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SHORT COMMUNICATION

Treatment with trabectedin: should be indicated to all soft tissue sarcoma histotypes?

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Summary

Trabectedin is a novel antineoplastic agent approved as monotherapy in patients with advanced soft tissue sarcoma (STS) after failure of standard therapy with anthracyclines or ifosfamide, or patients who are unsuited to receive these agents. Some histotypes of STSs appear to be particularly sensitive to trabectedin, but the sensitivity of some rare STSs histological subtypes to the drug is rather unknown. We report on two patients suffering from infrequent subtypes of STSs, fibrosarcoma and epithelioid sarcoma, who were treated with trabectedin. In these cases the treatment completely failed, and right after the first cycle of trabectedin administration an unusually rapid tumor growth and dissemination was documented. Of note, one of the patients showed objective response to MVIP chemotherapy (methotrexate, etoposide, ifosfamide and cisplatin), after trabectedin failure. Trabectedin activity against several subtypes has not been studied or well-documented due to the rarity and numerous histotypes of STSs. Case studies aiming at the individualization of treatment options against specific STS subtypes will further justify the usage of this agent in clinical practice.

Key words: epithelioid sarcoma, ET-743, histotype, fibrosarcoma, soft tissue sarcomas, trabectedin, yondelis

Introduction

Trabectedin (ET-743, Yondelis®) is a novel antineoplastic agent that was originally derived from the Caribbean marine tunicate Ecteinascidia turbinata and is now produced synthetically. Intravenous trabectedin, administered once every 3 weeks, is approved as monotherapy in Europe for patients with advanced STSs after failure of standard therapy with anthracyclines or ifosfamide, or patients who are unsuited to receive these agents [1-3].

STSs represent a highly heterogeneous family of malignancies of mesenchymal origin, accounting for less than 1% of all cancers worldwide each year in adults. Even in cases where control of localized disease is achieved, 40-50% will eventually develop local recurrence or metastatic disease. Inoperable STSs are nearly always incurable with maximal survival of 1 year [2,3]. STSs encompass numerous histological subtypes of different cellular-molecular structure and functionality, as well as biological behavior.

Analysis of clinical studies suggests that treatment with trabectedin is active against advanced STSs that have failed conventional chemotherapy [1,4]. Moreover, some STSs histotypes appear to be particularly sensitive to trabectedin [5]. However, the sensitivity or response to the drug in rarer STSs histologic subtypes is rather unknown.

Toward this quest we report on two cases of previously treated patients suffering from rare subtypes of STS. In these cases treatment with trabectedin resulted in an astonishing failure in controlling tumor progression with an unusually prompt tumor progression and dissemination. Statistically, although rarely, such unmitigated treatment failures can happen in cases of very aggressive and multiresistant to chemotherapy sarcomas. However, isolation of the details of these cases from the general statistical pattern of STSs' prognosis could lead to interesting conclusions.

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Case #1

A 30-year-old male was diagnosed with fibrosarcoma (COINDRE/FNCLCC), grade 3, T2bN0M0 (stage III) of the right scapula. After surgical tumor resection he received 3 cycles of postoperative (adjuvant) chemotherapy with doxorubicin, ifosfamide, and dacarbazine, followed by locoregional radiotherapy (total dose 5.5 Gy). Six months after adjuvant treatment the patient developed metastases in both lungs. After 6 cycles of 1st line treatment with liposomal doxorubicin, etoposide, vincristine and cyclophosphamide a partial response (RECIST criteria) was achieved and lung metastasectomies were carried out. However, 2 months postoperatively the disease relapsed and a 2 cm mass was detected in the left pulmonary hilum. It was then decided to start treatment with trabectedin at dose of 1.5 mg/m^2 every 21 days. Twenty days after the first administration the patient developed grade III hepatotoxicity and hemoptysis. Thoracic CT scan revealed rapid disease progression involving an increase of the mass size in the left hilum (7 cm in diameter) and multiple lung metastases (Figure 1). Hepatic function was fully restored 2 weeks later and it was decided to administer salvage chemotherapy with MVIP as it has been previously described [6]. After 2 cycles of chemotherapy with MVIP objective partial response was documented.

