REVIEW

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Cutaneous angiosarcoma: update on biology and latest treatment

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Purpose of review
The present review aims to provide readers with the latest updates on the biology and clinical management of cutaneous angiosarcoma (cAS).

Recent findings
The genomic alteration of cAS is heterogeneous. Mutations are enriched in the mitosis-activated kinase (MAPK) pathway. Functional analysis has identified molecules that may serve as potential markers and therapeutic targets of angiosarcoma. These molecules include survivin, HSP90, FOXM1, miR-497-5p, KCa3.1, and miR210.
This body of knowledge has not yet transferred to clinical practice. The mainstay of treatment for cAS remains surgery followed by postoperative radiotherapy. The efficacy of paclitaxel as an adjuvant chemotherapy is suggested.
For patients with advanced cAS, paclitaxel is the treatment of choice. There are also second-line treatment options that are supported by evidence of varying strength. A multikinase inhibitor, pazopanib, has been assessed in several studies, most of which support its efficacy for angiosarcoma. Bevacizumab monotherapy may be effective for angiosarcoma. The efficacy of eribulin mesylate and trabectedin for angiosarcoma is currently being assessed. Recent publications highlighted the role of the immune system in the biology of cAS.

Summary
Future research efforts should focus on the following aspects of cAS: drug development directed at recent molecular targets, clinical trials designed specifically for patients with cAS, and the role of immunotherapy for cAS.

Keywords
angiosarcoma, immunotherapy, paclitaxel, pazopanib

INTRODUCTION

Cutaneous angiosarcoma (cAS) is a rare soft tissue sarcoma (STS) with abysmal prognosis. cAS follows an aggressive course, with early propensity for metastasis. A major challenge physicians face when treating cAS is a sheer lack of information. Because angiosarcoma represents 2% of STSs, which occurs at the rate of two to five cases per 1 000 000 per year, limited information is available to physicians [1,2]. In this article, we review key articles on the biology and treatment of cAS, with an emphasis on recent publications.

There are several disease classifications that are used interchangeably in describing angiosarcoma. Angiosarcoma is often classified into cAS and visceral angiosarcoma according to the primary site of the tumor. Many consider cardiac angiosarcoma to be a distinct disease entity. Angiosarcoma is further classified into primary angiosarcoma and secondary angiosarcoma. Secondary angiosarcoma is usually related to a history of radiation treatment and chronic lymphedema. Therefore, secondary angiosarcoma is often termed 'radiation-associated angiosarcoma (RAAS)' in the first scenario, or Stewart–Treves syndrome in the latter [3,4]. The term, 'breast angiosarcoma' encompasses both cutaneous

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KEY POINTS

- Surgery followed by radiotherapy is the mainstay of treatment for localized angiosarcoma.
- Paclitaxel is the standard first-line treatment for advanced angiosarcoma.
- Second-line treatment options include pazopanib, eribulin mesylate, and trabectedin.
- Propranolol may be a promising treatment alternative.
- Immunotherapy may be active against angiosarcoma.

and noncutaneous lesions whose cause is presumably secondary. In this review, we focus our discussion mainly on primary, cAS.

BIOLOGY

During the last 10 years, our knowledge of cancer genomics has expanded owing to advancements in high throughput sequencing technologies and sophisticated computational biology techniques. We now know that angiosarcoma is a very complex, heterogeneous group of tumors (Table 1). The seminal paper by Behjati *et al.* [5] identified that protein tyrosine phosphatase, receptor type B (*PTPRB*), and phospholipase C, gamma 1 (*PLCG1*) are recurrently mutated in angiosarcoma. Their work is the largest and most comprehensive effort to characterize mutations in angiosarcoma to date. A potential caveat of their study is that the key mutations are rather uncommon; the frequency of mutations in *PTPRB* and *PLCG1* are 26% and 9%, respectively. These mutations explain oncogenesis in a fraction of patients with angiosarcoma.

An interesting study by Shimozono *et al.* [7] used RNA-seq to discover a fusion gene transcript that may confer growth advantage to the cells. They identified the *NUP160-SLC43A3* fusion gene from an angiosarcoma cell line, ISO-HAS. They further confirmed that *NUP160* truncation confers growth advantage using a mouse xenograft model. Murali *et al.* [6] used targeted panels to identify the enrichment of mutations in known oncogenes and tumor suppressor genes. Notably, their study reported the enrichment of mutations in the mitogen-activated protein (MAP) kinase pathway. They identified numerous mutations including *KRAS, HRAS, NRAS, BRAF, MAPK1*, and *NF1*. The role of H-RAS in angiosarcoma pathogenesis is supported by a study using a cAS cell culture system [8]. It is important to note that the frequency of each mutation identified in the genomic studies ranges between 5 and 35%. These genomic studies illustrate the complexity and heterogeneity of the angiosarcoma genome; finding a few unifying driver events in cAS is unlikely. It is conceivable that a one-size-fits-all approach for the treatment of cAS is unfruitful. In light of advancing clinical sequencing technologies, patients with cAS are likely to benefit from personalized, precision medicine.

