Clinical activity of pazopanib in metastatic extraosseous Ewing sarcoma

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Abstract

We report a response to pazopanib in a 69-year-old man with heavily pre-treated metastatic extraosseous Ewing sarcoma in addition to molecular profiling of his tumor. To our knowledge, this case is the earliest to demonstrate activity of an oral multi-targeted kinase inhibitor in Ewing sarcoma. This case provides rationale for adding a Ewing sarcoma arm to SARC024, a phase II study of regorafenib, another multi-targeted kinase inhibitor, in patients with liposarcoma, osteosarcoma and Ewing and Ewing-like sarcomas (NCT02048371). This national multi-institutional study is ongoing.

Case Report

In 2001, a 57-year-old male was diagnosed with primary systemic amyloidosis and received high dose melphalan with autologous stem cell transplantation, placing him in remission. In 2005, he developed intermittent right lower extremity radiculopathy. Magnetic resonance imaging (MRI) of his pelvis at an outside hospital was reportedly normal. His symptoms progressed and, in 2008, MRI revealed a right S2 nerve root mass radiographically consistent with a benign nerve sheath tumor. He was observed. The mass had enlarged on MRI a year later. Resection demonstrated a 2.2-cm poorly differentiated malignant neoplasm consistent with primitive neuroectodermal tumor/Ewing sarcoma (Figure 1A-C). Staging scans, including whole body positron emission tomography (PET) and high resolution computed tomography (CT) scan of the chest, abdomen and pelvis, revealed no signs of metastasis. A bone marrow biopsy was not performed.

He received 1 cycle of cyclophosphamide, doxorubicin and vincristine alternating with one cycle of ifosfamide and etoposide. He experienced severe fatigue and cytopenias. He declined further chemotherapy and radiation and was subsequently observed.

In 2010, a pelvic MRI showed a 2.9 cm enhancing mass in the right S2 neural foramen and biopsy confirmed Ewing sarcoma. He received 50.4 Gy to the sacrum with a 5.4 Gy gross disease boost. Thereafter, serial MRIs of his sacrum were stable.

In early 2011, several months after finishing radiation, new, innumerable bilateral pulmonary nodules were noted on CT. Transbronchial biopsy was histologically consistent with metastasis from Ewing sarcoma (Figure 1D,E). FISH indicated rearrangement involving the *EWSR1* gene region. He received cyclophosphamide and topotecan with disease stability noted after two cycles. After six cycles, enlarging lung, new liver and new diffuse sclerotic bony lesions were noted. He then received irinotecan with temozolomide. After two cycles, a dramatic response at all disease sites was noted. Over 10 four-week cycles, spanning a year with treatment breaks, he developed a near complete response with only several subcentimeter bilateral lung nodules remaining. Platelet counts on temozolomide ranged between 50,000 and 75,000. After 10 cycles, the lung nodules began to enlarge minimally (Figure 2). He received another three cycles during which time the lung nodules progressed. This regimen was stopped. He had exhausted all standard treatment lines for Ewing sarcoma, and was not eligible for a clinical study due to thrombocytopenia. Molecular testing on tissue retrieved prior to treatment with temozolomide and irinotecan (Caris, Table 1) was ordered at the patient's request. The test suggested that only temozolomide and dacarbazine had possible clinical benefit by virtue of loss of O-6-methylguanine DNA methyltransferase expression (Table 1).

The patient was discussed at a weekly multi-institutional, multi-disciplinary Sarcoma Tumor Board coordinated out of Mayo Clinic in Jacksonville, Florida, and now shared via video-link between 10 sarcoma centers throughout the United States and Europe.[1] This innovative conference has been functioning for five years and is staffed at each site by sarcoma specialists from medical oncology, radiation oncology, orthopedic and surgical oncology, pathology and radiology and reviews, in a de-identified manner, case history, imaging and pathology to determine a consensus treatment opinion. Pazopanib or a platinum agent were suggested as reasonable fourth line options as both were expected to have minimal impact as a single agent on his bone marrow function. He was started on pazopanib in late November 2012 at 800 mg a day. A chest CT scan obtained the day before he began pazopanib demonstrated bilateral lung nodules (Figure 2). No other sites of metastases were noted on contrast enhanced CT scan of chest, abdomen and pelvis and skeletal survey. Three weeks after starting pazopanib, a CT scan of the chest without contrast was obtained revealing that his lung nodules had diminished in size (Figure 2). He continued pazopanib. However, several weeks later, before another scan could be obtained, he fell in a bathroom, developed a subdural hematoma and died.

