Anti-PDL-1 response in metastatic soft tissue angiosarcoma: Clinical case and systematic review

Context Summary

Patients with advanced angiosarcomas have a poor prognosis, and there are few treatment options available to improve overall survival. Chemotherapy and targeted therapies offer short-lived disease control. We report a case of partial response with atezolizumab, an anti-PDl-1 antibody, in a personalized medicine approach based on TMB as a potential biomarker.

Abstract

Purpose: Angiosarcomas (AS) account for about only 1%-2% of soft tissue sarcomas, other than chemotherapy and target agents for metastatic disease there are few therapeutics options available. Immune checkpoint inhibitors have become the new paradigm in the management of malignancies but not yet in AS. The objective of this study was to report a case of a patient with angiosarcoma treated with atezolizumab, and to conduct a literature review including publications about the use of checkpoint inhibitors for AS.

Design: We performed a systematic search of electronic databases such as PubMed, EMBASE and Cochrane Registries using the following key words: "angiosarcoma" and "immunotherapy" or "pembrolizumab", "nivolumab", "atezolizumab", "ipilimumab" or "checkpoint".

Results: Institutional case: A 61-year-old man diagnosed with metastatic low grade angiosarcoma in May 2017. He received chemotherapy with doxorubicin, paclitaxel and target therapy with pazopanib. After progression, a Foundation One Heme assay was performed in July 2018, and reported a high Tumor Mutation Burden of 59 mutations/Mb, Treatment with atezolizumab was initiated in September 2018. After 3 cycles of immune checkpoint inhibitor immunotherapy, clinical response was evident. After a 12 month-follow up the patient remains on partial response.

Literature Review: Database search was performed on 8/27/2019. Two hundred thirty-six (236) studies were screened, and 26 articles and conference presentations were selected for full text analysis. After applying inclusion and exclusion criteria, 8 publications were identified, which documented the clinical course of 16 patients. Our patient was also included in the analysis.

Conclusion: The use of immune checkpoint inhibitors in angiosarcomas seems to be a promising and safe option demonstrating early responses in this case series. Confirmed responses were observed in our literature review, mainly in patients with an identified biomarker.

Keywords: angiosarcoma, tumor mutational burden, atezolizumab

Introduction

Angiosarcomas (AS) account for about only 1%-2% of Soft Tissue Sarcomas (STS). Treatment for localized AS includes mainly surgical resection. Treatment options for metastatic or recurrent unresectable disease are scarce. Doxorubicin and taxane-based chemotherapy are the most widely used systemic therapies, with a response rate of 10% to 30%.

In a phase II trial with weekly paclitaxel, Penel et al. reported a median Progression-Free Survival (PFS) of 4.9 months (95% Confidence Interval [95% CI] of 3.9-6.0 months), and median Overall Survival (OS) of 8.5 months (95% CI, 6.4-10.7 months) in patients with advanced AS [1-3].

Many other therapies have been described in recent years. Targeted therapies, especially

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the use of drugs associated with VEGF pathway inhibition have been studied by different investigators and collaborative groups. In this scenario, pazopanib is the only drug approved for STS, after achieving a 6% response rate in the second or third line setting in a phase III trial [4].

Angiogenesis is considered a key mechanism for tumor development, particularly in angiosarcomas. Nevertheless, targeted therapies such as the use of sorafenib, sunitinib and bevacizumab were not associated with a significant increase in tumor regression or overall survival [5,6]. Axitinib is under investigation in a phase II trial including soft tissue sarcoma patients [7].

Recently, β-adrenergic signaling has gained attention as a potential therapeutic target in vascular-related sarcomas. Activation of adrenergic receptors decreases infiltration by cytotoxic T-cells, increases the number of regulatory T-cells and the recruitment and differentiation of tumor-associated macrophages [8,9].

Propranolol is a β-adrenergic receptor inhibitor that has demonstrated clinical efficacy in benign infantile hemangioma, and is now being used experimentally for more aggressive vascular sarcomas and other malignancies in combination with chemotherapeutic agents that also inhibit angiogenesis [10,11]. In this setting, responses to combination treatment of propranolol with cyclophosphamide, paclitaxel or vinblastine have been reported in small series [12-14].