Case #2

A 43-year-old female was diagnosed with epithelioid sarcoma of the maxilla (grade 3, stage II [T1bN0M0]). She was treated with surgical tumor resection and adjuvant locoregional radiotherapy (total dose 10 Gy). Four months later she presented with locoregional tumor relapse and multiple metastatic lesions in both lungs. The patient was then treated with doxorubicin, dacarbazine and ifosfamide. However, after 6 cycles of treatment the disease progressed both locoregionally and in the lungs. Treatment was continued with trabectedin at dose of 1.5 mg/m^2 every 21 days. Sixteen days after the first trabectedin administration the patient developed grade III stomatitis and a thoracoabdominal CT scan showed a rapid progression of lung metastases (in size and number) as well as an impressive development of metastatic lesions in the liver (Figure 2).

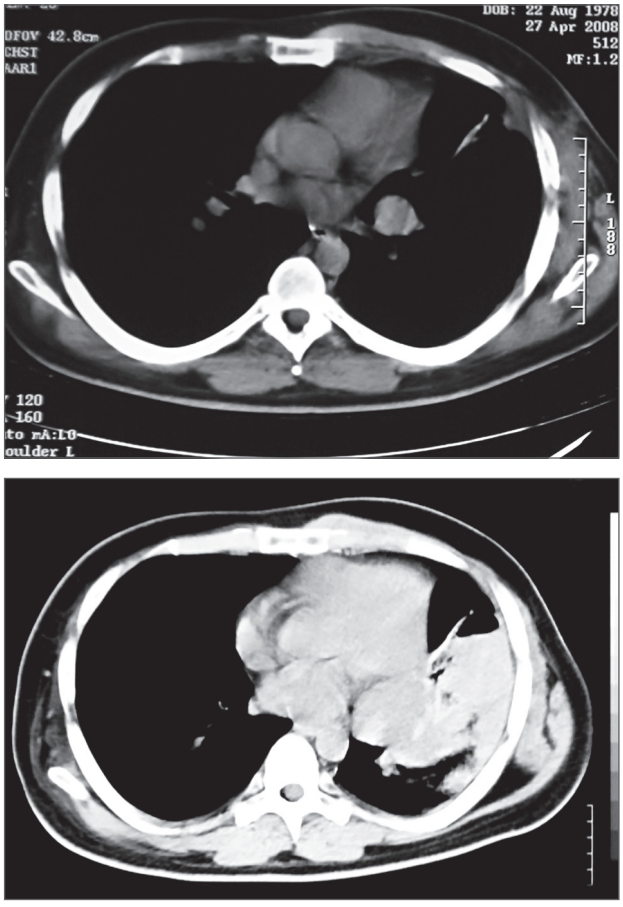

Figure 1. Case #1: CT scans show the growth of a lung metastatic lesion in less than one month and after one cycle treatment with trabectedin.

