Clinics in Oncology

Research Article
Published: 03 Oct, 2020

Primary and Secondary Angiosarcomas - A Single Center Analysis and Review of the Literature

*Oskar Steinbrecher[1], Marita Kölz[2], Martin Schmid[3], Thomas Brodowicz[1] and Wolfgang Lamm[1]**

[1]Department of Medicine I, Medical University of Vienna, Austria

[2]Department of Pathology, Medical University of Vienna, Austria

[3]Department of Radiation Oncology, Medical University of Vienna, Austria

Abstract

Introduction: The management of patients with primary and secondary Angiosarcomas (AS) is controversially. Management of primary AS includes resection, radiation therapy and chemotherapy. Radiation Induced AS (RIAS) are classified as secondary AS. RIAS is mostly diagnosed after breast conserving surgery for primary breast cancer and radiation therapy. Most common initial chemotherapy for AS is paclitaxel.

Methods: We have retrospectively analyzed all patients with primary and secondary AS who were treated at our institution.

Results: Thirteen and 3 patients were diagnosed with primary and secondary AS. Median age was 51 and 69 years, respectively. Most common first line chemotherapy in the metastatic setting was paclitaxel. Median overall survival was 59 months and rot reached, respectively.

Conclusion: The combination with local therapy and systemic therapy may be considered in patients with initial localized AS, for patients with initially metastatic AS systemic therapy should be offered to the patients.

Keywords: Primary angiosarcoma; Secondary angiosarcoma; Chemotherapy; Tyrosinkinase therapy

OPEN ACCESS

Correspondence:
Wolfgang Lamm, Department of Internal Medicine I, Clinical Division of Oncology, Medical University of Vienna, Währingergürtel 18-20, 1090 Vienna, Austria,
E-mail: wolfgang.lamm@meduniwien.ac.at

Received Date: *08 Sep 2020*
Accepted Date: *30 Sep 2020*
Published Date: *03 Oct 2020*

Citation:
Steinbrecher O, Kölz M, Schmid M, Brodowicz T, Lamm W. Primary and Secondary Angiosarcomas - A Single Center Analysis and Review of the Literature. Clin Oncol. 2020; 5: 1741.

Introduction

Angiosarcomas (AS) are a rare malignant subentity in the family of Soft Tissue Sarcomas (STS), originating from blood vessels. AS have a poor prognosis and can arise anywhere in the body [1]. Primary AS in the head and neck is associated with older age, male patients and is furthermore associated with poor prognosis [2]. Primary AS of the breast is a special type and rare disease (0.04% of all malignant breast tumors) in women between 30 and 40 years of age [3].

Radiation Induced AS (RIAS) is classified as secondary AS. RIAS is mostly diagnosed after breast conserving for primary breast cancer and radiation therapy. The incidence of RIAS is 0.05% to 0.3% [4]. Median latency for presentation after radiation therapy ranges from 6 to 7 years [5]. Overall, prognosis of RIAS is worse than primary AS of the breast [6].

Median Overall Survival (OS) for all AS patients is approximately 24 months with a median survival rate of 12% to 30% [7].

Standard treatment for patients with AS is conventional chemotherapy with paclitaxel with a median Progression Free Survival (PFS) of approximately 5 months [2].

Another option for metastatic/locally advanced AS is administration of anthracyclines, e.g. doxorubicin, which show similar response rates o other STS, with approximately 25% [8].

Gemcitabine, another option for primary as well as secondary AS shows overall response rates of 68% [9].

Bevacizumab, a VEGFR antibody was investigated in a phase II trial in 30 patients with AS and hemangioendothelioma. Thirteen patients were diagnosed with AS, 11 patients achieved Stable Disease (SD), whereas the remaining 2 patients achieved a Partial Remission (PR) [10].

Tyrosine Kinase Inhibitors (TKI), like sorafenib and pazopanib showed also promising results in patients with AS. Sorafenib was investigated in a phase II trial and showed limited antitumor

Table 1: Baseline characteristics: n=16.