Checkpoint Inhibitors (CPI) have become the new paradigm in cancer treatment. Ground-breaking results published for different tumor models, such as melanoma, lung and kidney cancer, have raised hope since many cancer patients would benefit substantially from immunotherapy CPI. Unluckily, only few case reports and small clinical trials have described responses in patients with soft tissue sarcomas.

The objective of this study was to report the case of a patient with angiosarcomas treated with CPI, and perform a literature review about the use of checkpoint inhibitors for this tumor type.

Material and Methods

We performed a systematic search of electronic databases (PubMed, EMBASE and Cochrane Registries), using the following key words: "angiosarcoma" and "immunotherapy" or "pembrolizumab", "nivolumab", "atezolizumab", "ipilimumab" or "checkpoint". Details of the search are described in the Supplemental Appendix. Study selection was performed by duplicate (MA and FW), and discrepancies were solved by consensus. Additionally, references of the selected articles, and conference abstracts were screened to identify other potential studies or case reports. Data extraction was performed by duplicate, and discrepancies were solved by consensus (MA and PM).

Studies that identified documents for individual patients, including biomarker analysis if available, previous treatments, tumor characteristics and the disease course with checkpoint inhibitors (best response achieved and follow up) were selected for analysis. Publications from the same institution were identified to avoid duplications. Studies or case reports assessing the use of IL-2 interleukin-2, interferon and vaccine therapies in patients with AS were excluded, since the focus of this study was to analyze the effects of immune checkpoint inhibitors.

Moreover, in the studies selected the data reported were extracted only when a minimum of relevant information was available (gender, age at diagnosis, primary tumor location, previous treatments, name of the immunotherapy agent, best response achieved).

Given the absence of validated tools to assess the risk of bias in case reports, we followed the recommendations of Murad et al. [15], and applied five appropriate criteria of the Newcastle-Ottawa Scale. We defined the quality of the studies as "high" if they met the 5 analyzed items, "moderate" when 4 items were met, and "low" for the remaining cases. In addition, the model proposed by the authors was also applied to assess methodological quality.

Considering the limited existing data about immunotherapy CPI in angiosarcoma and the expected heterogeneity of the population studied, patient demographics, clinical characteristics and outcomes were individually described, and no further statistical analysis was planned.

Patient gave written consent to publish his anonymous images and medical information.

Results

■ Institutional clinical case

We present a 61-year-old man diagnosed with a cavernous hemangioma with papillary endothelial hyperplasia (Masson's tumor) after a scalp resection in October 2016. In March 2017, the patient underwent a new surgical resection of a new scalp lesion finally identified as a cavernous hemangioma with focal thrombosis. Immunohistochemistry (IHC) was negative for D240/podoplanin and myc, and Ki-67 index was 10%.

After initial follow up, in May 2017, a PET-CT evidenced multiple liver nodules and an isolated spleen lesion with FDG uptake. The liver biopsy revealed prominent endothelial cell proliferation, and the IHC showed weak positivity for D240, a Ki67 index of 50% and the absence of myc. The final report was consistent with the diagnosis of low grade angiosarcoma.

In August 2017, first-line advanced setting treatment was initiated with doxorubicin (75 mg/m^2) every 21 days. In January 2018 a restaging study showed disease progression, including the presence of larger FDG-avid lesions both in the liver and the spleen and peritoneal sarcomatosis. A scalp lesion was also evident on physical examination and the Hematology Lab reported grade 3 thrombocytopenia, consistent with Kasabach-Merritt syndrome in the context of disease progression.

The patient started second-line treatment with weekly paclitaxel. After two cycles, the patient required an intra-arterial embolization for intra-abdominal bleeding due to a rupture of a liver metastasis. The patient regained stability after four liver intra-arterial embolization procedures and grade 2 alanine aminotransferase and grade 2 aspartate aminotransferase were tested on discharge.

In July 2018 a Foundation One Heme® performed in a newly obtained liver biopsy documented several genomic alterations: **APPENDIX TABLE 1,** and variants of unknown significance **APPENDIX TABLE 2**. Furthermore, microsatellite status was defined as stable, and Tumor Mutational Burden was high (59 Muts/Mb). The only approved therapy based on reported genomic alterations according to our regulatory agencies was pazopanib. An initial reduced dose of pazopanib (600 mg) was administered due to liver dysfunction. After 2 months, treatment was discontinued as a result of liver disease progression, and the requirement of a new intra-arterial embolization procedure [16,17].

