Case 1 – Maintenance treatment with trabectedin in advanced soft tissue sarcomas: when should we consider progression?

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Abstract
We present the case of a patient with a locally advanced synovial sarcoma treated with neoadjuvant chemotherapy and subsequent surgery who presented an early metastatic relapse, wherein a rapid and significant response was achieved with trabectedin, and in whom maintenance of the drug until clinical progression of the disease allowed 27 cycles of treatment to be administered despite the patient presenting radiological progression according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria 15 cycles earlier.

Key words: maintenance treatment, RECIST criteria, response evaluation, soft tissue sarcoma, trabectedin

Introduction

Soft tissue sarcomas (STS) represent a very heterogeneous group of tumors based on both their anatomical location and histological subtypes. In the localized stages, surgery with or without radiotherapy and in selected cases adjuvant chemotherapy, are the treatment of choice. In advanced stages, chemotherapy instead plays a leading role, with combination regimens including anthracyclines having demonstrated the best response rates in the first line setting [1]. Trabectedin is a drug that has been found to be effective and safe in a number of phase II clinical trials, and recently in a phase III trial *versus* dacarbazine, that have included patients with a range of histological subtypes, more often leiomyosarcoma and liposarcoma [2-5]. Moreover, retrospective and prospective studies comparing maintenance against interruption of treatment have demonstrated that maintenance treatment with trabectedin is associated with higher rates of progression-free survival compared to interruption, with a percentage of long-term responders [6, 7, 8]. This, together with its good safety profile and lack of cumulative toxicity, makes maintenance with trabectedin a very attractive therapeutic strategy. Here we present the case of a patient with advanced synovial sarcoma and rapid progression during neoadjuvant treatment with anthracyclines and ifosfamide, treated subsequently with trabectedin and achieving a very good response, and in whom maintenance of the drug until clinical progression of the disease allowed 27 cycles of treatment to be administered over more than two years, with good tolerance.

Clinical case study

A female patient, 61 years old, with a medical history of arterial hypertension and no significant history of cancer, was referred from the Traumatology Department of our hospital in October 2010 due to progressive pain and swelling in the right knee. Magnetic resonance imaging (MRI) was performed, which revealed a large soft tissue mass with probable involvement of the femoral condyle (Figure 1). In March 2011, she was referred to the Multidisciplinary Musculoskeletal Tumour Unit at the reference hospital. A percutaneous biopsy was performed and the histopathological diagnosis was found to be compat-

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CANCER BREAKING NEWS 2016;4(2):42-47
DOI: 10.19156/cbn.2016.0017

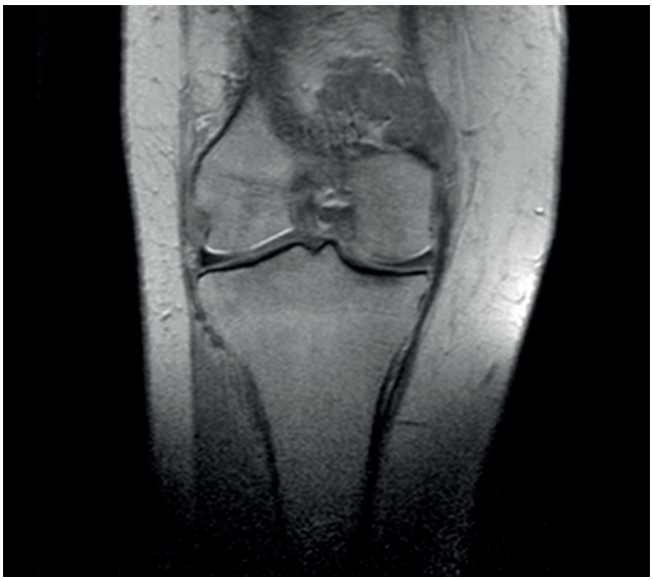

Fig. 1. Basal magnetic resonance image (MRI) of soft tissue mass with femoral condyle involvement.

ible with a malignant mesenchymal tumor, histologically and immunohistochemically very indicative of a monophasic fibroblastic synovial sarcoma. An extended computed tomography (CT scan) study ruled out the existence of remote metastasis. From April to May 2011, 3 cycles of high dose epirubicin and ifosfamide were administered as a neoadjuvant treatment. The re-evaluation MRI showed no changes to the local lesion.

