Paclitaxel as Neoadjuvant Therapy for High Grade Angiosarcoma of the Spleen: a Brief Report and Literature Review

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Abstract
Introduction: Splenic angiosarcoma is a rare tumor with only a few cases reported in the literature. Surgical resection offers the best chance of cure for this aggressive neoplasm but is often precluded by infiltration of the tumor to surrounding critical structures. We report a case of a locally advanced angiosarcoma rendered operable by treatment with Paclitaxel monotherapy.

Case presentation: A 69 year old female presented with a high grade splenic angiosarcoma, considered inoperable due to the extent of local spread. She received three cycles of single agent Paclitaxel and underwent a successful resection of the tumor.

Conclusion: Chemotherapy options for splenic angiosarcoma are not well studied. Paclitaxel as monotherapy is a useful therapeutic option in down staging tumors, facilitating surgical resection and merits further study in clinical trials.

Keywords: sarcoma, angiosarcoma, paclitaxel, spleen
Introduction
Splenic angiosarcomas are exceedingly rare tumors with a very poor prognosis. Only a few cases have been reported in the literature, since its original description by Langhans in 1879. Angiosarcomas have a highly variable histology and can be mistaken for vascular benign tumors or other non vascular malignant neoplasms. On microscopy most of them have a well defined nodular homogenous appearance and all of them show a vaso-formative component. Most of the tumors express at least one immunohistochemical marker of histiocytic differentiation (CD68 and/or lysozyme) and two or more markers of vascular differentiation (CD 34, CD31, FVIII R Ag, VEGFR3). On radiological imaging, these tumors show an enlarged spleen (>12 cm), usually with either a solitary complex mass or multiple diffusely infiltrative heterogeneous masses. Metastases are a frequent finding at the time of diagnosis with up to 70% of metastatic deposits involving the liver. Common sites of metastatic disease include lung followed by bone and liver. Low platelet counts are seen in 33% of splenic angiosarcoma cases, which should be considered in the differential diagnosis of unexplained thrombocytopenia.

In a retrospective study of 82 angiosarcoma patients, those with a primary resectable tumor had a 5 year disease specific survival (DSS) rate of 60%. Sixty seven percent of these patients received adjuvant radiation and 27% received chemotherapy. Tumors with intermediate or high grade pathology (76%) and those arising from previously irradiated or lymphedematous areas had worse disease specific survival. In another study looking at patients with advanced angiosarcomas, median disease-specific survival (DSS) for patients with locally recurrent disease and metastatic disease was 50 months (95% confidence interval (CI): 25.7–73.5 months) and 10 months (95% CI: 7.9–12 months) respectively. Most of these studies included patients with angiosarcomas arising from various sites including soft tissues, breast, skin, viscera and bone. Due to a paucity of data, it is however unclear if splenic angiosarcomas have a different natural course of progression than sarcomas arising from other organs.

Several chemotherapy treatment options have been tried in patients with locally recurrent/metastatic angiosarcoma, including Paclitaxel ± Gemcitabine, Doxorubicin ± Ifosfamide, Docetaxel ± Gemcitabine, Interferon alfa, Dacarbazine, Bevacizumab, Etoposide, Cisplatin and various combinations of these agents. Paclitaxel is an alkaloid ester extracted from the bark of the pacific yew tree (Taxus brevifolia) and the European Yew tree (Taxus baccata). It stabilizes the microtubules by inhibiting the process of tubular depolymerization. This process occurs during the metaphase/anaphase transition of the mitotic cell cycle, resulting in an arrest of cell division. It also demonstrates antiangiogenic activity by inhibiting endothelial cell proliferation, motility and invasiveness, both in vivo and in vitro. In a phase II study of paclitaxel therapy in advanced soft tissue sarcoma, a complete response was seen in a patient with angiosarcoma of the scalp. A retrospective study of patients with angiosarcoma of the scalp has shown that Paclitaxel is effective in the treatment of angiosarcoma of the scalp with a major response (complete response + partial response) seen in 8 out of 9 (89%) patients. The median duration of response was 5 months. A further phase II clinical trial of paclitaxel in advanced angiosarcoma suggested that weekly paclitaxel is well tolerated and is associated with a progression free survival rates of 74% and 45% at 2 months and 4 months respectively. At a median follow up of 8 months the study reported a progression free survival of 4 months and a median overall survival of 8 months.