Recent studies have focused on the functional aspects of cAS, and some have identified potential drug targets. Tsuneki *et al.* [9▪] showed that survivin is a potential marker and therapeutic target for cAS. They demonstrated that survivin is overexpressed in cAS, but not in hemangioma or pyrogenic granuloma. They further showed that the growth of ISO-HAS is inhibited by survivin siRNA constructs and the survivin inhibitor molecule. Ito *et al.* [10] found that forkhead box M1 (FOXM1) serves as a prognostic marker for patients with cAS, and is a candidate drug target. Yamada-Kanazawa *et al.* [11] highlighted the role of heat shock protein (HSP) 90 in cAS. They used various cAS cell lines to show that HSP90 inhibition suppresses the proliferation, migration, and invasion of cAS cells.

microRNA (miRNA) dysregulation has been gaining attention in recent studies. Chen *et al.* [12▪] observed miR-497-5p downregulation in five

Table 1. Reported genomic abnormalities in angiosarcoma

	Genes	Event/effect	Frequency	Reference
SNV / indel / CNAs	*TP53*	Loss of function, missense SNV	20%, 35%	[5,6]
	PTPRB	Loss of function	26%, 10%	[5,6]
	PLCG1	SNV	9%, 3%	[5,6]
	CDKN2A	Loss of function	9%	[6]
	MYC	Amplification	8%	[6]
Gene fusion	*NLP160-SLC43A3*		36%	[7]

Selected genomic abnormalities compiled from the literatures are shown.
CNAs, copy number aberrations; RAAS, radiation-associated angiosarcoma; SNV, single nucleotide variations.

Table 2. Systemic treatments for cutaneous angiosarcoma

		Study design	Key Findings	Selected Reference
First-line treatment	Paclitaxel	One-arm phase II trial	2-month, 4-month PFS were 74%, and 45%	[18]
		Phase II trial: patients randomized to wPac / wPac + Bev	6-month PFS was 54% in wPac, 57% in wPac + Bev	[19]
Second-line treatment options	Pazopanib	Retrospective study	Response rate for pazopanib was 26.7% in patient with cAS Median PFS and OS were 3 and 9.9 months	[20▪▪]
	Bevacizumab	One-arm phase II trial	2/23 had PR. 11/23 showed SD	[21]
		Randomized phase II trial	wPac + Bev is not better than wPac alone	[19]
	Propranolol	One-arm, prospective trial	1/7, and 3/7 showed CR, PR to propranolol given with vinblastine and methotrexate	[22▪]
	Eribulin mesylate	Case report	Recurrent angiosarcoma responded to eribulin for 9 months	[23▪]
	Trabectedin	Retrospective study	3-month PFS to trabectedin was 22% OS of angiosarcoma treated with trabectedin was 6.5 months	[24]
Potential therapy	Anti-PD1 / PD-L1 antibody	Case report	A patient had a significant response in a liver lesion to pembrolizumab treatment Autoimmune hepatitis necessitated termination of the therapy after 13 cycles of pembrolizumab	[25▪]

Treatment options based on the strength of available clinical evidence. Unless specified otherwise, key findings show data on angiosarcoma. Note that the order of the drugs within the second-line treatment options does not imply any priorities. This table contains drug indications not approved by US Food and Drug Administrations.
Bev, bevacizumab; cAS, cutaneous angiosarcoma, OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; wPAC, weekly paclitaxel.

cases of human angiosarcoma, but not in capillary hemangioma samples. Using ISO-HAS cell culture and a mouse xenograft model, they showed that miR-497-5p regulates KCa3.1, which promotes the proliferation, inhibition, and invasion of ISO-HAS cell lines. Nakashima *et al.* [13] reported that miR-210, a miRNA implicated in other cancer types, is downregulated in cAS. They further showed that E2F3 and ephrin A3, the putative targets of miR-210, regulate cell proliferation in angiosarcoma cell culture. These studies provide invaluable insights into the pathology of cAS. Some of them also suggest potential drug targets for cAS and may spawn future research on drug development.

