

Systemic therapy in primary angiosarcoma of the spleen

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Abstract

Primary splenic angiosarcoma is a very rare neoplasm with a high propensity for metastatic disease and poor prognosis. There is a paucity of literature concerning this specific sarcoma subtype and the role of systemic therapy is not well defined. A retrospective review of the prospectively maintained University of Washington/Seattle Cancer Care Alliance Sarcoma Unit database was performed to identify patients with splenic angiosarcoma treated between 2007 and 2012. In total there were 19 patients with angiosarcoma treated at the Seattle Cancer Care Alliance from 2007 to 2012. The number of patients with splenic angiosarcoma was 2 (11%). The first patient was a woman aged 57 years who was referred with metastatic splenic angiosarcoma to the liver, post-splenectomy. She was treated with 4 cycles of weekly paclitaxel prior to metastatic resection and 4 cycles of the same drug in an adjuvant scenario, achieving a pathological complete response to treatment. She is alive and on third-line systemic therapy. The second patient was a male patient aged 30 years who presented with metastatic high-grade splenic angiosarcoma and was treated with 3 lines of systemic therapy, including doxorubicin, paclitaxel and gemcitabine+docetaxel, but developed a gastrointestinal metastasis with subsequent gastrointestinal bleeding. Splenic angiosarcoma is a very rare neoplasm. Surgery remains the mainstay of management for localized disease. Paclitaxel administered weekly proved to be well-tolerated and resulted in a good radiological response in one of our patients, enabling resection of metastatic disease. Durable clinical benefit can be achieved in metastatic splenic angiosarcoma with multi modality management.

Introduction

Primary splenic angiosarcoma is a very rare neoplasm with a high rate of metastatic disease and poor prognosis.¹ Although this pathological entity is rare, it is now regarded as the most frequent primary non-lymphoid malignant tumor of the spleen.^{2,3} The literature is very limited concerning this specific sarcoma subtype, and due to its unique features and prognosis it is hard to standardize treatment strategies. Moreover, the morphologic spectrum of this disease is highly variable being similar in some aspects to vascular tumors such as hemangiomas, epithelioid hemangioendotheliomas and Kaposi's sarcoma, or malignant non-vascular tumors like lymphangiomas and secondary metastatic cancers, causing diagnostic difficulty.

The clinical presentation of this disease is variable. Upper left abdominal pain, weight loss, fatigue, generalized weakness and fever are common symptoms.⁴⁻⁸ Three common findings are splenomegaly, defined as splenic weight >250 μg ,⁴ anemia and thrombocytopenia. Spontaneous splenic rupture can occur with a rate between 13-22%.⁹ Splenectomy remains the mainstay of management, with little data on the utility of chemotherapy and radiation. Some case-reports have reported potential benefit from systemic therapy in splenic angiosarcoma, in terms of down staging tumours and possibly improving outcome.^{1,10}

The aim of this study was to evaluate our experience with systemic therapy in patients with splenic angiosarcoma, with particular regard to response and outcome.

Materials and Methods

A retrospective search of the prospectively maintained University of Washington/Seattle Cancer Care Alliance Sarcoma Unit Database was performed to identify patients with splenic angiosarcoma treated between 2007 and 2012. The study was approved by the Institutional Review Board.

The diagnosis was confirmed by an experienced soft tissue sarcoma pathologist in each case. Patient details obtained included age at diagnosis, tumor size, tumor stage, surgery, radiation and number of lines of systemic therapy, toxicity, time to progression, date of last follow-up/death. Descriptive statistics were used.

Results

In total there were 19 patients with angiosarcoma treated at the University of Washington

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between 2007 and 2012. The number of patients with splenic angiosarcoma was 2 (11%), represented by one female and one male.