	Primary angiosarcoma	Secondary angiosarcoma
	No. (%)	No. (%)
	13 (100%)	**3 (100)**
Sex:		
- Female	7 (54)	3 (100)
- Male	6 (46)	
Current status:		
- alive/dead	6 (46) / 7 (54)	2 (67) / 1 (33)
ECOG		
- 0 - 1	13 (100)	3 (100)
Grade:		
- I	2 (15)	
- II	8 (62)	1 (33)
- III	3 (24)	2 (67)
Primary disease:		
- Breast cancer with Radiation therapy		3 (100)
Age:		
- years, median (range)	51 (35-77)	69 (60-76)
Location of primary disease:		
- Head and Neck	4 (31)	
- Breast	2 (15)	3 (100)
- Heart	2 (15)	
- Splen	2 (15)	
- extremities	3 (24)	
Sites of primary tumor:		
- primary localised	7 (54)	2 (67)
- primary metastatic	6 (46)	1 (33)
Metastatic sites:		
- Lung	5 (71)	1 (33)
- Lymph nodes	3 (43)	1 (33)
- Bone	2 (29)	
- Liver	1 (14)	
Localised disease:		
Therapy:		
- Surgery	**n=7**	**n=2**
- radical	3 (43)	2 (100)
- marginal/debulking	4 (57)	
- Radiotherapy	4 (31)	
- Chemotherapy		
- Paclitaxel	7 (100)	2 (100)
- Response to chemotherapy		
- NED	6 (87)	2 (100)
- PD	1 (13)	
Metastatic disease:		
Therapy:		
- Surgery	n=6	n=1
- radical	3 (50)	1 (100)
- marginal/debulking	3 (50)	
- Radiotherapy		
- Chemotherapy for advanced disease		
- Paclitaxel	5 (83)	1 (100)
- Pazopanib	1 (17)	
- Repsonse to first line chemotherapy		
- PR	4 (67)	1 (100)
- SD	1 (16.5)	
- n.a.	1 (16.5)	
- Second line chemotherapy for advanced disease	**n=7**	**n=2 (100)**
- Yondelis	1 (14)	
- Doxorubicin	4 (58)	1 (50)
- Pazopanib	2 (28)	1 (50)
- Repsonse to second line chemotherapy		
- PR	1 (14)	
- PD	6 (86)	2 (100)
- Third line chemotherapy for advanced disease	**n=4**	**n=2**
- Pazopanib	2 (50)	1 (50)
- Bevacizumab	2 (50)	1 (50)
- Response to third line chemotherapy		
- PR	2 (50)	2 (100)
- PD	2 (50)	

activity only in pretreated patients [11]. Pazopanib, another multi-targeted TKI, showed also promising anti tumor activity in patients with AS [12].

The aim of our single center retrospective analysis was to evaluate efficacy of different chemotherapy and antibody agents, response to therapy and survival on patients with primary and secondary AS.

Patients and Results

We have retrospectively analyzed all patients with histological confirmed primary and secondary AS who were treated at our institution. Review of our charts identified a total of 13 patients (female: n=7; male: n=6) with primary AS and 3 female patients with secondary AS treated between October 2009 to March 2019. The baseline characteristics are outlined in Table 1. All patients in both groups had an ECOG performance status 0-1.

Primary AS

For patients with primary AS the median age was 51 years (range; 35 to 77), most common tumor grade was grade II (62%) and most common tumor sites for primary AS were head and neck (31%) followed by extremities (24%). Seven out of 13 patients with primary localized AS underwent radical (43%) and marginal (57%) surgery resection, respectively. Radiotherapy was necessary in 4 patients. First line chemotherapy for all 7 patients with initial localized disease was paclitaxel, which resulted in No Evidence of Disease in 6 patients (NED) (87%) and Progressive Disease in 1 patient (PD) (13%), necessitating further chemotherapy with doxorubicin, which lasted in further PD. Trabectedin was initiated and the patient died due to further tumor progression after the second cycle of trabectedin.

For patients with initially metastatic disease, all 6 patients received

Table 2: Outcomes.

Overall Survival	Months, median (95% CI)
- primary angiosarcoma	59.9 (18.1 - 101.7 95% CI)
- localized	n.r.
- metastatic	18.8 (4.1 - 33.4 95% CI)
- secondary angiosarcoma	n.r.

surgery resection followed by chemotherapy with paclitaxel (83%) and 1 patient received pazopanib (17%), which resulted in Partial Remission (PR) in 4 patients and Stable Disease (SD) as well as not available (n.a.) due to death in each 1 patient. Most common second line therapy was doxorubicin (58%). Second line therapy resulted in PR in 1 patient and PD in the remaining 6 patients (86%). Two patients died during second line therapy and the reaming 4 patients received third line therapy with and pazopanib and bevacizumab (each 50%) which resulted in PR and PD in each 2 patients. The two patients, who had PD died due to further tumor progression.