Discussion and Conclusions

The specific cell of origin in Ewing sarcoma is not known, unlike liposarcoma (adipocyte), leiomyosarcoma (smooth muscle), rhabdomyosarcoma (skeletal muscle), chondrosarcoma (cartilage) and osteosarcoma (bone), though these tumors are believed to be of neuroectodermal origin. Nearly all cases demonstrate a reciprocal translocation involving the *EWSR1* gene on chromosome 22.[2] The primary tumor of Ewing sarcoma is most commonly noted in the long bones of the extremities and pelvis in children and adolescents, but also observed in adults,[3] more commonly in soft tis-

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sue than bone.[4] Patients with localized Ewing sarcoma are understood to have micrometastases at presentation, even if they are not radiographically apparent, as the majority of patients who do not receive chemotherapy will develop metastasis within a year.[5] Thus, the standard of care for these patients involves not only local control but intensive systemic chemotherapy, such as in the control arm of the current non-metastatic Ewing sarcoma protocol (AEWS1031, NCT01231906). Our patient declined further chemotherapy after two cycles due to intolerance and later developed metastatic disease.

Pazopanib is an oral multi-targeted tyrosine kinase inhibitor that is approved for the treatment of advanced soft tissue sarcoma (excluding gastrointestinal stromal tumor and liposarcoma) after progression on first line chemotherapy.[6] The precise mechanism of action of pazopanib in soft tissue sarcomas is unclear. Pazopanib is not considered a standard therapy in Ewing sarcoma; however, it was considered a reasonable option for our patient by our multi-institutional tumor board as he had exhausted standard regimens and given the activity of pazopanib in other soft tissue sarcomas, and his persistent thrombocytopenia. Interestingly, molecular testing did not predict response to pazopanib. Molecular testing may have value in predicting response in advanced sarcoma and require validation prospectively.

To our knowledge, this response, noted in late 2012, was the first demonstration of clinical activity of pazopanib in extraosseous Ewing sarcoma. This case was initially reported at the Sarcoma Alliance for Research through Collaboration (SARC) meeting in June 2013 providing the rationale for adding a 30 patient Ewing sarcoma arm to SARC024, a phase II study of regorafenib, another TKI that inhibits angiogenesis, in patients in liposarcoma, osteosarcoma and Ewing and Ewing-like sarcoma (NCT02048371). This multi-institutional study is ongoing. Later, in October 2014, consistent with our observation, a case report of response in a 24 year old patient with extraosseous Ewing sarcoma was published.[7] Other interesting ongoing studies along these lines include a phase II study of regorafenib in 108 patients with metastatic Ewing sarcoma, chondrosarcoma and osteosarcoma (NCT02389244), and a phase II study in children aged 1-18 years through the Children's Oncology Group in advanced solid tumors including Ewing sarcoma (NCT01956669). The results of these studies are awaited.

Given the small sample size, lack of correlative data from this patient, and uncertainty as to the mechanism of action of pazopanib in sarcomas, it is not surprising there is not a good understanding of how pazopanib causes tumor shrinkage in Ewing sarcoma. Despite now two reports of activity of pazopanib in extraosseous Ewing sarcoma, we do not know if there is a differential sensitivity to the extraosseous variety as compared to that of bone. We have also treated a young woman

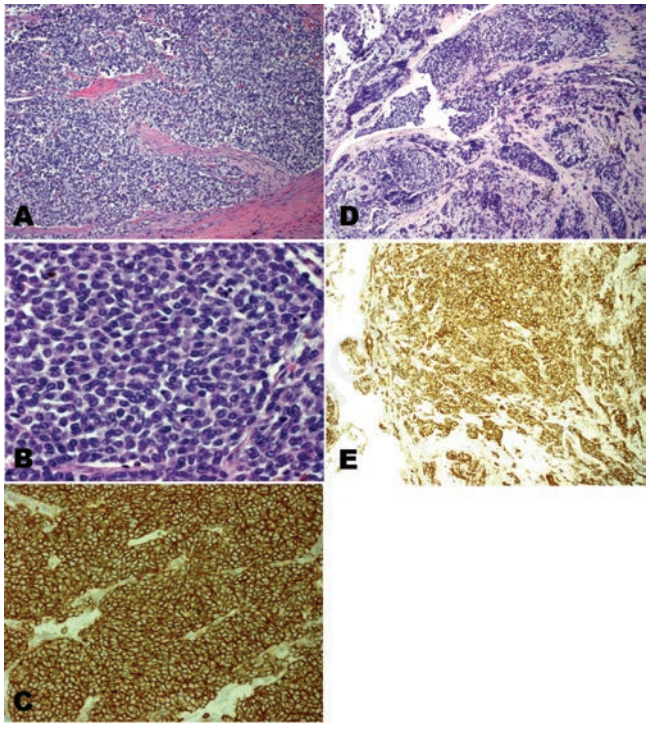

Figure 1. (A) Low and (B) high power view of Hematoxylin & Eosin stain of S2 nerve root tumor showing primitive neuroectodermal tumor/Ewing's sarcoma; (C) CD99 immunostain was positive. Chromogranin, synaptophysin, keratin (AE1/AE3), actin, desmin and melan-A were negative. Low power view of (D) Hematoxylin & Eosin and (E) CD99 immunostains of a transbronchial lung nodule biopsy confirming Ewing sarcoma metastasis.