PROGNOSIS AND MANAGEMENT OF THE DISEASE

The prognosis of patients with cAS is abysmal, and publications have recently reiterated this problem in greater depth. A recent meta-analysis provides the most reliable statistics on patients with cAS [14▪▪]. The pooled analysis showed that the mean 5-year survival rate of patients with angiosarcoma was 33.5%. Their analysis identified age more than 70 years, tumor greater than 5 cm in size, and angiosarcoma of the head as predictors of poor prognosis.

Although our understanding of the biology of cAS has advanced considerably, these findings have not yet transferred to clinical practice. The standard of care for patients with cAS remains surgical resection with or without postoperative radiation therapy. A recent report assessing 764 case records retrospectively found that only surgery, but not radiotherapy or chemotherapy, is correlated with improved survival [15]. In their meta-analysis, Shin *et al.* [14▪▪] found that surgery improves the 5-year survival rate compared with other treatments [odds ratio (OR) = 4.369; $P = .002$]. Sinnamon *et al.* [16] found that positive resection margins are associated with worse overall survival (OS). Curative surgery should always be considered for patients with cAS.

cAS is associated with a high chance of recurrence even after complete resection of the tumor. In their retrospective analysis, Fujisawa *et al.* [17] showed that maintenance therapy with taxane is effective for patients who underwent surgical resection and postoperative radiotherapy. At our institute, we treat cAS with surgery when feasible, and also consider postoperative radiotherapy and adjuvant chemotherapy.

Patients with unresectable or metastatic disease require systemic treatments (Table 2). Clinical trials assessing the systemic treatments for cAS are scarce. Traditionally, doxorubicin-based chemotherapy has been the treatment of choice for advanced STS. The efficacy of doxorubicin for cAS has, however, only been assessed in retrospective studies, and the value

of doxorubicin in the treatment of cAS thus remains unclear [26]. We do not routinely use doxorubicin as a first-line therapy to treat patients with cAS at our institution. Instead, we favor paclitaxel as the treatment of choice for advanced cAS. The efficacy of paclitaxel treatment was rigorously assessed in a phase II trial enrolling 30 patients with unresectable or metastatic angiosarcoma [18]. The nonprogression rate at 2 and 4 months was 74 and 42%, respectively. Paclitaxel with or without bevacizumab was tested in a randomized phase II trial [19]. The study found that both paclitaxel with and without bevacizumab were supported as active treatment regimens, although they did not find a benefit of adding bevacizumab. Overall, solid lines of evidence support the use of paclitaxel as a first-line therapy for treatment of advanced cAS.

A microtubule-targeting agent, eribulin mesylate, was originally approved for the treatment of breast cancer by the United States Food and Drug Administration in 2010 [27]. Eribulin mesylate was later reported to be effective in studies enrolling patients with advanced STS, although neither of the studies included patients with angiosarcoma [2,28]. In response to these findings, eribulin mesylate was approved in Japan for the treatment of 'malignant sarcoma', and eribulin mesylate is therefore covered for patients with cAS in Japan [29▪]. A recent case report from Japan described an patient with angiosarcoma whose disease was controlled successfully with eribulin mesylate [23▪]. A multicenter, prospective study assessing the efficacy of eribulin to cAS is ongoing in Japan (UMIN000023331).

A histone deacetylase inhibitor, trabectedin, has been used in phase II trials enrolling various patients with STS. Most of these trials do not include patients with angiosarcoma. A French retrospective study, however, analyzed a cohort of 885 patients with STS, including nine patients with angiosarcoma [24]. They found only marginal activity of trabectedin given to cAS patients; the 3-month progression free survival (PFS) rate was 25%. We consider that the use of trabectedin should be reserved for patients with cAS whose treatment options have been exhausted.

Bevacizumab, a vascular endothelial growth factor receptor inhibitor, has been studied in the context of combination therapy and monotherapy. Considering the antiangiogenic property of bevacizumab, it is natural to assume that bevacizumab may be effective for the treatment of cAS. In fact, a phase II study found that bevacizumab as a monotherapy is effective for angiosarcoma, with a mean time-to-progression of 26 weeks [21]. A bevacizumab plus paclitaxel regimen did not, however, offer additional benefit over paclitaxel monotherapy in a phase II study, probably because of the overt toxicity of the combination regimen [19]. We consider that bevacizumab as a monotherapy is an attractive option for the second-line treatment of cAS.