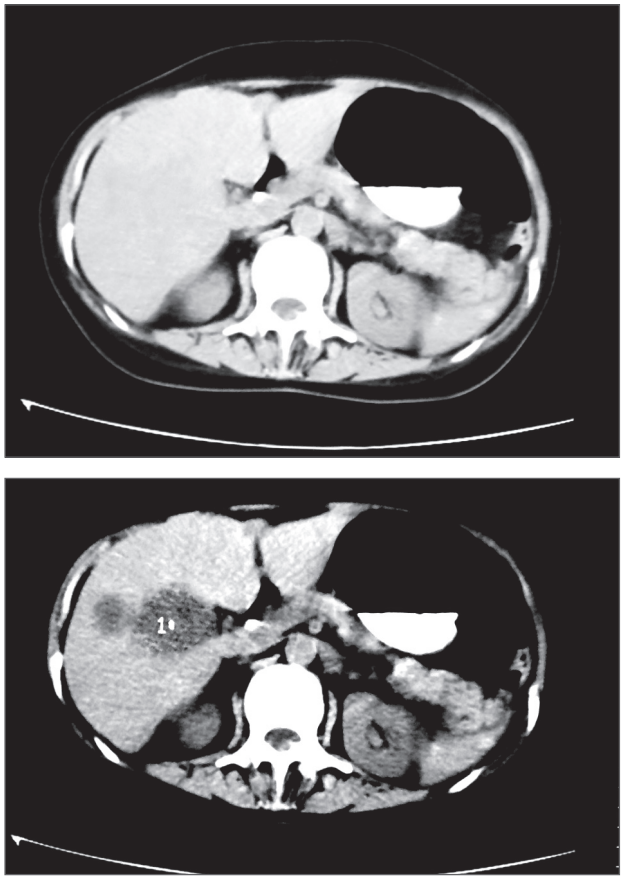

Figure 2. Case #2: CT scans reveal the development of massive hepatic metastatic lesions, 20 days after the first administration of trabectedin.

Discussion

Leiomyosarcomas and liposarcomas appear particularly sensitive to trabectedin. This observation contributed to the approval of the drug in the treatment of STSs [4]. Moreover, in myxoid and round-cell liposarcomas trabectedin seems exceptionally active. Trabectedin is also active in synovial sarcoma, Ewing's sarcoma and other translocation-related STSs. However, trabectedin's activity against several rarer STSs subtypes has not been studied or documented [5,7].

Schöffski et al. [5] reported a pooled analysis of phase II studies suggesting that around 50% of STS patients who had failed conventional chemotherapy, experienced long-lasting tumor control (either objective response or stabilization of disease) when treated with trabectedin. Twenty-nine per cent of patients were alive at 2 years, and median overall survival was 10.3 months. Trabectedin wasn't cardio- or neurotoxic and at the same time neutropenia and hepatic toxicity which occurred were non-cumulative, reversible, and lessened by steroid premedication. Nevertheless, despite the positive results of treatment with trabectedin and its favorable toxicity profile, the authors recommended further exploration of trabectedin's potential in STSs, not only in general but also in specific subtypes. Trabectedin has shown evidence for efficacy and is a promising new agent for the systemic management of several histologic subtypes of sarcoma with durable objective responses in a subset of sarcoma patients refractory to conventional chemotherapy, but, due to the rarity and the histological complexity of STSs, its critical validation seems difficult [8].

Since trabectedin produces an objective response rate of <10% and disease stabilization in 30% at best in non-selected aggressively pretreated sarcomas, it is not surprising that no response was observed in the reported cases. Furthermore, trabectedin failure in only two STS cases cannot lead to safe conclusions over its efficacy. Nevertheless, the unusually prompt tumor growth observed in the two patients immediately after the first course of treatment could suggest a drug-stimulating effect. Of course in very rare cases, multirefractory and highly aggressive sarcomas can present this kind of rapid growth and progression despite any treatment given. However, because of the objective response of the first patient to MVIP chemotherapy after treatment with trabectedin, such a case doesn't seem to be true. The biological mechanisms that could explain a possible tumor growth-stimulating effect are not clear and further studies for assessing this hypothesis are needed. Moreover, fibrosarcoma and epithelioid sarcoma are very rare sarcoma subtypes and the clinical study or trial in such cases is rather difficult or even impossible.

In the cases reported here in, trabectedin was administered because of failure of ifosfamide and anthracyclines, and resulted in impressive failure to control tumor progression, whereas an expeditious tumor growth was documented soon after the first trabectedin administration. In our opinion the generalization of treatment effectiveness against STSs is rather risky. Furthermore, development of molecular markers for the prediction of trabectedin activity is needed. Case studies aiming at the individualization of treatment options will further justify the usage of this and other agents in clinical practice, especially in histologically non-homogeneous and rare tumor groups, such as the STSs group.

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