Secondary AS

All 3 female patients with secondary AS were diagnosed with primary breast cancer, following breast conserving surgery and local radiation therapy. Median time from end of radiation therapy until diagnosis of secondary AS was 59 months (range; 11 to 110 months). Median age was 69 years (range; 60 to 76). For the 2 patients with localized secondary AS, radical surgery resection was done followed by adjuvant chemotherapy with paclitaxel which resulted in NED.

In the remaining patient with primary metastatic AS, also radical surgery resection, followed by adjuvant chemotherapy with paclitaxel was given. Two patients had further tumor progress, 1 with initially localized and 1 with initially metastatic disease. Therapy with doxorubicin and pazopanib was initiated and resulted in further PD necessitating further chemotherapy with pazopanib and bevacizumab which resulted in PR in both patients.

Additional patients' characteristics and disease related features are summarized in Table 2. All patients consented to treatment according to institutional guidelines and all patients had consented to anonymized assessment and analysis of data and outcome of therapy.

At time of analysis, 6/13 with primary AS and 2/3 with secondary AS patients are still alive.

Median Overall Survival (OS) for patients with initially localized and initially metastatic primary AS were not reached (n.r.) and 18.8 months (range; 4.1 to 33.4, 95% CI), where as median OS for patients with secondary AS was not reached (n.r.) at time of analysis (Figure 1).

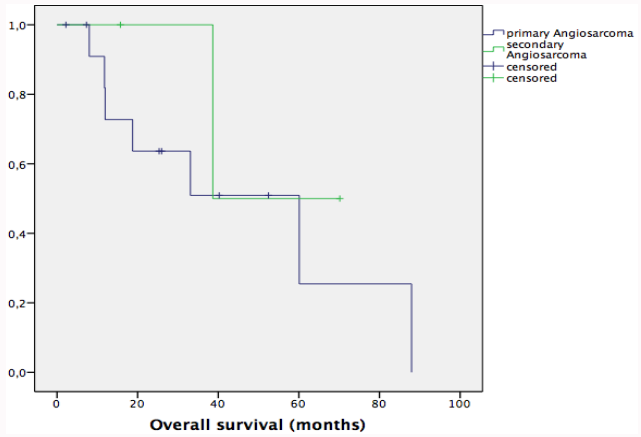

Figure 1: Overall Survival (OS): Primary *vs.* secondary angiosarcomas.

Discussion

We report our experience with patients with primary and secondary AS seen at our institution. For patients with primary AS most affected organs was the head and neck as described in the literature [1]. Primary localized and primary metastatic AS were nearly equal with a little part of more patients with initially localized AS (54% *vs.* 46%). Initially treatment of primary localized AS is radical resection. An incomplete resection is associated with worse outcome (5 year OS 46% *vs.* 0%) [13]. Six patients in our institution underwent surgical resection with each 3 with radical and marginal resection. All patients received adjuvant paclitaxel after resection, which results in NED in 6 cases (87%) and the remaining patient had PD after 3 cycles of chemotherapy, necessitating further chemotherapy with docetaxel. Paclitaxel mono therapy in patients with AS was only investigated in small retrospective analyses. Fata et al. treated 9 patients with AS located in the scalp. Three patients had initially metastatic disease, whereas the remaining 6 patients had unresectable or recurrent disease. ORR in these patients was 89%. When compared to our study, paclitaxel monotherapy resulted in NED in 87%. For patients with initially metastatic disease, ORR in our study population was lower with 67%. Another study could demonstrate an ORR of 62% in patients with metastatic AS with paclitaxel, which is comparable with our data [14].

In advanced setting doxorubicin showed an ORR 6% in a phase II trial, but it has to be mentioned that different subtypes of STS were included in this trial [15]. Four patients received doxorubicin in our patients for advanced disease, which resulted in only one PR and 3 PD.

Pazopanib, a multi targeted tyrosine kinase inhibitor, has been shown to be active in different STS. It was investigated in different advanced vascular sarcomas. In this trial, 40 patients were diagnosed with AS and response rate was 20%. Furthermore, for all included 52 patients, no differences could be observed between radiation-associated and non-radiation-associated AS. Median PFS and OS were 3 and 9.9 months. Pazopanib showed also improvement of response rate in radiation-associated AS when compared to no-radiation-associated AS (28.6% *vs.* 15.4%; p=0.39) [12]. One patient, in each group, in our analysis qualified for PR with pazopanib in advanced setting.