Recently, there have been mixed reports on the activity of pazopanib for the treatment of cAS. The PALETTE study, a large phase III study enrolling 372 patients with STS of various histological subtypes showed the efficacy of a multityrosine kinase inhibitor, pazopanib [30]. The PALETTE study did not, however, address whether pazopanib is effective for cAS. Kollár *et al.* retrospectively assessed 40 patients with angiosarcoma treated with pazopanib. Median PFS and median OS were 3 and 9.9 months, respectively [20▪▪]. Another study from Japan reported a PFS of 94 days for patients with cAS treated with pazopanib [31]. These numbers are in line with those from the PALETTE study, showing the value of pazopanib for the treatment of cAS. By analyzing eight patients with cAS treated with pazopanib, Kitamura *et al.* [32] showed, however, that there was no significant difference in OS between patients with cAS treated with and without pazopanib. We consider pazopanib as one of the second-line treatment options for cAS, because Kitamura *et al.*'s study is felt underpowered to reliably discredit the efficacy of pazopanib. The Dermatologic Oncology Group, a division of the Japan Clinical Oncology Group (JCOG), are planning a phase II study assessing the efficacy of pazopanib for treatment of patients with advanced cAS in Japan.

Aside from chemotherapy and molecular-targeted therapies, the role of propranolol in treating patients with cAS has been suggested. Propranolol is a nonselective β-adrenergic receptor blocker that is widely used for treating hypertension and chronic heart failure. Propranolol was serendipitously found to inhibit the growth of infantile hemangioma [33]. Since this discovery, there has been mounting evidence showing the efficacy of propranolol on infantile hemangioma [34,35]. Furthermore, propranolol was found to suppress cancer metastasis in several cancer types [36]. Based on these findings, Chow *et al.* [37] showed that oral propranolol monotherapy was effective in an patient with advanced angiosarcoma whose tumor was positive for β-adrenergic receptors ADRB1, ADRB2, and ADRB3. Propranolol has been tested in combination with other chemotherapeutic agents such as vinblastine and cyclophosphamide [22▪,38]. There is not enough evidence to make any recommendations regarding the use of propranolol for treatment of patients with angiosarcoma at this point. Considering its wide availability, low cost, and favorable safety profile, however, propranolol may be a promising treatment alternative for patients with angiosarcoma.

FUTURE DIRECTIONS

The field of cancer immunology has grown rapidly since the introduction of new generations of immune checkpoint inhibitors. At present, there is no immunotherapy approved for cAS. There have, however, been studies linking the immune system to angiosarcoma. Shimizu *et al.* [39] found that programmed death ligand-1 (PD-L1) expression is inversely correlated with the prognosis of patients with cAS. Our work has shown somewhat conflicting results; we have demonstrated that PD-L1 expression at the tumor site, and the number of PD-1-positive infiltrating cells are positive prognostic markers of patients with cAS [40]. The reason for the discrepancy is unclear at this point. Nonetheless, these two studies show that the immune system plays a role in the progression of cAS, although the value of PD-L1 positivity as a prognostic marker remains unclear. One surprising case report described a remarkable response to anti-PD-1 treatment in a patient with angiosarcoma, although the patient experienced drug-induced hepatitis that necessitated systemic corticosteroid treatment [25▪]. There is only one prospective study on the role of immunotherapy in the treatment of angiosarcoma; a phase II trial found that PD-1 inhibition had limited activity in 57 patients with STS, including one patient with angiosarcoma [41]. This study is too underpowered, to draw any conclusions from on the role of immunotherapy in the treatment of angiosarcoma. A phase II study to assess the efficacy of a combination immunotherapy is currently enrolling patients with advanced sarcoma in the United States (NCT02815995). This study is projected to enroll a proportion of patients with angiosarcoma.

CONCLUSION

Advances in basic research have unveiled genomic alterations characteristic of angiosarcoma. This knowledge has not yet transferred to clinical practice. Paclitaxel is the mainstay of the systemic treatment for unresectable or metastatic cAS. Studies have shown the activity of eribulin mesylate and, to a lesser extent, trabectedin. Propranolol is an emerging treatment modality with a favorable safety profile. Studies have shed light on the role of the immune system in patients with cAS. Preliminary reports show that patients with angiosarcoma may benefit from anti-PD-1 therapy. Larger research efforts to clarify the role of immune checkpoint therapy in angiosarcoma are urgently needed.

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Conflicts of interest

Y.I. declares no conflict of interest. Most drugs discussed in this article are not approved for the treatment of angiosarcoma by the US Food and Drug Administration (FDA).

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