Acta Oncologica, 2015; 54: 1063–1082

informa
healthcare

LETTERS TO THE EDITOR

Response of refractory Ewing sarcoma to pazopanib

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To the Editor,

Although localized Ewing sarcoma is usually curable, its prognosis when metastatic or recurrent is much poorer as chemotherapy resistance develops [1]. Therefore, there is an unmet need for novel therapies. We report here a case of recurrent metastatic Ewing sarcoma, refractory to several lines of cytotoxic chemotherapy, which responded to pazopanib.

Case report

A 24-year-old female with no particular past medical history sought medical attention for sudden onset of tingling and numbness in her right upper limb. A paravertebral mass was seen by magnetic resonance imaging (MRI) along the cervical spine (C1–C7 levels) with no other site of disease after evaluation by computed tomography (CT) and positron emission tomography (PET.) A biopsy only retrieved normal neural tissue, so she underwent surgery which resulted in incomplete resection. Comprehensive pathologic work-up revealed Ewing sarcoma.

The residual disease, which infiltrated the epidural canal and the adjacent cord, was deemed unresectable. The patient received a full course of chemotherapy, consisting in alternating cycles of vincristine/doxorubicin/cyclophosphamide and ifosfamide/etoposide, for a total of 14 cycles. After a cumulative dose of 375 mg/m^2 of doxorubicin, this drug was changed to dactinomycin. Radiotherapy was concomitantly administered for a period of 5 weeks. A complete remission by CT and PET imaging was achieved at the end of therapy.

One year later, on routine imaging studies, the patient was found to have one biopsy-proven metastatic focus in the lungs and another one in the T4 vertebra. Despite aggressive treatment with stereotactic therapy and resumption of chemotherapy, her disease progressed in the form of pleural infiltration and bulky pulmonary metastases. She received the following regimens: topotecan/cyclophosphamide, irinotecan/temozolomide, ifosfamide/etoposide, and temsirolimus on a clinical trial. After 6 weeks of treatment with temsirolimus, she was very symptomatic with dyspnea at rest from metastatic disease progression, weight loss and a Karnofsky score of 70.

On the basis of biological plausibility of activity, and the existing indication for other sarcoma types, with verbal informed consent, the patient was given a prescription for pazopanib (800 mg orally daily). No side effect was observed, but in only 2 weeks, her condition had significantly improved with only persistence of mild dyspnea on exertion, and restoration of her performance status to 90. After 4 weeks of treatment, a chest CT showed very significant decrease of the intrathoracic burden of disease, qualifying for partial response according to RECIST criteria. Treatment was continued.

At the 12th week of treatment, the patient complained of tenderness on the scalp and recurrent dyspnea. Her serum LDH level that had normalized with increasing pazopanib. A subcutaneous mass was seen in the scalp, suspicious for metastasis. A chest CT at that point showed disease progression in the form of new lesions and regrowth of older ones.

Discussion

Despite the number of salvage regimens available, refractory recurrent or metastatic Ewing sarcoma is usually fatal. Given the limited success of cytotoxic chemotherapy in this setting, research efforts have recently focused on identifying targetable molecular aberrations that could play a role in the pathogenesis

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(Received 9 September 2014; accepted 25 September 2014)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2014.971938

of this disease. For instance, the insulin-like growth factor 1 (IGF1) and its receptor (IGF1-R) play a key role in Ewing sarcoma. Unfortunately, recent clinical trials with two antibodies directed at IGF1-R have shown disappointing results [2,3], though concomitant blockade of IGF1-R and of the mammalian target of rapamycin (mTOR) may be more promising [4].

The importance of angiogenesis is suggested by high vascular endothelial growth factor A (VEGF-A) serum levels in half of Ewing sarcoma patients [5]. VEGF-A, in turn, contributes to tumor growth and metastasis. The fusion oncoprotein EWS/Fli-1 decreases the expression of thrombospondins, which are believed to be in part responsible for tumor vascularization [6]. It also upregulates VEGF-A mRNA and protein [5]. Inhibition of this effect by siRNA in nude mice was reported in a recent paper [7], and synergy with platelet-derived factor growth (PDGF) knockdown suggested as well [5]. It is interesting to note that pazopanib, used in the case herein described, inhibits the action of both VEGF-A and PDGF through interaction with VEGF receptor 2 (VEGFR-2) and PDGF receptors α and β, respectively [8]. We are aware of an ongoing clinical trial with regorafenib, another multikinase inhibitor with antiangiogenic properties for various sarcomas, including Ewing sarcoma (clinicaltrials.gov/show/NCT02048371).

In summary, we report the first case of refractory Ewing sarcoma responding to pazopanib with concomitant symptom palliation. Our article suggests that antiangiogenic molecules, alone or in combination with cytoxic chemotherapy, could be useful in the management of this disease.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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