infusion schedule, could be effective in advanced uterine leiomyosarcoma.

It is clear that objective tumor shrinkage may not be the only manner in which therapeutic activity is manifest in soft tissue sarcoma subtypes [3, 4]. Response evaluation criteria for soft tissue sarcoma will almost certainly be modified in the upcoming years [5].

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Commentary

The concept of tumor response in medical oncology dates back to David Karnofsky, as early as in 1948 [1, 2]. It was conceived as a means to standardize how antitumor activity was assessed in Phase 2 studies, which are usually followed by Phase 3 trials to evaluate efficacy. Viewed as a tool to "screen" potential new drugs, reproducibility was the main concern. Throughout the years, tumor response assessment was standardized, and simplified, even further, with RECIST criteria measuring just one diameter of selected target lesions [3], in spite of two diameters, as originally meant and then formalized in ECOG and WHO criteria [4, 5]. However, tumor response is also a clinical concept, since it is the best criterion to modulate treatment as long as it is administered. If the patients responds, one goes on with therapy, and vice versa. This implies that "validity" of tumor response assessment is even more important than reproducibility, response being intended to measure if a treatment is active against the tumor or not, i.e. possibly effective in a given patient.

In this sense, the concept of tumor response has always been weak to some extent. At the very least, the choice of a completely arbitrary threshold for regression in size is devoid of any clinical meaning. In addition, response assessment based exclusively on shrinkage is well known to fail in some instances even with classic cytotoxic chemotherapy. For example, tumor response to induction chemotherapy in osteosarcoma may well be lacking any regression in size. With targeted therapies, this has become even more clear. For example, tumor response to targeted agents in gastrointestinal stromal tumors may well be marked by radiological changes in tumor tissue without any shrinkage, and sometimes tumor volume may even increase, especially at the beginning of therapy [6].

Trabectedin is a cytotoxic, whose mechanism of action, however, is more complex than originally believed. This is certainly the case with myxoid liposarcoma, where the drug has specific effects on gene transcription in the context of a translocation-related sarcoma [7]. In uterine sarcoma, the mechanism of action does not seem so specific, but it happens to see patients responding in a non conventional fashion. In this case, there was a RECIST response, indeed. However, it did not took place immediately. On the contrary, the first tumor assessment was marked by an apparent progression, slight though it was. The clinician felt that it could be worthwhile to go on trying the drug, and this policy was successful. It is impossible to recommend such a policy in all cases of early progression. However, in a limited number of cases it may happen that progression is minor, and/or that the patient subjective status has improved in spite of radiology, and/or that a discordant behavior is seen across lesions, and so on. In these cases, one should be aware that tumor response to trabectedin may establish slowly in sarcomas, so that what is seen early may not be the definitive answer.

It is difficult to explain biologically all this. In principle, it may well depend on peculiarities of the disease and/or the drug. Likewise, it is difficult to work out new tumor response criteria, fit for new anticancer agents, including trabectedin, accomodating all this for clinical research. However, the clinical setting does not pose the same requirements of the research setting of a Phase 2 study. The medical oncologist should and can exercise his/her clinical skill to individualize tumor response assessment, with a view to a personalized medical decision in the single patient.

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