Treatment of Metastatic, Refractory Alveolar Soft Part Sarcoma: Case Reports and Literature Review of Treatment Options in the Era of Targeted Therapy

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Background: Alveolar soft part sarcoma is a rare soft tissue sarcoma that is characterized by a pattern of slow growth with metastases to the lung, bone, and brain that is not responsive to conventional cytotoxic chemotherapy.

Observations: We describe 2 patients, with a combined 19 years of treatment experience including multiple different chemotherapeutic and targeted therapy regimens, surgery, and radiotherapy. We also present a review of the literature regarding treatment options to highlight recent findings.

Conclusions: Alveolar soft part sarcoma is an indolent, but persistently progressive disease. Novel therapeutic agents hold promise in its management.

Key Words: alveolar soft part sarcoma, chemotherapy, tyrosine kinase inhibitor, molecularly targeted therapy

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BACKGROUND

Alveolar soft part sarcoma (ASPS) is a rare tumor of unknown histogenesis representing 0.5% to 1% of soft tissue sarcomas and presenting mostly between 15 and 35 years of age.[1] The tumor is characterized by the fusion protein ASPSCR1-TFE3 from translocation t(X;17)(p11.2;q25.3).[2] ASPS has a slowly progressive course, is poorly responsive to conventional cytotoxic chemotherapy and often metastasizes to lungs, bones, and brain.[3] In this report we describe 2 cases of ASPS spanning a combined 19 years of treatment to illustrate the responses of these patients' tumors to multiple series of treatments, including surgery, radiation therapy, and chemotherapy (Table 1).

OBSERVATIONS

Case Report 1

A 12-year-old female was diagnosed in January 2006 with ASPS after resection of a left shoulder mass. Over the subsequent 2 years she had 2 local recurrences with subsequent surgeries and local radiotherapy. Chest computerized tomography in 2007 showed 1 pulmonary nodule, which was not treated at the time. In October 2009 she had multiple lung nodules on chest computerized tomography, the largest being 3 cm in size. Biopsy of the lung lesion confirmed the diagnosis of ASPS. Owing to the extensive pulmonary nodules, complete resection was not possible.

She started on a pazopanib trial in November 2009. She developed oral lesions that responded to pyridoxine but otherwise tolerated therapy well. The pulmonary lesions were stable in size, until the disease progressed 6 months later in May 2010. Pazopanib was discontinued and we would have preferred to have her enrolled on a cediranib trial; however, she did not meet the age requirement. Instead, sorafenib was started in June 2010. She experienced alopecia totalis, rashes, abdominal pain, and diarrhea and the dose was decreased for better tolerability. She had stable disease (SD) for almost 22 months on sorafenib until April 2012 when she developed headaches and vomiting and was found to have 3 new brain lesions. She received surgery and gamma knife radiotherapy. Further evaluation revealed multiple thoracic, lumbar, and sacral vertebral lesions.

Having reached the age of eligibility for the cediranib trial at this time, she was enrolled in June 2012. She experienced diarrhea, hypertension, abdominal discomfort, weight loss, and subclinical hypothyroidism. After the initial 2 cycles, there was decrease in the size of the lung and brain metastases. After 13 months on cediranib she developed severe headaches and pain in her left buttock. Magnetic resonance imaging (MRI) of the brain showed no change in the size of the tumors, but there was significant increase in vasogenic edema. This was suggestive of disease progression so cediranib was discontinued in August 2013.

Restaging in September 2013 showed increasing size of the pulmonary and bone lesions. She started sunitinib in October 2013, but stopped 2 months later due to neuropathic pain, mucositis, thrombocytopenia, rashes, facial swelling, and yellow-green skin discoloration. In January 2014, she developed severe left buttock pain. Imaging showed significant increase in the size of her spinal and sacral lesions with involvement of the L5 and S1 nerve roots. Radiation therapy to the lesions was administered over the subsequent 3 months with improvement in her pain.

