Extended Progression-Free Survival in Two Patients With Alveolar Soft Part Sarcoma Exposed to Tivantinib

Introduction

Alveolar soft part sarcoma (ASPS) is a rare malignancy that tends to strike young adults and adolescents. It has an unusual clinical behavior; it is somewhat indolent, with slow progression, and yet is incurable once metastasized. Patients with ASPS often present with extensive metastatic disease, frequently involving the lungs and sometimes the brain.¹⁻² On the basis of functional data linking the characteristic translocation found in ASPS, *ASPL-TFE3*, to upregulation of expression of the MET receptor tyrosine kinase,^{3,4} we proposed to conduct a clinical trial of tivantinib, an orally available, selective inhibitor of MET, for patients with ASPS and other cancers with expression of MET. This was a phase II study with response as the primary outcome (A Phase II Study of ARQ 197 in Patients With Microphthalmia Transcription Factor Associated Tumors).⁵ Herein we report two young patients from this trial who have continued on therapy for more than 3 years each, with stable disease and minimal adverse effects, despite metastases at study entry. During the time of the trial, the study dose of tivantinib was increased from 120 mg twice a day to 360 mg twice a day, on the basis of ongoing parallel pharmacokinetic studies. The study was Institutional Review Board approved at each institution where these patients were treated. The consent process for these minors included obtaining the appropriate assent from the patient and informed consent from the parents.

Case Report 1

A previously well 15-year-old girl was diagnosed with ASPS of the left lateral thigh in January 2007, 1.2 years before study entry. Her disease was widely metastatic to the lungs at diagnosis. She was initially treated in 2007 with resection of the thigh mass followed by radiation

of 59.8 Gy to the tumor bed. Later in 2007, she underwent resection of a tumor nodule in her right lung. She began treatment with sorafenib in December 2007 and stopped taking it in March 2008, having developed progressive disease in the lungs during this time. Her leg mass has never recurred.

After giving informed consent, the patient commenced taking tivantinib in April 2008 at a dose of 120 mg twice a day. The dose was escalated to 240 mg twice a day in October 2008, then to 360 mg twice a day in November 2008, after the amendment to the protocol to increase the dose was approved at her treating institution. She continues to receive tivantinib as of January 2013. The drug was temporarily interrupted for 4 days in May 2008 because of grade 2 hyperbilirubinemia, which resolved. This patient had no baseline measurable lesions (waiver granted before enrollment) and her disease at study entry was comprised of several pulmonary nodules. These have been stable. She has been taking tivantinib continuously, save for the interruption described, for 248 weeks as of January 2013. During this time, the initial clinical trial onto which she was enrolled was closed because it met accrual requirements, and she continued to receive the study agent by being rolled over to a follow-up protocol for patients who experienced benefit associated with tivantinib administration.

Case Report 2

A 12-year-old boy, who had no significant past medical history, presented to his pediatrician with a lump in his left thigh in July 2007. Evaluation demonstrated no evidence of bone or brain metastases, but numerous, bilateral lung nodules were noted on the initial chest computed tomography (CT) scan. A biopsy that was performed of the thigh tumor in August 2007 demonstrated ASPS. The patient was otherwise doing well, and he denied any symptoms aside from the leg mass. He received initial local control of the left thigh lesion that consisted of preoperative radiation therapy of 50.4 Gy. In October 2007, surgery was performed, with complete excision of the thigh mass, which again demonstrated ASPS on pathologic examination,

Fig 1.

Fig 2.

with extensive vascular invasion and tumoral thrombosis. There were numerous satellite nodules around the border of the main mass. Chemotherapy was not administered to the patient at that time.

A CT scan in late 2008 continued to show numerous lung nodules, and the patient began a course of 600 mg of imatinib once a day from October 2008 through January 2009, when he had another CT scan. This showed an increase in the size of the previously reported nodules and the presence of new pulmonary nodules. He stopped imatinib therapy at that time. In March 2009, now 13 years old, he began tivantinib as part of a study at a dose of 360 mg twice a day after giving informed consent. A target lesion in the left upper lobe was identified and is shown in Figures 1A (at study entry), 1B (initial evaluation at 8 weeks), and 1C (evaluation after 3 years), and has been observed since. A right lower-lobe pleural-based lesion has been also been observed (Figs 2A, 2B, and 2C). Despite variability owing to poor inspiration in the first CT and growth of the patient throughout treatment, the images suggest stable disease. Since March 2009, he has received tivantinib at a dose of 360 mg twice every day, through the writing of this report, and suffered no adverse events. He has grown 5.4 cm in height during this time, to 179 cm, and has completed puberty. CT scans of his lungs were initially performed every 2 months and now are performed every 4 months. Review of these numerous images demonstrates no progression when all slices are compared. He has had no demonstrable progression of disease for more than 3 years; all lung lesions are stable in size and there has been no development of new lesions. His leg mass has also never recurred. He has also been transitioned to the follow-up protocol, like the patient described in Case Report 1. He has been receiving tivantinib for 199 weeks continuously as of January 2013.

Discussion

The two patients described have both had extended progression-free survival in association with exposure to tivantinib. These patient cases demonstrate the typical, widespread nature of lung metastases in ASPS. Although ASPS is known to grow slowly, both patients experienced disease progression during previous therapy. Tivantinib is a selective inhibitor for MET, with little cross reactivity to other receptor tyrosine kinases. MET is known to be expressed in ASPS.⁶⁻⁷ Immunohistochemistry for MET was negative in the tumor samples from both patients. This may be a result of problems in tissue preservation in the specimens, which were not obtained specifically for the study, and the

tumors from these patients may in fact be MET dependent and MET expressing. However, it is possible that these specimens did not express high levels of MET but were still dependent on MET as a trigger for the angiogenic behavior that is characteristic of these tumors, given that MET activity can stimulate the vascular endothelial growth factor receptor (VEGFR) pathway through upregulation of VEGF secretion and downregulation of thrombospondin-1.⁸ Antiangiogenic therapy has been associated with responses in ASPS and is under active development, although sorafenib was not of benefit in the first patient described. Sorafenib only impairs VEGF signaling through inhibition of VEGFR2, which may not have been a sufficient angiogenic blockade to affect the patient's tumor. Cediranib has been the most promising of antiangiogenic agents in ASPS, with a high response rate in ASPS reported after exposure to this pan-VEGFR inhibitor.⁹⁻¹¹ It is possible that by impairing MET activity, even when the MET activity was at a low level, tivantinib impaired VEGFR activity in the lung metastases of these patients and prevented tumor growth as a result. Many of the patients with ASPS who benefitted from cediranib had tumor shrinkage while receiving the agent, whereas the two patients presented here had prolonged stable disease after progression during previous therapy. This suggests a different mechanism of action on angiogenesis in ASPS, or at least a different magnitude of effect, from tivantinib versus cediranib. Another possibility is that inhibition of MET activity led to inhibition of phosphatidylinositol 3-kinase and other pathways that are known to be downstream in some models of oncogenic MET.¹² Given the tolerability to tivantinib in these two patients, further consideration of the agent in select cases of ASPS or in combination is warranted, particularly if combined with a VEGFR inhibitor such as cediranib.

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