Considering [18-20] TMB status, treatment with atezolizumab was initiated in September 2018. After 3 cycles of CPI, clinical response was evident. ECOG score improved from 2 to 0 and ALT/AST were within the normal ranges. A CT scan showed partial response of the liver, splenic and peritoneal lesions. After 12 months of follow up the patient remains on partial response **FIGURES 1-3**.

Literature Review

A database search was performed on 8/27/2019, 236 studies were screened, and 26 articles and conference presentations were selected for full text analysis. After applying inclusion and exclusion criteria, 8publications documenting the clinical course of 16 patients were identified. Our patient was also included for analysis.

Our search flow is represented in **FIGURE 4**, and a summary of extracted data is available on **TABLE 1**.

After applying the modified Newcastle-Ottawa Scale, one of the studies included was considered of high methodological quality and 4 were defined as moderate **FIGURE 5**. This analysis should be interpreted with caution, since some of the case reports were taken from conference presentations.

Nine males and 8 females were included. Considering the information available, median age was 65 (range 32-89), 76.5% of included subjects had a primary cutaneous AS, and 52.9% had evidence of lymph node involvement or metastatic disease. Median of systemic previous lines for advanced disease was 3 (0-6) and immune checkpoint inhibitors were used in combination with other active treatments in 23.5% of the patients. Individual follow up was available for 47.1% and only for 4 patients follow up was longer than 12 months.

Considering that a selection bias is expected in case reports and small series, it should be highlighted that tumor response was described in 14 of the 17 patients included (82.35%). Four complete responses were reported by Floriou et al. [21], and Hofer and collaborators [22], and

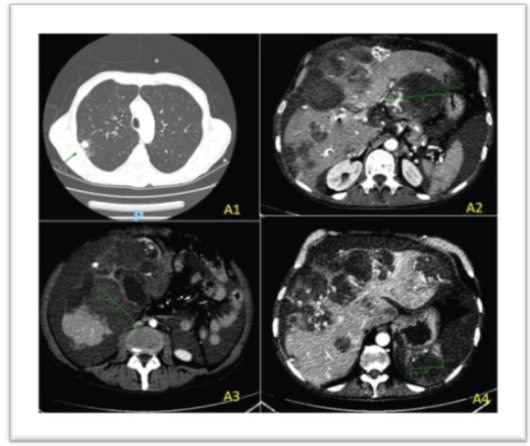

FIGURE 1. Initial scan after chemotherapy and target therapy failure. 23-Aug-2018: A1: lung involvement with signs of alveolar hemorrhage; A2: diffuse liver metastasis (target lesion 75 mm); A3: Peritoneal nodules; A4: Splenic lesion (49 mm).

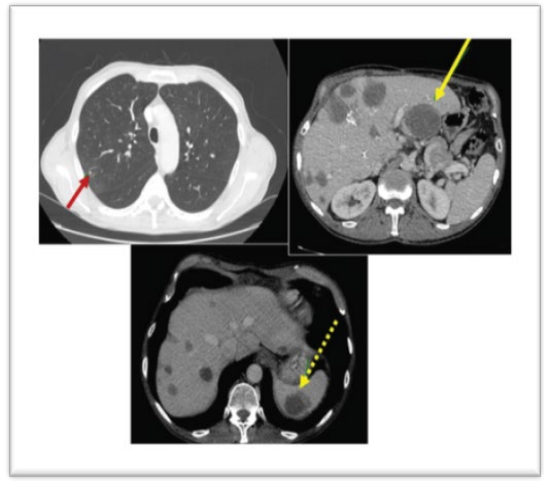

FIGURE 2. First scan after 3 cycles of Atezolizumab. 31-Oct-2018: significant reduction of lung nodules and hemorrhage signs (red arrow). Partial response: liver lesion (yellow arrow: 49 mm) and splenic lesion (dotted arrow: 28 mm).