The female patient was aged 57 years at diagnosis and presented with a history of left-sided lower abdominal pain, weight loss, decreased appetite and dyspnea. Investigations included a splenic biopsy, which revealed an angiosarcoma. A positron emission tomography-computed tomography (PET-CT) demonstrated hypermetabolic foci in the enlarged spleen and 2 hypermetabolic foci in the liver. The CT revealed several hypodense lesions in the liver. She underwent splenectomy and a liver biopsy. The pathology showed a spleen almost completely replaced by angiosarcoma and the liver biopsy showed a benign hemangioma. A further percutaneous liver biopsy of one of the FDG (fluorodeoxyglucose) avid liver lesions revealed metastatic angiosarcoma.

She was subsequently referred to the University of Washington and commenced on weekly paclitaxel (90 mg/m²). A re-staging PET-CT scan following two cycles of chemotherapy showed resolution of the previously hypermetabolic hepatic foci, without new foci of disease. She then received a further two cycles of paclitaxel followed by hepatic resection. The post-operative pathology showed no angiosarcoma. She subsequently received 4 post-operative cycles of paclitaxel. Ten months following liver resection a re-staging MRI (magnetic resonance imaging) scan showed 3 new lesions in the liver, which were not FDG avid on PET and a biopsy of one of these lesions showed no evidence of metastatic angiosarcoma. Twelve

months following liver resection she underwent a hernia repair and repeated liver biopsies of the previous observed liver lesions. One showed pathology consistent with recurrent angiosarcoma and was treated with radiofrequency ablation. Her disease progressed in the liver and she was treated with pazopanib followed by doxorubicin and a novel agent within a Phase II trial. She is alive over 2 years from diagnosis and tolerating therapy well.

The second patient was a 30 year-old hispanic male, who presented with a history of left upper abdominal pain, night sweats, fevers, weight loss and fatigue. Imaging showed a splenic cyst measuring 10×9 cm, as well as multiple liver cysts, ranging from 2.5 to 5.9 cm. The differential diagnosis included an *Echinococcal* cyst or malignancy. Due to the risk of splenic rupture, a splenectomy and liver biopsy were performed. The pathology showed a splenic angiosarcoma with metastases to the liver. The patient was treated with an anthracycline-based regimen within a randomized Phase III trial. Re-staging following two cycles of therapy showed progressive disease, with new lesions in the splenic bed, omentum and pancreas. He then commenced second-line therapy with weekly paclitaxel (90 mg/m²). The patient underwent 2 cycles of treatment, but was hospitalized with hematemesis during the second cycle. He underwent an esophagogastros- copy which showed an ulcerated mass in the stomach with active bleeding, proven to be metastatic angiosarcoma. This was treated with radiation. He was subsequently treated with third-line therapy consisting of gemcitabine and docetaxel. He tolerated the first cycle well, but during the second cycle the patient was hospitalized and died 8 months from diagnosis.

Discussion

Angiosarcomas are rare soft-tissue sarcomas of endothelial cell origin that have a poor prognosis.¹¹ They account for less than 2% of all visceral and soft tissue sarcomas, and various clinical forms have been described, including primary scalp, radiation-induced, primary breast, angiosarcoma associated with lymphedema (Stewart-Treves Syndrome)¹², and vinyl-chloride induced liver sarcomas.¹³ Most are spontaneous, however, several well described risk factors exist, including radiation, chronic lymphoedema, exogenous toxins and familial syndromes.¹¹ In contrast, no associative or causative factors were found for splenic angiosarcomas in two large case studies performed by Falk *et al.* and Neuhauser *et al.*^{4,5} No etiologic association with chemotherapeutic agents has been substantiated in the literature.⁵