In May 2014, she developed dizziness and was found on MRI to have increase in size of the right parietal brain lesion with surrounding vasogenic edema. She received zoledronic acid for pain due to bone metastases. In June 2014 she enrolled in a trial of trabectedin, but progressed after 2 months. She then enrolled on a trial of ganetespib (heat shock protein inhibitor) and sirolimus (mechanistic target of rapamycin [mTOR] inhibitor), for 2 months but progressed again. She received gamma knife for a growing brain lesion. She restarted sunitinib and zoledronic acid

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TABLE 1. Treatment and Response Summaries of 2 Cases of ASPS

Time Period	Duration (mo)	Treatment	Clinical Trial	Pediatric/Adult Trial	Best Response/Reason for Stopping
Case 1					
2006-2007		Surgery ×3 then RT			
11/2009-5/2010	6	Pazopanib 500 mg PO daily	Yes	Pediatric NCT00929903	Stable disease/disease progression
6/2010-4/2012	22	Sorafenib 400 mg PO bid, decreased to 200 mg bid	No	N/A	Stable disease/disease progression
4/2012		Neurosurgery, gamma knife			
6/2012-8/2013	14	Cediranib 30 mg PO daily	Yes	Adult NCT00942877	Stable disease/disease progression
10/2013-12/2013	3	Sunitinib 37.5 mg PO daily	No	N/A	Progressive disease/side effects
12/2013-8/2015	20	Zolendronic acid 4 mg IV × 12 doses	No	N/A	Improved bone pain/completed a total of 12 mo of treatment
1/2014-4/2014		RT to spinal lesions			
6/2014-7/2014	2	Trabectedin 1.5 mg/m^2 IV over 24 h every 21 d	Yes	Adult NCT00210665	Disease progression
8/2014-10/2014	2	Ganetespib 200 mg/m^2 IV on days 1, 8, and 15. Sirolimus 4 mg PO daily	Yes	Adult NCT02008877	Disease progression
11/2014		Gamma knife to CNS			
12/2014 present		Sunitinib 25 mg PO daily	No	N/A	Stable disease
Case 2					
12/2004-2/2005	3	Vincristine, cyclophosphamide and doxorubicin × 2. Ifosfamide and etoposide × 2	No	N/A	Stable disease
4/2005-7/2006	14	Interferon α-2a 3 million unit injection daily	No	N/A	Stable disease/side effects
1/2007-10/2008	22	Sorafenib 105 mg/m^2 PO bid	Yes	Pediatric NCT01445080	Partial response/disease progression
10/2008		Mediastinal debulking, RUL wedge resection			
11/2008-1/2009	2	Trabectedin 1.5 mg/m^2 IV over 24 h every 21 d	Yes	Pediatric NCT00070109	Disease progression
2/2009		Laminectomy, tumor debulking			
3/2009-2/2010	12	Sorafenib 200-400 mg PO bid. Rapamycin 6 mg PO daily	No	N/A	Disease progression
3/2010-12/2010	8	Cediranib 30 mg PO daily	Yes	Adult NCT00942877	Minor response/disease progression
12/2010		L3-L5 debulking			
1/2011-7/2011	7	Pazopanib 800 mg PO daily, then 600 mg PO daily	Yes	Pediatric NCT00929903	Stable disease/disease progression
7/2011-8/2011		L1/L2 laminectomy, debulking, RT			Not assessed
9/2011-1/2013	16	Sunitinib 37.5 mg PO daily with 1 wk break every q6-8 wk; then decreased to 25 mg daily	No	N/A	Mixed response/disease progression
2/2013		Thoracotomy, resection mediastinal mass, adjuvant SBRT, low dose pazopanib 200 mg PO daily	No	N/A	Disease progression
7/2013-10/2013	3	Axitinib 5 mg PO bid	No	N/A	Disease progression
11/2013-7/2014		Palliative orthopedic procedures, RT, ongoing axitinib	No	N/A	Disease progression
7/2014		Gamma knife to CNS	No	N/A	
8/2014		L4/L5 laminectomy, debulking, SBRT	No	N/A	
10/2014-1/2015	3	Cabozantinib 140 mg PO daily, then 60-80 mg daily, then 20 mg daily	No	N/A	Disease progression/side effects
		Orthopedic procedures for pathologic fractures			
2/2015-4/2015	2	MGCD516 80 mg PO daily	Yes phase 1/1b	Adult NCT02219711	Stable disease/side effects and disease progression
6/2015-9/2015	3	Nivolumab 3 mg/kg/dose IV every 2 wk	No	N/A	Disease progression

ASPS, alveolar soft part sarcoma; CNS, central nervous system; IV, intravenous; N/A, not applicable; PO, oral; RT, radiation therapy; RUL, right upper lobe of the lung; SBRT, stereotactic body radiation therapy.

with improved pain control and SD for 7 months at the time of manuscript submission.