In June 2011, surgery was performed to amputate the right lower extremity. The definitive pathological anatomy was of a monophasic fibroblastic synovial sarcoma.

At the first follow-up a CT scan (October 2011) showed the existence of multiple pulmonary nodules consistent with metastasis. The patient was referred back to our center and a new CT scan was performed (December 2011), in which numerous bilateral pulmonary nodules were discovered that had significantly increased in number and size since the previous study.

Because of the previous treatment with anthracyclines and the rapidly progressive disease, we decided to start chemotherapy with trabectedin at a dose of 1.5 mg/m^2 in a 24-hour continuous infusion administered every 21 days. The CT scan performed after 4 cycles of treatment showed significant reduction in the pulmonary lesions (Figure 2). After 6 treatment cycles, positron emission tomography (PET) was performed to verify metabolic activity in the pulmonary lesions, which revealed persistent tumor metabolic activity in both lungs (Figure 3). For this reason, the decision was made to continue treatment with trabectedin. After 12 treatment cycles, a new CT scan showed the appearance of a new subpleural lesion and slight growth of some nodules, compatible with disease progression according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria (Figure 4). The patient remained asymptomatic with good tolerance of the treatment, and for this reason the decision was made to continue the treatment with trabectedin with close clinical and radiological follow-up. She remained clinically and radiologically stable at subsequent follow-up until cycle 23. After 23 treatment cycles, the new CT scan revealed a slight increase in the size of the pulmonary nodules and subpleural metastasis. As the patient remained clinically asymptomatic, the treatment with trabectedin was continued. After 27 cycles, in May 2014, the patient presented a clinical deterioration with dyspnea and thoracic pain and the CT scan revealed a significant increase in the pulmonary lesions (Figure 5). Given the clinical and radiological progression as evaluated based on the RECIST criteria and the

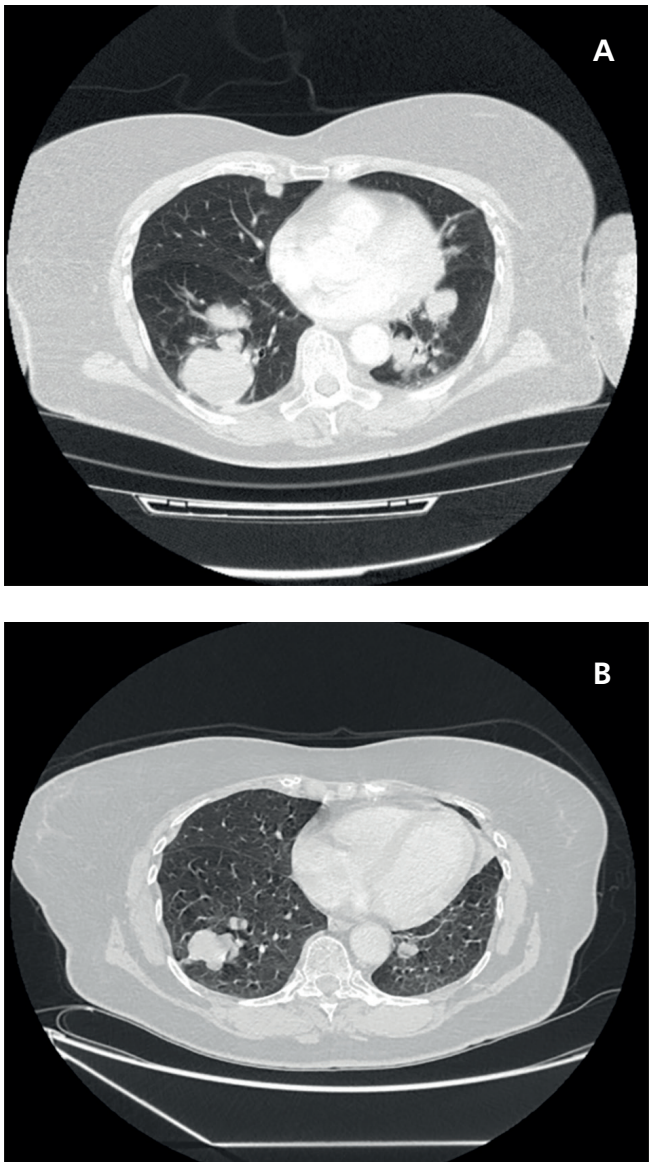

Fig. 2. Computed tomography (CT) scan prior to initiating trabectedin (A) and after 4 treatment cycles (B) showing partial response according to RECIST criteria.