Secondary AS may be treated with cyclophosphamide and prednisone [16]. Our patients with secondary AS underwent chemotherapy with paclitaxel, which resulted in PR. Thus, also taxanes may be offered to these patients.

Radiation therapy in patients with secondary AS is feasible, but no patients received radiation therapy in this setting [17].

Novel treatment approaches in patients with locally advanced or metastatic AS are immunecheckpoint inhibitors, but only small case series (7 patients) are reported [18]. Overall Response rate in this study was 71%.

In summary, surgery in combination with chemotherapy is an optional treatment in patients with primary as well with secondary AS. Immuncheckpoint inhibitor therapy is feasible, but randomized

trials are necessary.

References

1. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. Lancet Oncol. 2010;11(10):983-91.
2. Fata F, O'Reilly E, Ilson D, Pfister D, Leffel D, Kelsen DP, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer. 1999;86(10):2034-7.
3. Liberman L, Dershaw DD, Kaufman RJ, Rosen PP. Angiosarcoma of the breast. Radiology. 1992;183(3):649-54.
4. Cohen-Hallaleh RB, Smith HG, Smith RC, Stamp GF, Al-Muderis O, Thway K, et al. Radiation induced angiosarcoma of the breast: Outcomes from a retrospective case series. Clin Sarcoma Res. 2017;7:15.
5. Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG. A 14-year retrospective review of angiosarcoma: Clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 2005;11(3):241-7.
6. Mentzel T, Schildhaus HU, Palmedo G, Buttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: Clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol. 2012;25(1):75-85.
7. Espat NJ, Lewis JJ, Woodruff JM, Antonescu C, Xia J, Leung D, et al. Confirmed angiosarcoma: Prognostic factors and outcome in 50 prospectively followed patients. Sarcoma. 2000;4(4):173-7.
8. Young RJ, Natukunda A, Litiere S, Woll PJ, Wardelmann E, van der Graaf WT. First-line anthracycline-based chemotherapy for angiosarcoma and other soft tissue sarcoma subtypes: Pooled analysis of eleven European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials. Eur J Cancer. 2014;50(18):3178-86.
9. Stacchiotti S, Palassini E, Sanfilippo R, Vincenzi B, Arena MG, Bochicchio AM, et al. Gemcitabine in advanced angiosarcoma: A retrospective case series analysis from the Italian Rare Cancer Network. Ann Oncol. 2012;23(2):501-8.
10. Agulnik M, Yarber JL, Okuno SH, von Mehren M, Jovanovic BD, Brockstein BE, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol. 2013;24(1):257-63.
11. Ray-Coquard I, Italiano A, Bompas E, Le Cesne A, Robin YM, Chevreau C, et al. Sorafenib for patients with advanced angiosarcoma: A phase II Trial from the French Sarcoma Group (GSF/GETO). Oncologist. 2012;17(2):260-6.
12. Kollar A, Jones RL, Stacchiotti S, Gelderblom H, Guida M, Grignani G, et al. Pazopanib in advanced vascular sarcomas: An EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. Acta Oncol. 2017;56(1):88-92.
13. Lydiatt WM, Shaha AR, Shah JP. Angiosarcoma of the head and neck. Ame J Surg. 1994;168(5):451-4.
14. Schlemmer M, Reichardt P, Verweij J, Hartmann JT, Judson I, Thyss A, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: A retrospective study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer. 2008;44(16):2433-6.
15. Skubitz KM, Haddad PA, Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. Cancer. 2005;104(2):361-6.
16. Mir O, Domont J, Cioffi A, Bonvalot S, Boulet B, Le Pechoux C, et al. Feasibility of metronomic oral cyclophosphamide plus prednisolone in elderly patients with inoperable or metastatic soft tissue sarcoma. European J Cancer. 2011;47(4):515-9.
17. Smith TL, Morris CG, Mendenhall NP. Angiosarcoma after breast-conserving therapy: Long-term disease control and late effects with Hyperfractionated Accelerated Re-Irradiation (HART). Acta Oncol. 2014;53(2):235-41.
18. Florou V, Rosenberg AE, Wieder E, Komanduri KV, Kolonias D, Uduman M, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: A case series of seven patients from a single institution. J Immunotherapy Cancer. 2019;7(1):213.