Case Report 2

A 17-year-old female presented with constipation and abdominal pain in November 2004. She had a left psoas muscle mass, bilateral pulmonary nodules, and a lytic lesion of the left distal femur. Biopsy of the psoas mass demonstrated ASPS. She received 2 cycles of vincristine, cyclophosphamide, and doxorubicin, feeder vessel embolization and resection of the primary mass with residual positive margins and minimal necrosis at resection. She received 2 cycles of ifosfamide and etoposide and underwent right thoracotomy, revealing miliary lung involvement with $<25\%$ necrosis. She received interferon-α-2a as a standard of care treatment for 14 months with disease

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TABLE 2. Summary of Case Series of ASPS

References	No. Patients (Dates of Review)	Median Age at Diagnosis (y) (Range)	Outcome
Portera et al[1]	74 (1959-1998)	26 (3-68)	Patients without metastases at presentation: 5 y PFS 71%, 5 y OS 87% Patients with metastases at presentation: 5 y OS 20%
Lieberman et al[4]	102 (1923-1986)	22 (2-71)	Patients without metastases at presentation: OS 77% at 2 y, 60% at 5 y, 38% at 10 y, 15% at 20 y Median survival after development of metastases: 2 y
Kayton et al[5]	20 (1974-2004)	16.5 (6-24)	5 y PFS 22% and OS 83%
Orbach et al[6]	51 (1980-2009)	13 (2-21)	5 y EFS and OS 68.2% and 87.2% 10 y EFS and OS 62.8% and 78%
Pappo et al[7]	11 (1962-1994)	9.8 (2.8-16)	2 patients passed away 9 patients were disease free with a median follow-up of 11.9 y

ASPS, alveolar soft part sarcoma; EFS, event-free survival; OS, overall survival; PFS, progression-free survival.

stability, but impaired quality of life due to flu-like symptoms and depression led to self-discontinuation.

In January 2007, imaging studies demonstrated pulmonary progression. She enrolled on a study of sorafenib achieving a partial response (PR), but developed recurrent, suppurative groin nodules. After 22 months of sorafenib, the disease progressed in a subcarinal node, which was resected. In November 2008, she enrolled on the trabectedin trial, but progressed after 2 cycles. She underwent an L4 laminectomy for epidural disease and received rapamycin and sorafenib for 1 year until progression.

In March 2010, she enrolled on a study of cediranib, which was complicated by hypertension and hypothyroidism. She stopped after 8 months due to new hepatic metastases and progression in the spine requiring L3-L5 debulking. She enrolled on a trial of pazopanib where dynamic MRI demonstrated a decrease in the fractional tumor blood volume and permeability, and a minor response was observed after 2 cycles. She experienced treatment-limiting anorexia, nausea, and tumor-associated pain and received 7 courses until clinical progression required a third spinal surgery and lumbar radiotherapy.

She started sunitinib in September 2011, tolerating only 50% of the adult dose. She experienced slow extrapulmonary progression. She underwent hepatic left lateral segmentectomy in October 2012, and subcarinal node and right lung wedge resection in February 2013. Surgery was followed by mediastinal radiotherapy and low-dose pazopanib. As bony disease progressed, axitinib was started in July 2013, which she tolerated well, but she experienced disease progression after 3 months. She received palliative radiotherapy to several bone lesions, ultimately requiring placement of an intramedullary rod in the left femur. She received gamma knife to a right frontal brain metastasis in July 2014 and had her fourth L4-L5 spinal debulking with reirradiation in October 2014.