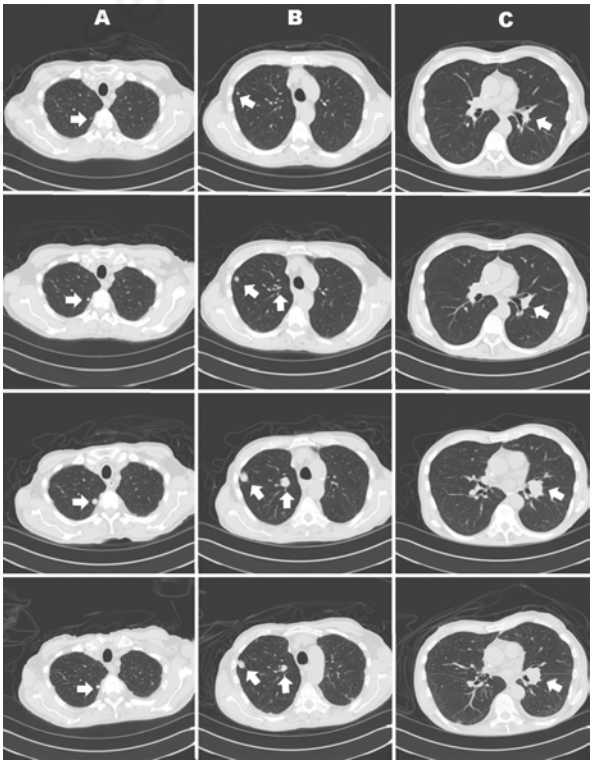

Figure 2. Computed tomography of the chest showing three separate lung nodules (Column A: nodule 1; Column B: nodule 2; Column C: nodule 3) at 15 weeks prior to starting pazopanib (first line), receiving temozolomide and CPT-11 (irinotecan); 7 weeks prior to starting pazopanib (second line), on no treatment; one day prior to starting pazopanib (third line); and 21 days after starting pazopanib (fourth line). Nodule 1: 7 weeks pre pazopanib, 5 mm; one day pre pazopanib, 11 mm; 21 days after starting pazopanib, 7.5 mm. Nodule 2: 7 weeks pre pazopanib, 9&6 mm; one day pre pazopanib, 20&19 mm; 21 days after starting pazopanib, 15&10 mm. Nodule 3: 7 weeks pre pazopanib, 14 mm; one day pre pazopanib, 27 mm; 21 days after starting pazopanib, 25 mm.

Table 1. Results of selected immunohistochemical and genetic testing for this patient.

Gene	Meaning	Method	Result
MGMT	O-6-methylguanine-DNA methyltransferase	IHC	Negative
BRCA1	Breast cancer gene 1	RT-PCR	Low
ERCC1	Excision repair cross complementation group 1	RT-PCR	High
PGP	P-glycoprotein	RT-PCR	Low
TOP2A	Topoisomerase II alpha	RT-PCR	Low
TOPO1	Topoisomerase 1	RT-PCR	Low
RRM1	Ribonucleotide reductase subunit M1	RT-PCR	High
MET	Tyrosine kinase inhibitor for hepatocyte growth factor	FISH	Not Amplified
TOPO1	Topoisomerase 1	IHC	Negative
PIK3CA		Seq	Wild Type
PTEN	Phosphatase and tensin homolog	IHC	Positive
KIT		Seq	Wild Type
BRAF		Sanger sequencing	Wild Type
ALK	Anaplastic lymphoma kinase	Fragment analysis	Negative

IHC, immunohistochemistry; RT-PCR, real time polymerase chain reaction.

with an osseous primary Ewing and widespread metastases with pazopanib (Dr. Jones) in the fourth line setting. In her case no clinical benefit was documented. Pazopanib targets vascular endothelial growth factor (VEGFR) 1-3 as well as platelet derived growth factors,[8] and targeting of VEGFR2 and PDGF have been shown to inhibit Ewing sarcoma preclinically.[9-11] Further study is merited to clarify its relevant mechanism of action.

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