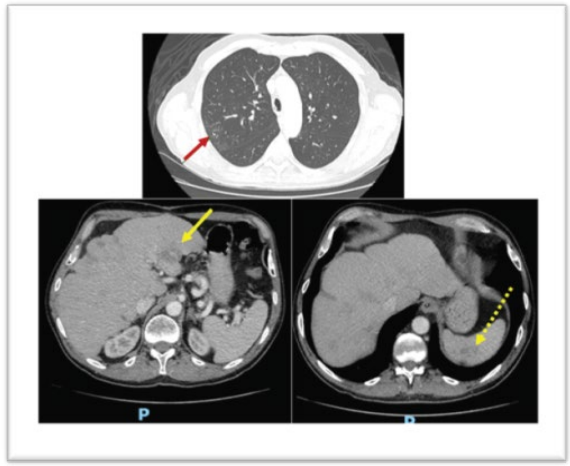

FIGURE 3. After 11 months of Atezolizumab treatment: 07-Aug-2019. The patient maintains partial response. Non-measurable lung nodule (red arrow). Partial response: liver lesion (yellow arrow: 15 mm) and splenic lesion (dotted arrow: 22 mm).

Pointer and colleagues in a patient enrolled in an Anti-CTLA4 clinical trial, after treatment with nivo lumab, and it two patients receiving off-label pembrolizumab, respectively.

Nevertheless, it should be noticed that some of the cases were extracted from series or studies that documented outcomes of more patients with diagnosis of AS. That information was not initially considered in the data extraction process, since patient characteristics and response to immune therapy was not completely described in the analyzed studies.

In this context, Kelly and colleagues presented a Phase II trial with 20 patients. Two of the 3 patients with AS had a documented response with Pembrolizumab and T-VEC

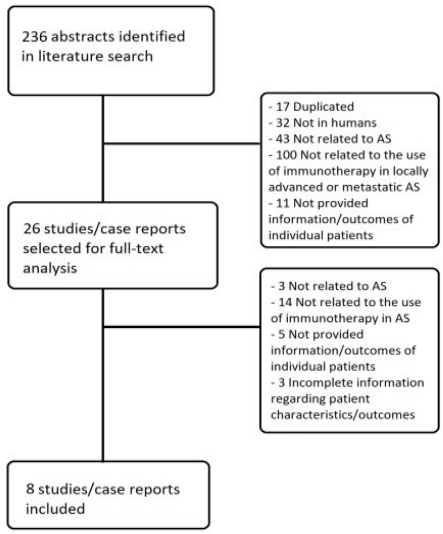

FIGURE 4. Literature search. Search flow.

TABLE 1. Individual characteristics and outcomes with immunotherapy of patients reported in selected trials.

Study/Case report	Sex, Age	Primary tumor	Metastatic evidence of disease	Previous treatments[α]	Therapy (When not specified: doses)	Initial Biomarker analysis	Best response (months)	Status at the time of publication (Follow up months)
Sindhu, 2017	M, 63	Cutaneous, Nose	Multiplelive-rmetastases, tongue mass	1) Nab-paclitaxel[λ] 2) Evofosfamide 3) Nab-paclitaxel	Pembrolizumab (13)	PDL-1 >5%	PR (NS)	PR (NS)
Hofer, 2018	F, 81	Cutaneous, Scalp	Locally advanced	1) Paclitaxel	Nivolumab (11 months)	PDL1 TPS %0^ No MSI	CR -5	CR -11
Qiao, 2018	M, 78	Liver	Multiple liver lesions	None	Pazopanib, pembrolizumab and allogenic RAK cells therapy (15 months)	PDL1 negative	PR (1ϕ)	PR -15
Hammacher, 2018	M, 74	Cutaneous, Retroauricular	Locally advanced Lymphnode	1) Liposomal doxorrubicin 2) Paclitaxel 3) Trabectedin 4) Pazopanib	Pembrolizumab (10)	PDL-1 10% High level of TILs TP53 mutation	PR (NS)	PR -9
Kelly, 2018	F, 64	Cutaneous	Locally advanced	1) Doxorubicin	Pembrolizumab T-VEC (16 weeks)	NA	PR -4	PR -4
D'Angelo, 2019	F, 66	Stewart Treves Left lower extremity	Locally advanced, subcutaneous and intramuscular involvement	1) Liposomal doxorrubicin 2) Paclitaxel 3) Gemcitabine Vinorelbine 4) Pazopanib	Nivolumab NKTR-214 (10 months)	NA	PR (NS)	PR -10
Florou, 2019	F, 32	Breast	Soft tissue Bones	1) GD	Axitinib Pembrolizumab (4)	NA	PD -3	PD (NA)