Primary splenic angiosarcoma constitutes one of the rarest type of neoplasm, having its estimated annual incidence ranging from 0.14 to 0.25 cases per million persons.¹⁴ Some studies have suggested this neoplasm shows a slight male predominance,¹⁵ with no predilection for race, geographic location or heritability. Conversely, some studies have suggested a slight female predilection,⁵ but no gender predilection was observed in the two largest studies.^{4,5} The mean age at presentation is 59 years with a range between 14 months and 89 years.^{3-5,16} A study by the French Sarcoma Group reported primary angiosarcomas of the liver, heart, bone and spleen as having a poor progression-free and overall survival.¹⁷ It is also known that this rare neoplasm has a very poor prognosis, primarily as a consequence of the high rate of metastatic disease, ranging from 69-100%. The main metastatic sites are liver (89%), lungs (78%), lymph nodes (56%) and bone (22%).¹ Other known metastasis sites from primary splenic angiosarcoma are bone marrow, gastrointestinal tract, brain, adrenal gland, omentum, peritoneum and pleura.^{3,18} Falk *et al.* reported that the median interval to metastases in their study was 8 months.⁴ Hsu *et al.* found in his study that patients with metastatic or recurrent disease had a median interval survival of 6.5 months (range 3-11 months).⁶ In our two cases, the patients did present with liver metastases, but had markedly different outcomes. In the first case, following a response to first-line chemotherapy the metastatic liver disease could be resected. In the second case, the disease was too advanced for any form of surgical intervention.

Patients can present with a number of non-specific symptoms and findings, such as upper abdominal pain and fullness, fatigue, weight loss, splenomegaly and anemia.^{1,4,5,16-23} Splenic rupture can also be a presenting finding, sometimes resulting in acute hemoperitoneum in up to 30%.¹⁹ It has been proposed that splenic rupture does not relate to outcome,⁵ but splenectomy in both emergent and elective cases is rarely curative.² Conversely, others have proposed that splenic rupture is the worst prognostic factor for survival, due to increased risk of peritoneal dissemination with direct implantation of neoplastic tissue associated with vascular access and hematogenous spread.¹⁵ One rare clinical manifestation is gastrointestinal bleeding secondary to metastatic disease, and to our knowledge there have only been two previous reported cases.⁹ In the case of gastrointestinal bleeding, the clinical course is poor, with a survival rate ranging between 10.3 to 13 months.⁹ Our second patient died 7 weeks after the initial bleeding episode.

The pathogenesis of splenic angiosarcoma is still uncertain. Some authors have hypothesized that it develops from previously existing

benign counterparts, such as hemangioma or hemangioendothelioma.^{1,4,5}

Microscopically, these tumours are very heterogeneous, but in most cases a focal vasoformative component is the dominant pattern with vascular spaces lined by atypical endothelial cells and a sarcomatous stroma,^{4,6,8} which is the most important criterion to establish the diagnosis of angiosarcoma.⁹ Chen *et al.* were the first to establish the blood vessel origin of these tumours in 1979.²⁴ Angiosarcomas are usually composed of malignant spindled, polygonal, epithelioid and primitive round cells as well as clearly recognizable endothelial cells.⁴ Patient outcome has no relation to histological appearance or grade.^{14,16} On immunohistochemistry, neoplastic cells express Factor VIII-associated antigen and 2 or more markers of vascular differentiation such as CD34, CD31 and VEGFR3.^{4,5,10,11} CD68 and lysozyme, known as histiocytic differentiation markers are often also expressed.⁵ Angiosarcomas tend to display complex karyotypes and no consistent recurrent chromosomal abnormalities have been found.²⁵

There has been interest in the role of angiogenesis and the angiogenic factors in the pathogenesis of angiosarcoma and the potential utility of anti angiogenic agents in these tumors. As previously reported, vascular endothelial growth factor (VEGF) and its receptors can be overexpressed in angiosarcomas,¹¹ however, overexpression of VEGF and fibroblast growth factor (FGF) are associated with tumor growth and poor outcome in soft tissue sarcoma.²⁶ The use of broad-spectrum tyrosine-kinase inhibitors to target VEGFRs has been assessed in several Phase 2 trials.¹¹ Maki *et al.*²⁷ performed the largest study, which included 37 angiosarcoma patients treated with sorafenib. The overall-response rate was 14% with a median progression-free survival of 3.8 months. In contrast, von Mehren *et al.* showed no response to sorafenib administration in various soft tissue sarcoma histological subtypes in their study, apart from modest activity in patients with vascular sarcomas.²⁸ Similarly, another multitargeted tyrosine kinase inhibitor, sunitinib, did not demonstrate activity in non-gastrointestinal stromal sarcomas.²⁹ A Phase III study of bevacizumab in combination with docetaxel and gemcitabine in advanced and recurrent soft-tissue sarcomas included three angiosarcomas with complete responses reported in two of them.¹¹ Thalidomide and interferon also have antiangiogenic properties and a few case reports have shown response to them in advanced or metastatic angiosarcoma.¹¹ However, due to the rarity of angiosarcoma the exact role of anti angiogenic agents remains to be clarified, and consequently, further evaluation is required within well designed clinical trials. Notably, pazopanib was approved in 2012 by the FDA for patients with progressive metastat-

ic soft tissue sarcoma previously treated with chemotherapy.