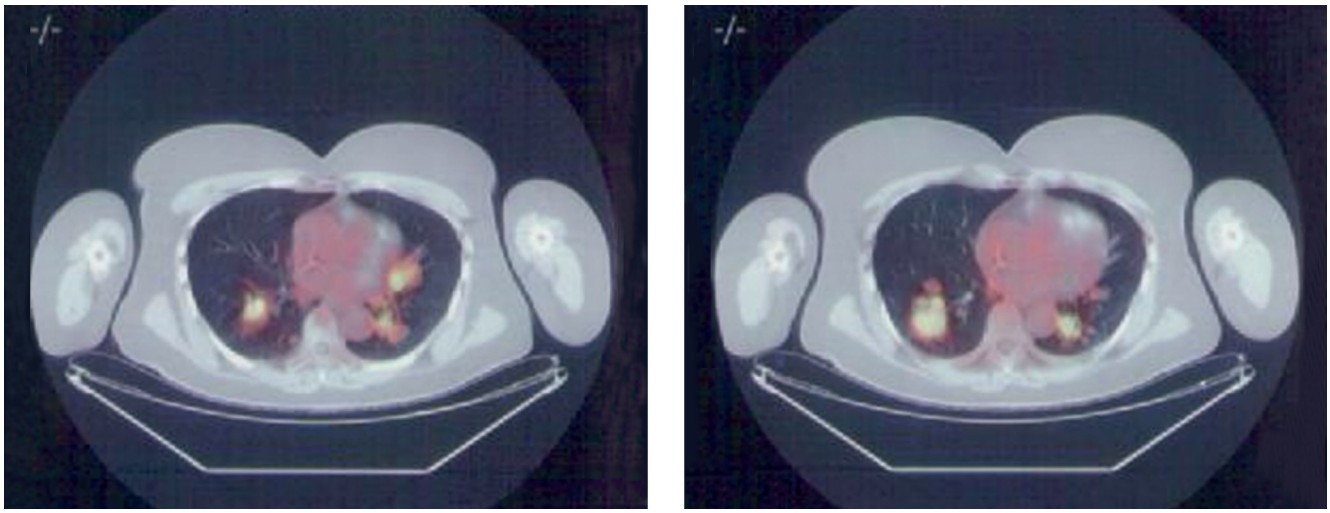

Fig. 3. Positron-emission tomography (PET-CT) scan after 6 cycles of treatment with trabectedin, showing tumor activity in metastases.

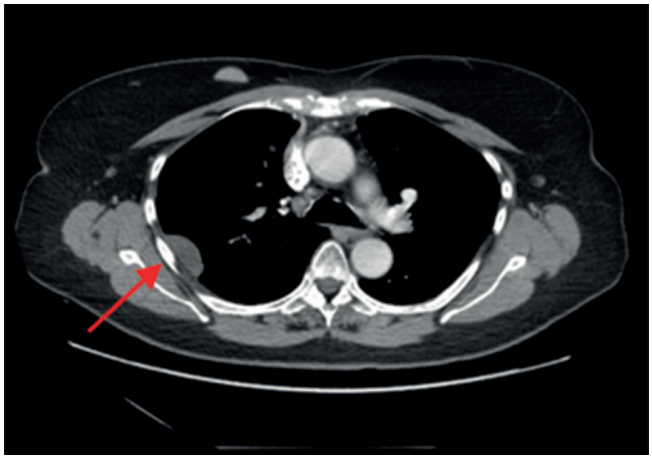

Fig. 4. Computed tomography (CT) scan after 12 cycles of treatment with trabectedin, showing disease progression according to RECIST criteria.

worsening of the patient's clinical condition, the treatment was discontinued and third line treatment with pazopanib was begun, with no clinical or radiological response and death at three months.

Discussion

We present a case report of a patient with synovial sarcoma with early progression after neoadjuvant treatment with epirubicin and ifosfamide who achieved a rapid radiological response following treatment with trabectedin. As a point of interest in the case, it should be noted that despite slow radiological progression from cycle 12 due to the appearance of a new tumor lesion, treatment was maintained until clinical progression and was able to be continued until cycle 27.