Florou, 2019	F, 71	Breast	Mediastinal LN, Lung	1) DO	Pembrolizumab (5)	NA	PR	PR
				2) GD			-3	(NA)
				3) Pazopanib				
Florou, 2019	F, 62	Cutaneous, Face	Locally advanced	1) Doxorubicin	Anti-CTLA4 (14)	TMB 0.09 mut/MB[$]	CR	CR
				2) GD		PDL-1 positivity in TILs		(NA)
				3) Pazopanib				
				4) Ifosfamide				
				5) Notch inhibitor				
				6) TMZ/BVZ				
Florou, 2019	F, 68	Cutaneous,	Lymph nodes	1) IL-2	Pembrolizumab (6)	TMB 15mut/ MB[%]	PR	PR
		Scalp		2) Cyclophosphamide			-3	(NA)
				3) Methotrexate, paclitaxel, bevacizumab				
Florou, 2019	F, 89	Cutaneous, Scalp	Locally advanced (multifocal)	1) Gemcitabine	Pembrolizumab (5)	TMB 12 mut/MB[&]	PR	PR
				2) Paclitaxel			-3	(NA)
				3) Pazopanib				
Florou, 2019	M, 76	Cutaneous, Scalp	Locally advanced (multifocal)	1) Pazopanib/ TRC105	Pembrolizumab (5)	NA	PR	PR
				2) DOC			-3	(NA)
				3) GD				
Florou, 2019	M, 64	Cutaneous,	Locally advanced (multifocal)	1) DI	Anti-CTLA-4	NA	PD	PD
		Nose		2) AC	-7		-3	(NA)
				3) GD				
Pointer, 2019	M,	Cutaneous, brow	Locally advanced	NA	Pembrolizumab (1)	TMB 62.3 mut/Mb	PD	PD
	NA						(NA)	(NA)
Pointer, 2019	M, 62	Cutaneous, scalp	Locally advanced.	1) Clinical trial	Pembrolizumab (219 days)	TMB 78.5 mut/Mb	CR	CR
			Lung, liver, lymph node	2) Cyclophosphamide		UV signature	(NA)	-32.9
				3) Clinical trial				
				4) Crizotinib				
Pointer, 2019	M, 58	Cutaneous,	Locally advanced.	1) Paclitaxel protein bound	Pembrolizumab (249 days+30 days)[π]	TMB 138.9 mut/Mb	CR	CR
		nose	Lung, liver, lymph node	2) Clinical trial		UV signature	(NA)	-44.3
				3) Paclitaxel protein bound				

Our case report	M, 63	Cutaneous, Scalp	Lung, liver, spleen, peritoneum	1) Doxorubicin 2) Paclitaxel 3) Pazopanib	Atezolizumab (16)	TMB 59 mut/Mb	PR	PR -12

GD: Gemcitabine/Docetaxel; DO: Doxorrubicin/Olaratumab; TMZ/BVZ: Temozolamide/Bevacizumabd; DOC: Doxorrubicin/Olaratumab/Cyclophosphamide; DI: Doxorrubicin/Ifosfamide; AC: Doxorrubicin/Cyclophosphamide, MSI: Microsatellite Inestability; RFA: Radiofrequency Ablation; ND: No Immunotherapy-Related Biomarkers were Described; NS: Not Specified; PR: Partial Response; SD: Stable Disease; CR: Complete Response; PD: Progression of Disease.

[α]Treatments with curative intention are not described

[*]:According to RECIST 1.1 Criteria

[§]:The patient was enrolled into a Phase 1 trial, and baseline and post therapy samples were taken for different biomarker analysis, including TILS, IL-6, IFN-G, whole exome and RNA sequencing. Missense mutations were appreciated in the genes NBPF10, NBPF15, ZNF678, VPS8, PCLO and ABCB1[Floriou]

And Principal genomic findings include CDKN2A/B loss, CHEK R1117G, DNMT3A R771, FANCDN E118, MLL3 splice site 255-13G>A and TP53 L145R, splice site 673-1G>A[Floriou]

%:Principal genomic findings include CRKL amplification, DNMT3A R635W subclonal, MAPK1 amplification, SFB1 K7003 subclonal and ZRSR2 splice site 121+2 T>G[Floriou]

[^]:In the vertex of the tumor the authors described de presence of a squamous cell carcinoma. In this area, 1% tumor cells expressed PDL-1 and 8% of tumor associated immune cells expressed PDL-1

[λ]: Adjuvant treatment.