A number of chemotherapy regimens have been used in angiosarcoma, including cyclophosphamide, doxorubicin, epirubicin, ifosfamide, daunorubicin, vincristine, docetaxel, dacarbazine, bevacizumab, etoposide, cisplatin and paclitaxel.^{8,10} The main drug groups used are anthracyclines, ifosfamide and taxanes.¹¹ Therapeutic responses to liposomal doxorubicin have also been reported. A comparison of doxorubicin and weekly paclitaxel in metastatic angiosarcoma has been reported, suggesting similar efficacy,¹⁷ however, weekly paclitaxel showed a longer median PFS of 5.8 months and in elderly patients it can be better tolerated than doxorubicin. There is no evidence from prospective randomized trials that combination chemotherapy can improve outcome compared to single agent sequential treatment in metastatic angiosarcoma, but combination chemotherapy is associated with increased toxicity. Furthermore, many angiosarcoma patients are elderly, so comorbidities and the risk of treatment related to toxicity can limit the use of chemotherapy.¹¹

In vitro, paclitaxel has exhibited potent antiangiogenic activity at low-dose concentration and when weekly administered it proved to be an effective and well-tolerated treatment for patients with unresectable angiosarcoma, achieving a median duration of response of 5 months.¹³ The mode of action of paclitaxel involves the stabilization of microtubules through the inhibition of the depolymerization process.¹³ In a large retrospective study of 32 patients with angiosarcoma, 63% responded to paclitaxel treatment, with progression-free-survival of 7.6 months.¹¹ A prospective Phase II trial of weekly paclitaxel for angiosarcoma, showed good tolerability and reported a median survival of 8 months.¹³ Vakkalanka *et al.* reported a case showing the benefit of using paclitaxel every 3 weeks for down-staging an unresectable splenic angiosarcoma, followed by surgery and adjuvant paclitaxel.¹⁰ Our female patient with splenic angiosarcoma also had a good radiological response to paclitaxel followed by hepatic resection. There has been another report of successful hepatic resection in metastatic splenic angiosarcoma.⁶ These observations suggest that multi modality treatment may be employed in metastatic splenic angiosarcoma with meaningful clinical benefit. In addition, others have observed good clinical responses to chemotherapy in patients with splenic angiosarcoma.

The optimal systemic therapy for metastatic splenic angiosarcoma remains to be defined, with a number of agents, including cytotoxic chemotherapy and antiangiogenic agents, showing some degree of activity. However, this is an aggressive disease, as illustrated by our second patient who pro-

gressed on three lines of systemic therapy and radiation. There is an unmet need for a better understanding of the underlying biology of this disease as well as the identification of targetable molecular drivers.