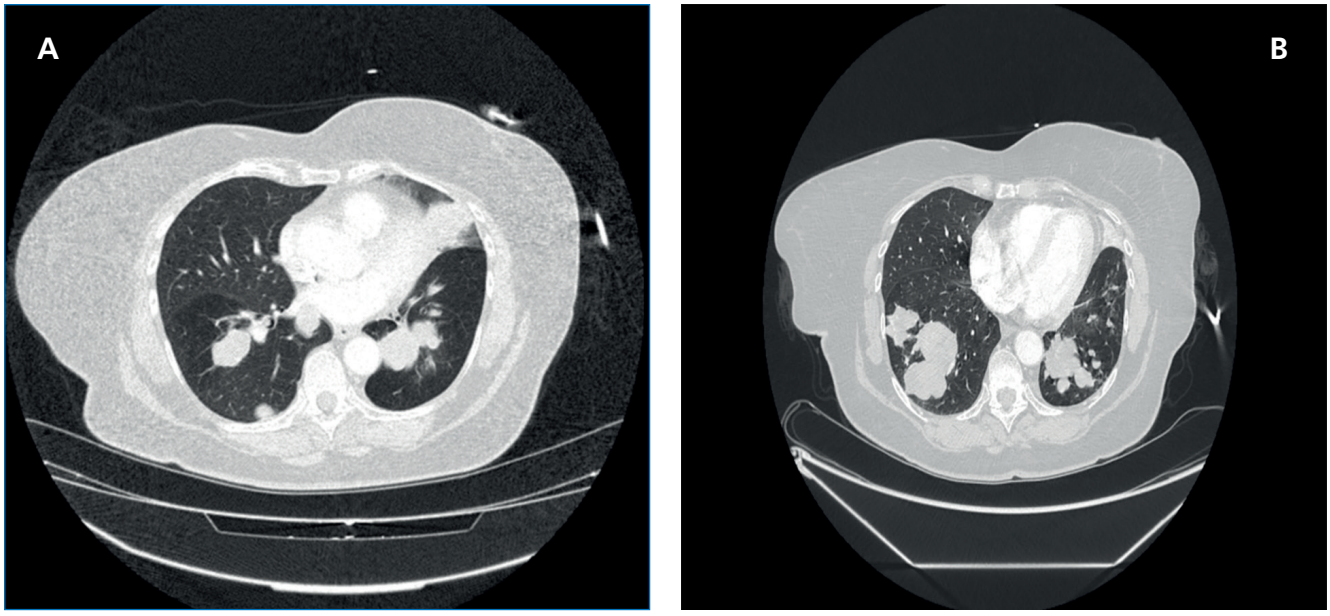

Fig. 5. Computed tomography (CT) scan showing disease progression from cycle 24 (A) to cycle 27 (B).

Despite the fact that data on the effectiveness of trabectedin beyond 6 cycles was not available at the time of treatment, the existence of remaining tumor activity together with the good response to trabectedin led us to maintain the treatment with this drug. A randomized phase II trial comparing maintenance of trabectedin after 6 treatment cycles in responsive patients against interruption of treatment followed by retreatment on progression of the disease has since been conducted. In this study, those patients in the maintenance arm had higher rates of progression-free survival (PFS) and overall survival (OS) than those who underwent interruption and retreatment on progression [8]. Data from retrospective series indicate that those patients who receive 7 or more cycles of treatment experience a significant increase in PFS and OS compared to those who interrupt treatment [6, 7, 9], and there is a percentage of long-term responders in whom the interaction between trabectedin and the tumor microenvironment probably plays a significant role [10], especially in the myxoid liposarcoma subtype [11].

Another important highlight of this case report is whether progression based on RECIST criteria is sufficient motive to abandon treatment in patients with slow and asymptomatic radiological progression. Several cases have been published in which it was confirmed that the use of the RECIST criteria is not the most suitable means of evaluating the effectiveness of this drug [12-14]. These means of measurement can underestimate the effectiveness of treatment in tumors of this type that often present a highly hyalinized desmoplastic stroma that remains unchanged even when chemotherapy leads to massive cell death, resulting in false negatives on imaging. This is the case for trabectedin, the antineoplastic effect of which appears to be due not only to its direct effects on cancer cells but also on the tumor microenvironment [15]. This mechanism of action is responsible for the peculiar response of some tumors to trabectedin, wherein the reduction in tumor size is preceded by changes in tumor tissue density, with the consequence that the RECIST criteria may be inadequate when evaluating the response. As a result, one topic in current debate is centered on what should be the clinically appropriate endpoint in clinical trials in STS [16]. Another way to evaluate the clinical benefit of trabectedin is the concept of growth modulation index defined as the ratio of time to progression with the nth line (TTP(n)) of therapy to the TTP(n)(-1) with the n-1th line. A high growth modulation index is associated with favorable efficacy outcomes in patients treated with trabectedin [17]. The patient received only two lines of therapy for metastatic disease and this is often unusual for advanced STS. After the first progression she was not changed to another active regimen (e.g. high dose ifosfamide) because the poor clinical condition of the patient discouraged its use.