[ϕ]: Not possible to assess the effect of immunotherapy, considering that pazopanib was started before pembrolizumab initiation and patient underwent restaging studies 2 weeks after the beginning of immunotherapy

[π]: Patient firstly received treatment for 249 days, then was without treatment for angiosarcoma for 213 days, and finally received pembrolizumab for another 30 days. Reasons for treatment suspension and rechallenge are not specified

	Florou[18]	D'Angelo[24]	Kelly[20]	Hamacher[31]	Qiao[32]	Painter[22]	Hofer[19]	Sindhu[33]
Adapted Newcastle-Ottawa scale								
Did the patient(s) represent the whole case(s) of the medical center?	■					■		
Was the diagnosis correctly made?	■	■	■	■	■	■	■	■
Were other important diagnoses excluded?	■	■	■	■	■	■	■	■
Were all important data cited in the report?	■			■	■			■
Was the outcome correctly ascertained?	■	■	■	■	■	■		■
METHODOLOGICAL QUALITY (High: 5, Moderate: 4, Low≤3)	High	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Murad et al Tolo								
Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	■					■		
Was the exposure adequately ascertained?	■	■	■	■	■	■	■	■
Was the outcome adequately ascertained?	■	■	■	■	■	■		■
Were other alternative causes that may explain the observation ruled out?	■	■	■	■	■	■		■
Was there a challenge/rechallenge phenomenon?								
Was there a dose–response effect?								
Was follow-up long enough for outcomes to occur?	■	■	■	■	■	■	■	■
Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	■			■	■			■

FIGURE 5. Application of modified Newcastle Ottawa Scale and the tool proposed by Murad et al. to analyze the methodological quality of the included studies and case reports. Grey represents a positive assessment [18-20].

[23]. Also, D'Angelo and collaborators reported the results of a pilot study of Nivolumab and NKTR-214 that included 57 patients. NKTR-214 is a novel IL-2 agonist that specifically binds to the IL-2Rβγ subunit. The limited activity of NKTR-214 in the ILR2α subunit, allows CD8+T lymphocytes activation, with limited expansion of regulatory T cells. The authors reported that, of 6 patients with a diagnosis of AS, 1 included in this study achieved a confirmed partial response and 4 presented stable diseases as best response [24].

Pointer and collaborators described confirmed tumor responses with checkpoint

inhibitors in two of three patients with a Head, Neck, Scalp or Face (HNFS) localization, high TMB and UV-signature mutations **TABLE 1**. Interestingly, the authors described 3 additional non-HNFS that received off-label immunotherapy CPI without documenting tumor response [25]. The latest patients were not included in our initial analysis, considering that we lacked information on best response achieved. Information regarding reported responses in case reports and studies analyzed in our systematic review is available in **APPENDIX TABLE 1**. The presence of a potential predictive biomarker, including TMB, PDL-1 and TILs, in the patients included in our analysis could be the rationale for immunotherapy CPI indication in 52.9% of the cases. Tumor PDL-1 expression was observed in two patients with partial response and comparably to our case, tumor response was described in other four patients with high or intermediate values of TMB.

Discussion

Limited evidence has been reported on the outcomes of immunotherapy in soft tissue sarcomas. However, tumor response with checkpoint inhibitors in patients with soft tissue sarcomas had already been described in other published studies and conference abstracts.

While low response rates were described in phase II trials considering all included patients with soft tissue sarcomas (16-18%) [26,27] better efficacy results were observed in certain histologic subtypes. For example, a disease control rate of 83% was reported for patients with alveolar soft tissue sarcoma that received durvalumab and tremelimumab Somaiah. Also, an overall tumor response of 40% was reported for patients that received pembrolizumab in the SARC028 study [26].

The information of all angiosarcoma patients included was not part of our initial analysis due to the absence of individual participant data. Considering the information available, as documented in **APPENDIX TABLE 1**, we found that 17 of 35 (48.5%) reported angiosarcoma patients, achieved at least partial response with immune checkpoint inhibitors. Clinical benefit rate was documented in 21 (59.9%) patients. Importantly, in the analyzed case series, all patients maintained achieved response at the end of the reported follow up **TABLE 1**.

In this context, the design of specific trials for particular subgroups of patients with soft tissue sarcomas is essential to better estimate the real efficacy of immune checkpoint inhibitors. As the benefits of checkpoint inhibitors are limited to a group of patients with STS, there is increased interest in the development of specific biomarkers.