She started cabozantinib in October 2014, but did not tolerate even low doses, and experienced disease progression 3 months later. She subsequently underwent intralesional tumor excision of the left humeral head and a fifth spinal debulking. In February 2015 she enrolled on phase 1 trial of a novel multitargeted tyrosine kinase inhibitor (TKI) from Mirati Therapeutics, but self-discontinued after an echocardiogram demonstrated a transient decrease in left ventricular systolic function. Disease progression was discovered in the bone and spine lesions. She was started on programmed death-1 inhibitor, nivolumab, but had disease progression after 3 months.

CONCLUSIONS

There are only a few large published case series of ASPS with 3 focused specifically on children, adolescents, and young adults (Table 2).[1,4–7] These case series show that the frequency of metastasis at presentation increases with age at diagnosis, and the median survival decreases with increasing age.[5,7]

Studies have not demonstrated the efficacy of cytotoxic chemotherapy in the metastatic or adjuvant settings.[1,4,6] Ultimately, complete surgical resection gives the best chance for prolonged survival, but relapse remains common. Radiotherapy may be effective for patients with nonmetastatic disease with inadequate surgical margins or for palliation.[6]

Given the treatment refractoriness of ASPS, there has been extensive interest in using novel therapeutic agents. Many of these approaches have focused on antiangiogenesis because of ASPS's vascular nature and angiogenesis-related molecular targets.[8] The fusion protein ASPSCR1-TFE3 results in autophosphorylation of mesenchymal epithelial transition factor, increasing angiogenesis, cell division, and cell survival.[8] Studies of bevacizumab showed efficacy in 2 published cases.[9,10]

Small molecule inhibitors of VEGF receptor tyrosine kinases have also been investigated. Cediranib inhibits VEGFR-1, -2, and -3. A recent phase II trial of cediranib found that 15 of 43 evaluable patients achieved a PR (35%), and 26 patients (60%) had SD with a disease control rate of 84% at 24 weeks.[11] The tyrosine kinases inhibited by sunitinib closely match those upregulated in ASPS.[12] Sunitinib may have both antiangiogenic activity and direct antitumor activity through its inhibition of c-KIT, PDGFRβ, and RET. In a study of 9 patients treated with sunitinib, 55% had PRs, with a median progression-free survival (PFS) of 17 months. Despite tumor flare with temporary discontinuation, responses occurred upon reintroduction.[8] The comparative efficacy of single agent cediranib or sunitinib is the subject of an ongoing randomized crossover trial (NCT01391962). In our patients, we observed that sequential treatment with different TKIs can produce responses, despite their having overlapping target profiles. This observation has also been seen in other cancers such as renal cell carcinoma.[13] Variations in the binding affinities for and

interactions among specific targeted kinases for multitarget TKIs may explain this counter-intuitive finding. However, in 1 patient the duration of response diminished with each subsequent TKI therapy.

Targeting mesenchymal epithelial transition directly with the inhibitor tivantinib was relatively ineffective when studied.[14] There were no objective responses, SD was observed in 78% of patients at 4 months, with a median PFS of 6 months. Similarly, in 7 patients with metastatic or advanced ASPS on trabectedin, 6 patients had SD with a mean PFS of 7 months.[15] Both of our patients progressed after 2 cycles of trabectedin. mTOR is another potentially therapeutic target in ASPS. A study of 22 cases of ASPS compared with 81 non-ASPS soft tissue sarcomas found increased mTOR activity in ASPS cases, which may be related to the ASPL-TFE3 fusion protein.[16]

Summary

Various ASPS drug trials show modest efficacy, but the confidence intervals are wide and the chance of false-positive observations are considerable given ASPS's indolent nature.[17] Our patients' ages complicated participation in clinical trials, causing a delay in eligibility in one of patients for 2 years, while she waited to reach 18 years of age. Each transitioned between pediatric and adult developmental therapeutics programs depending on protocol age eligibility. Although molecularly targeted therapies provided short periods of stabilization, the disease ultimately continued to progress. New medications in development, including tumor vaccines, immune checkpoint inhibitors against targets such as programmed death-1, and targeted drug combinations may hold promise for further disease control.[18] Future studies should be designed to include patients across the adolescent and young adult years.

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