The good safety profile and lack of cumulative toxicity of trabectedin allows prolonged treatment [5], and for this reason maintenance with trabectedin may be a good therapeutic option for patients with slow and asymptomatic progression. In this case, the ineffectiveness of a regimen as active as the combination of anthracyclines and ifosfamide administered as a neoadjuvant therapy, as well as the excellent response to trabectedin, led us to opt to continue with the drug despite radiological progression based on the RECIST criteria.

Conclusions

Many aspects should be considered when confirming disease progression and discontinuing a treatment. The RECIST criteria may underestimate the effectiveness of treatment in some cases of STS treated with trabectedin, primarily for its interactions with the tumor microenvironment. Moreover, maintenance treatment after 6 cycles of trabectedin obtains better results with a percentage of long-term responders. The good safety profile and lack of cumulative toxicity of trabectedin make maintenance with trabectedin a very attractive therapeutic strategy.

Acknowledgments

The authors thank Ray Hill, an independent medical writer, who provided native English editing and journal styling on behalf of HPS. This editorial assistance was funded by PharmaMar, Spain.

Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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Commentary

In this case report, the authors present a synovial sarcoma patient with a prolonged clinical benefit achieved with trabectedin, with a very rapid clinical deterioration after stopping the drug. This case gives the opportunity to make some reflections on this drug and on its use in daily clinical practice.

While the response rates reported from trials of trabectedin in advanced soft tissue sarcoma (STS) patients were not particularly impressive, ranging from 4% to 8%, it became apparent from the early trials that the drug was exerting a meaningful effect in terms of disease control rate, with improved time to progression and progression-free survival (PFS) rates. This apparent dissociation between response rate and PFS may be explained, at least partially, by some aspects of the drug mechanism of action, that should be clarified only some years after the introduction of trabectedin in clinical practice.

In addition, trabectedin has no the same long-term toxicity of the cytotoxic agents commonly used to treat STS patients. For this reason, studies have addressed whether maintenance treatment with trabectedin should be employed or whether trabectedin retains activity if patients are rechallenged on progression after a treatment break.

Both a retrospective study and a small prospective randomized trial from the French Sarcoma Group addressed this specific question.

More in details, in the recent prospective study published on Lancet Oncology, the authors explored whether, in patients with locally advanced or metastatic STS demonstrating a response or stable disease, trabectedin treatment beyond the sixth cycle should be continued. The study aim was to investigate the clinical benefit of continual maintenance administration of trabectedin until progression versus *a discontinuation therapy, in which patients stop treatment after six cycles, but are rechallenged at disease progression. In the evaluable patients, the rate of non-progression after the initial six trabectedin cycles was 29.7%. The median PFS after randomization was 7.2 months in the*

maintenance arm and 3.7 months in the discontinuation arm, with a statistically significant difference. Therefore, the median PFS was improved for those patients receiving the maintenance schedule when compared to a discontinued schedule. On the basis of these results, the authors concluded that trabectedin should be given until progressive disease, intolerance, or patient choice to discontinue.
Given the recent data about the role of trabectedin maintenance, the other key point is how to assess response or, even more important, how to assess and define disease progression.
Traditional methods of response assessment may significantly underestimate activity of those anticancer drugs that can produce nondimensional alterations as sign of their activity. Additional parameters, other than radiological dimensions, must be considered: first, clinical parameters and, by a radiological point of view, tissue density. All these aspects must be considered in patients treated with trabectedin, due to the real risk of underestimate its anticancer effect if evaluated only by RECIST criteria. This led to extreme caution during decision making about continuing or ceasing therapy. Where possible, a radiologist with understanding of the radiological changes seen with this agent can assist in accurately determining radiological benefit.
Choi criteria may feature more commonly in assessing the response to agents such as trabectedin in the future, and could help to better identify patients who are really progressing and patients who do not.

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