References

- Hara T, Tsurumi H, Kasahara S, et al. Long-term survival of a patient with splenic angiosarcoma after resection, high-dose chemotherapy, and autologous peripheral blood stem cell transplantation. *Intern Med* 2010;49:2253-7.
- Safapor F, Aghajanzade M, Kohsari MR, et al. Spontaneous rupture of the spleen: a case report and review of the literature. *Saudi J Gastroenterol* 2007;13:136-7.
- Ozturk E, Mutlu H, Sonmez G, Sildiroglu HO. Primary angiosarcoma of the spleen. *Turk J Gastroenterol* 2007;18:272-5.
- Falk S, Krishnan J, Meis JM. Primary angiosarcoma of the spleen. A clinicopathologic study of 40 cases. *Am J Surg Pathol* 1993;17:959-70.
- Neuhauser TS, Derringer GA, Thompson LD, et al. Splenic angiosarcoma: a clinicopathologic and immunophenotypic study of 28 cases. *Mod Pathol* 2000;13:978-87.
- Hsu JT, Chen HM, Lin CY, et al. Primary angiosarcoma of the spleen. *J Surg Oncol* 2005;92:312-6.
- Valbuena JR, Levenback C, Mansfield P, Liu J. Angiosarcoma of the spleen clinically presenting as metastatic ovarian cancer. A case report and review of the literature. *Ann Diagn Pathol* 2005;9:289-92.
- Liu Z, Du X, Li H, et al. Primary splenic angiosarcoma. *Vasa* 2012;41:57-62.
- Aviles-Salas A, Luevano-Gonzalez A. [Primary angiosarcoma of the spleen: report of one case]. *Rev Med Chil* 2007;135:1178-81. [Article in Spanish].
- Vakkalanka B, Milhem M. Paclitaxel as neoadjuvant therapy for high grade angiosarcoma of the spleen: a brief report and literature review. *Clin Med Insights Oncol* 2010;4:107-10.
- Young RJ, Brown NJ, Reed MW, et al. Angiosarcoma. *Lancet Oncol* 2010;11:983-91.
- Heitmann C, Ingianni G. Stewart-Treves syndrome: lymphangiosarcoma following mastectomy. *Ann Plast Surg* 2000;44:72-5.
- Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol* 2008;26:5269-74.
- Hamid KS, Rodriguez JA, Lairmore TC. Primary splenic angiosarcoma. *JLS* 2010;14:431-5.
- Manouras A, Giannopoulos P, Toufektzian

L, et al. Splenic rupture as the presenting manifestation of primary splenic angiosarcoma in a teenage woman: a case report. *J Med Case Reports* 2008;2:133.

- Hsu JT, Ueng SH, Hwang TL, et al. Primary angiosarcoma of the spleen in a child with long-term survival. *Pediatr Surg Int* 2007;23:807-10.
- Italiano A, Cioffi A, Penel N, et al. Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. *Cancer* 2012;118:3330-6.
- Takeuchi T, Iwasaki S, Miyazaki J, et al. Matrix metalloproteinase-1 expression in splenic angiosarcoma metastasizing to the serous membrane. *Int J Clin Exp Pathol* 2010;3:634-9.
- Alvite Canosa M, Alonso Fernandez L, Seoane Vigo M, et al. [Primary angiosarcoma of the spleen]. *Rev Esp Enferm Dig* 2008;100:375-6. [Article in Spanish].
- Suzuki K, Nakazato T, Mihara A, et al. Primary splenic angiosarcoma mimicking splenic lymphoma. *Intern Med* 2010;49:203-4.
- Vaiphei K, Singh V, Varma S. Splenic angiosarcoma presenting with jaundice, ascites and bone marrow fibrosis. *Sarcoma* 2003;7:183-4.
- Schattner A, Bassevitch A, Diment J. An elderly man with fever and hypodense lesions in the spleen and liver. *CMAJ* 2006;174:163-4.
- Verge J, Albiol J, Navas M, Martin C. [Primary angiosarcoma of the spleen with liver metastases. Case report and literature review]. *Cir Esp* 2005;78:50-2. [Article in Spanish].
- Chen KT, Bolles JC, Gilbert EF. Angiosarcoma of the spleen: a report of two cases and review of the literature. *Arch Pathol Lab Med* 1979;103:122-4.
- World Health Organization Classification of Tumours. Pathology and genetics of tumours of soft tissue and bone. IARC Press; 2002.
- Schmitt T, Kasper B. New medical treatment options and strategies to assess clinical outcome in soft-tissue sarcoma. *Expert Rev Anticancer Ther* 2009;9:1159-67.
- Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol* 2009;27:3133-40.
- von Mehren M, Rankin C, Goldblum JR, et al. Phase 2 Southwest Oncology Group-directed intergroup trial (S0505) of sorafenib in advanced soft tissue sarcomas. *Cancer* 2012;118:770-6.
- George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. *J Clin Oncol* 2009;27:3154-60.