Complete remission of relapsing high-grade angiosarcoma with single-agent metronomic trofosfamide

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A limited repertoire of chemotherapeutics is available for the therapy of metastasizing angiosarcoma. Moreover, response rates are typically low and outcomes are unfavorable. Metronomically, dosed oral chemotherapy provides a convenient treatment option and surprisingly high response rates have been published for small patient groups. We report on a case from our clinic, in which a complete response with oral trofosfamide was achieved in a patient suffering from relapsed high-grade angiosarcoma metastasizing to the liver and lung. The patient experienced minimal side-effects from her trofosfamide treatment. Responses like this are encouraging and should make us rethink treatment approaches for metastasizing soft-tissue sarcoma. The mechanism of action of metronomic chemotherapy, although thought to be antiangiogenic in nature, is still unclear, as is the additive effect of angiogenic inhibitors like cyclooxygenase II inhibitors or peroxisome proliferator-activated receptor-γ agonists. Prospective studies that include the examination of patient samples during treatment are ongoing in order to optimize further development of this novel therapeutic approach. ***Anti-Cancer Drugs*** **17:997–998 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Current treatment options for metastatic soft-tissue sarcomas, especially angiosarcomas, are limited and associated with poor response rates [1]. Therefore, new therapeutic agents and new forms of treatment with established agents are warranted to improve outcome in these patients [2]. The safety and efficacy of oral trofosfamide in the treatment of metastatic soft-tissue sarcoma was reported in 1995 [3]. Phase II studies underscored the role of trofosfamide in the palliative therapy of pretreated metastatic soft-tissue sarcoma [4,5] with disease stabilization in up to 50 or 70% of patients, respectively. It has been proposed for metronomic chemotherapy to be mainly antiangiogenic by targeting endothelial progenitor cells, which were previously thought to be genetically more stable – and therefore less likely to become treatment-resistant – than tumor tissue itself [6]. This view, however, has been challenged ever since the genetic instability of tumor endothelial cells has been described [7].

Recently, oral trofosfamide has been used in conjunction with the cyclooxygenase II inhibitor rofecoxib and the peroxisome proliferator-activated receptor-γ agonist pioglitazone in the treatment of vascular soft-tissue sarcomas, in particular, and surprisingly high response rates have been reported ($n = 6$ patients total, with two complete remissions one partial remission and stable disease in the remaining three patients after 8 months) [8]. Nevertheless, the exact mechanism of action of trofosfamide in this setting remains unclear, and the importance of rofecoxib and pioglitazone has not been established. Here, we describe a complete remission of a relapsing, metastatic high-grade angiosarcoma treated with single-agent trofosfamide.

Case report

Our patient is a 64-year-old woman, who was in good health until July 2003, when a left-sided ovarian tumor was found as a cause for bloody vaginal discharge. At the time of diagnosis, metastases were found throughout the peritoneal space, and macroscopically visible manifestations were removed with partial resections of the small and large bowel, the left ureter, the left-sided pelvic wall, and pelvic lymph nodes. Histology revealed a high-grade angiosarcoma. Starting in September 2003, the patient received six cycles of doxorubicin at 75 mg/m^2 to a total dose of 450 mg/m^2. Two months later, however, a relapse was found with metastases in the left pelvic wall, involving the distal ureter. After surgical removal of all visible manifestations and resection of the left distal ureter, the left pelvic wall was irradiated up to a total dose of 59.4 Gy. Nonetheless, local manifestations recurred 3 months later and were again surgically removed in

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November 2004. In addition, the patient complained of increasing dyspnea on exertion and dilative cardiomyopathy was diagnosed most likely as a sequel of the earlier anthracycline treatment. In April 2005, a solitary hepatic metastasis ($7 \times 6 \times 4\,cm^3$) and two pulmonary metastases were found, and the patient presented to our outpatient clinic 1 month later. In June 2005, oral metronomic chemotherapy with trofosfamide at 150 mg/day in three divided doses was started. At the first follow-up visit after 2 months of treatment, the patient was in good overall condition and the hepatic metastasis had responded to therapy ($4 \times 3 \times 2\,cm^3$). When the patient was monitored in December 2005 under continuing therapy with oral metronomic trofosfamide, abdominal ultrasound and conventional chest X-rays showed a complete remission of all manifestations.

In summary, this is a complete remission of a metastatic high-grade angiosarcoma that had relapsed after prior surgical removal, chemotherapy and radiation. The treatment was well tolerated and without significant toxicity.

Conclusion

We propose that prospective clinical trials with single-agent metronomic trofosfamide in vascular soft-tissue tumors should be initiated. Careful analyses of radiological images and histological specimens for necrotic changes as well as the examination of blood specimens for the identification of novel surrogate markers such as circulating endothelial progenitors or comobilized proangiogenic hematopoietic cells are obligatory in order to learn more about the mechanism of action of metronomic trofosfamide.

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