Specifically, certain biomarkers have been described as prognostic factors in angiosarcoma. For example, in a meta-analysis including 2820 patients, the neutrophil/lymphocyte ratio was associated with poor prognosis in patients with soft tissue sarcomas [28].

In contrast, Honda et al. analyzed 106 cases of cutaneous angiosarcomas and found that 30.2% of the patients had immune histo chemical expression of PDL-1. 93% of the patients had tumors located in the face or scalp and 87% were stage I. The authors concluded that the infiltration of cells with PD-1 expression and PD-L1 tumor expression were associated with better overall survival [29]. In our literature review, two patients with PDL-1 expression in tumor cells achieved partial response and an additional patient with PDL-1 positivity in TILs had a complete tumor response. In contrast, two additional responses were also evidenced in patients without immunohistochemistry expression of this biomarker.

Tumor Mutational Burden (TMB), defined as the total number of somatic mutations in a defined region of a tumor genome, is an emerging predictive biomarker currently under investigation for immunotherapy. While the predictive role of this biomarker had already been described in clinical trials on lung melanoma and bladder cancer, its utility for soft tissue sarcomas has not been validated [24-29]. Chalmers et al., performed comprehensive genomic profiling on 157 samples of AS with Foundation one assay. The authors documented that the median reported TMB was 3.8 mutations/mb, and only 13.4% of patients with AS had more than 20 mutations/mb [30]. This study set an interesting starting point to define TMB as a possible biomarker for AS.

Pointer et al., on behalf of the Angiosarcoma Project, described a cohort of 47 patients where patients with tumors located in the Head, Neck, Face or Scalp (HNFS) presented a median TMB of 20.7 muts/Mb, and that 9 of the 10 patients with HFNS angiosarcoma had high TMB and

presented a similar pattern of somatic mutations to melanoma samples (UV-signature) [25]. In another study, "UV-signature", was found in 14% of 189 cases of angiosarcoma, and a median TMB of 19 mut/Mb was described in this subgroup [31].

Pointer et al, observed tumor response in two of the three patients in their series with HNFS primary location and high TMB and no response was documented in the 3 reported patients with non-HNFS angiosarcoma.

In the individual cases analyzed in our literature review, we found that five of the six patients with a TMB higher that 10 muts/Mb had tumor response after receiving checkpoint inhibitors. Although the mutational signature was only studied all patients with high TMB -including our case report had HNFS primary tumor localization. Of note, a complete response was also described by Florou et al. [21] in a patient with a TMB value of 0.05.

It should be considered that essential aspects of TMB determination, such as the inclusion of synonymous mutations and predefined genes for mutation analysis varied among studies included in our review. Antibodies and target cells defined for PDL-1 expression also differed as described in **APPENDIX TABLE 3**.

To the best of our knowledge, we present the first described case with confirmed tumor response with a PDL-1 inhibitor (atezolizumab). The characteristics of our patient support that TMB, in the context of HNFS angiosarcoma, and possibly "UV signature", might be potential predictive biomarkers for immune checkpoint inhibitors **APPENDIX TABLE 4**.

Although our literature review may reveal intriguing results, the scope of our analysis is limited by the short follow-up of the reported cases, unavailable data, selection and publication biases. In addition, 3 of the 7 studies included were defined as low methodological quality.

In conclusion, a certain subgroup of patients with angiosarcoma may benefit from immunotherapy CPI or the combination of checkpoint inhibitors and anti angiogenic therapies. Durable responses obtained in heavily pretreated patients support the fact that further clinical research with immune checkpoint inhibitors in this tumor model is necessary. Clinical trials addressing the efficacy and safety of immunotherapy in angiosarcoma are ongoing [32,33].

Conclusion

The treatment of angiosarcoma, among soft tissue sarcomas, is a real challenge for the oncologist. Several attempts have been proposed to improve both response rates and survival in the absence of a reliable biomarker for higher patient selection. The use of immunotherapy in angiosarcomas seems to be a promising and safe option demonstrating early responses in this case series. Confirmed responses were observed in our literature review, mainly in patients with an identified biomarker.

Efforts should be made to identify reliable biomarkers in soft tissue sarcomas. In this context, we would like to recognize the importance of patient advocacy group initiatives, such as The Angiosarcoma Project (www.ascproject.org) which has already provided useful information to understand the real-world scenario in this uncommon disease.

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