Here we present a patient with locally advanced splenic angiosarcoma treated with single agent with neo-adjuvant Paclitaxel. Based on an extensive search of the available literature, we believe this is the first report of Paclitaxel facilitating surgical resection in locally advanced splenic angiosarcoma.

Case Presentation
A 69 year old Caucasian female presented to us with a 4 month history of pain in the left upper quadrant of the abdomen, associated with a 30 lb weight loss and progressive shortness of breath. A CT scan of the chest, abdomen and pelvis revealed an enlarged spleen containing multiple heterogeneous hypodense masses, extending through the capsule into the peritoneal cavity, left anterolateral abdominal wall, left retrocrural space, and invading the left hemidiaphragm with the presence of at least 2 soft tissue implants superior to the left hemidiaphragm. A moderate sized left pleural effusion was also noted. An MRI scan of the brain...
and an isotope bone scan were performed to stage her disease but no metastatic disease was identified.

A biopsy of this mass confirmed it to be a high grade angiosarcoma. She was assessed for surgery, but the tumor was considered too extensive for a surgical resection. She was then offered chemotherapy for downstaging the tumor, and though there was no precedence for its usage in splenic angiosarcomas, Paclitaxel was chosen in view of its established efficacy in other locally advanced, unresectable soft tissue sarcomas. She received a total of three cycles of Paclitaxel at a dose of 175 mg/m² every three weeks, the most frequently used dose schedule in a retrospective review of nine patients with angiosarcoma of the face and scalp.¹⁶ She experienced grade 2 tiredness and neutropenia but otherwise remained free of systemic toxicity.

A repeat CT of the chest abdomen and pelvis after the third cycle of chemotherapy showed a 33% decrease in the tumor size, indicating a partial response as per RECIST criteria.¹⁸ There was also a complete resolution of her left hemidiaphragmatic tumor implants along with the left sided pleural effusion.

A splenectomy was then performed along with a resection of the left hemidiaphragm followed by a graft repair of the diaphragm. Pathological examination of the resected specimen showed areas of extensive necrosis and also confirmed that her splenic angiosarcoma was completely resected, with clear margins (Figs. 1 and 2). Also, no tumor extension was seen in 12 regional lymph nodes that were resected during surgery. She was discharged home after a short, uneventful postoperative stay in the surgical intensive care unit.

Following a four week break to allow recuperation from surgery, she was restarted on paclitaxel and has received a further three cycles of adjuvant therapy without any significant toxicity. She continues to remain well at the time of this report, 14 months following the initiation of her chemotherapy.

**Discussion**

Splenic angiosarcoma is a rare tumor often presenting with unresectable disease. The propensity of the tumor to disseminate locally and its proximity to critical intra-abdominal structures often precludes surgery at presentation. Chemotherapy is often used to downstage locally advanced angiosarcomas to improve respectability, but data on the efficacy of available therapeutic agents is limited. Treatment with Paclitaxel based regimes is shown to predict better DSS with a trend towards statistical significance (HR: 0.67, P = 0.06).⁸ Paclitaxel had also been shown to achieve high rates of objective response in patients with Kaposi’s sarcoma, another vascular tumor, commonly seen in the immunocompromised individuals.¹⁹

Paclitaxel is a generally well tolerated drug and can be used even in patients with a relatively modest performance status. The proximity of splenic angiosarcomas to the kidneys often causes ureteric obstruction resulting in renal impairment. Renal clearance of Paclitaxel and its metabolites is minimal and accounts only for less than 10% of the excretion of the drug.²⁰ Though a three weekly regime is the commonest schedule of administration of this drug, studies attempting to increase the dose intensity by more frequent administration of the drug have shown such regimes to be well tolerated, simultaneously achieving good response rates.¹⁷,²¹ However, there are no comparative studies of the various dosing regimes to guide therapy at this stage, making it difficult to choose...
between the various available scheduling options. These factors would make Paclitaxel a strong choice for the management of splenic angiosarcomas.

**Conclusion**

Our report shows that Paclitaxel can be administered safely and effectively in the patients with locally advanced splenic angiosarcoma, and renders the tumor highly resectable. Further randomized studies are required to define the role of Paclitaxel in comparison to other chemotherapeutic agents and also to determine its ideal dose schedule, in the treatment of visceral angiosarcomas.

**Authors Contributions**

Bhanu Vakkalanka: Involved with data collection, literature search and initial writing up of the manuscript.

Mohammed Milhem: Supervising consultant who identified the case, offered constant guidance during the preparation of the report and responsible for the final write up of the manuscript.

**Disclosures**

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient for publication of this study.

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