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Paclitaxel in patients with advanced angiosarcomas of soft tissue: A retrospective study of the EORTC soft tissue and bone sarcoma group

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ABSTRACT

Rationale: Angiosarcomas of soft tissue represent a heterogenous group of rare sarcomas with specific clinical behaviour and risk factors. Paclitaxel appears to induce tumour control in a higher proportion of patients with angiosarcoma, as compared to other sarcomas. The objective of this retrospective study was to assess the anti-tumour activity of this compound in a multicentre setting.

Method: Clinical data from patients with angiosarcomas of soft tissue treated with single agent paclitaxel were collected from the centres of the soft tissue and bone sarcoma group of EORTC, using a standardised data collection form. Paclitaxel could be given every three weeks, or weekly. Statistical analysis was performed using SAS software.

Results: Data from 32 patients were collected from 10 centres. There were 17 males, 15 females, with a median age of 60.4 years (range, 25–91). Primary angiosarcomas were located in scalp and face in 8 patients (25%) and at other primary sites in 24 patients (75%). All patients had intermediate ($n = 13$) or high grade ($n = 19$) primary tumours. Thirteen (40%) patients had been pretreated with doxorubicin-based first-line-chemotherapy and three of them (9%) had also received second-line chemotherapy with ifosfamide. Eleven (34%) patients had been irradiated before as treatment for angiosarcoma. In 8 (25%) patients, the angiosarcoma occurred at sites of prior radiation therapy for other malignancies. The response rate was 62% (21/32) in the whole series, 75% (6/8) in scalp angiosarcomas and 58% (14/24) in other primary sites. The median time to progression was 7.6

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months (range, 1–42) for the whole group. For the face/scalp group it was 9.5 months, and for patients with angiosarcomas at other sites it was 7.0 months, respectively.
Conclusion: Paclitaxel was found to be an active agent in angiosarcoma of soft tissue in this retrospective analysis. These results need to be confirmed in a prospective randomised phase II study.

1. Introduction

Angiosarcomas of soft tissue represent a heterogenous subgroup of soft tissue and visceral sarcomas, showing histological differentiation of endothelial cell lineage. Angiosarcomas can occur everywhere in the body, but are most often found in the head and neck, followed by extremities and trunk.[1] Predisposing factors include chronic lymphedema (Stewart–Treves syndrome) and radiation,[2] furthermore genetic predisposition may play a role in the development of angiosarcoma after radiation therapy.[3] Risk factors for poor prognosis are old age, retroperitoneal location, size and elevated Ki-67 immunoreactivity.[4–7]

As for other soft tissue sarcoma complete excision is the treatment of choice, but in most cases, due to localisation in face, scalp, heart or liver complete radical resection is not possible. Therefore, surgery is often combined with adjuvant radiation therapy, chemotherapy or combination of these modalities,[8] albeit that there is no scientific justification for the latter. Radiation after resection is correlated with improved outcome.[9] Although no phase II trials were performed specifically in angiosarcomas, doxorubicin and ifosfamide are generally considered to be the most active chemotherapeutic agents.

Paclitaxel is an anti-tumour drug with proven activity in solid cancers such as ovarian-, breast- and lungcancer, but limited activity in advanced soft tissue sarcomas.[10,11] The main mechanism of action is the inhibition of normal mitotic spindle formation by tight binding to beta tubulin, resulting in a blockage of microtubules depolymerisation and mitotic arrest in the late G2/M phase.[12] Additionally, paclitaxel exhibits strong antiangiogenic inhibitory activity.[13,14] In small retrospective series, paclitaxel was found to have a promising efficacy in angiosarcomas.[15,16] To confirm these observations, we performed a retrospective analysis of angiosarcomas treated with single agent paclitaxel in centres of the EORTC soft tissue and bone sarcoma group.

2. Patients and methods

2.1. Patients and treatment

Patients with histologically confirmed angiosarcoma were retrospectively identified in 10 centres of the EORTC soft tissue and bone sarcoma group. Treatment was performed between 1996 and 2005. The diagnosis of angiosarcomas was confirmed by histopathological review at the treating centre. Paclitaxel was given as a 3 h infusion either at a dose between 135 and 175 mg/m^2 in a 3 weekly schedule ($n = 21$), or at a dose of 75–100 mg/m^2 ($n = 11$), given weekly. Tumour assessment was performed using WHO or RECIST criteria. In case of scalp lesions, the reduction of visible and measurable skin involvement was measured, usually monitored by clinical photographs. Assessments were made every 3 months, or earlier when progressive disease was clinically suspected. Responses were subject to independent peer-review.

As there are no general follow-up guidelines especially for angiosarcomas of the face and scalp, follow-up was at the discretion of the treating physician.

2.2. Data collection and statistics

Retrospective collection of data was obtained using a standardised data collection form. Data collected were entered into a specific database. Statistical analysis was performed using the SAS software.

3. Results

Characteristics of the 32 patients are listed in Table 1. There were 15 females and 17 males. The mean age was 60, 4 years (range, 25–91). Angiosarcomas were located in scalp and face in 8 patients (25%) and at other primary sites in 24 patients (75%). All patients had intermediate ($n = 13$) or high grade ($n = 19$) primary tumours. Thirteen (40%) patients had been pretreated with doxorubicin-based first-line-chemotherapy regimens – three of them (9%) also had second-line chemotherapy with ifosfamide.

Eleven (34%) patients had been irradiated before as treatment for angiosarcoma. In 8 (25%) patients, the angiosarcoma occurred at sites of prior radiation therapy for other malignancies.

All 32 patients were evaluable for response to paclitaxel. The overall response rate was 62% (CR, $n = 1$ (3%), PR, $n = 19$ (59%)). The clinical benefit rate was 78%. Angiosarcomas of the face and scalp showed an overall response rate of 75% (1 CR and 5 PR among 8 patients). Patients with location of angiosarcomas at other sites had a response to paclitaxel therapy of 58% (1 CR and 14 PR among 24 patients).

The median time to progression for the whole series of patients was 7.6 months (range, 1–42), for the face/scalp group it was 9.5 months, and for the patients with angiosarcomas at other sites it was 7.0 months, respectively.

4. Discussion

Angiosarcomas of soft tissue are rare, accounting for 1% of all sarcomas. Clinical features vary depending on the anatomic

Table 1 – Patients characteristics

Number	Sex	Age	Location	Prev. therapy	Surgery for angio	Status	Applied cycles	Best response	Response duration
1	F	70	Trunk	dox	No	Relapse	3	PR	16 months
2	F	65	Ankle	dox	Yes	Primary	4	NC	4 months
3	M	49	Trunk	dox/ifo	No	Primary	4	NC	3 months
4	M	78	Scalp	dox	Yes	Primary	3	NC	2 months
5	F	48	Breast	dox/rt	No	Relapse	4	PR	7 months
6	F	41	Breast	dox/rt/surg	Yes	Relapse	4	PR	4 months
7	F	70	Breast	rt/surg	Yes	Relapse	6	PR	10 months
8	M	62	Trunk	none	No	Primary	2	PD	2 months
9	M	48	Heart	dox/ifo	Yes	Primary	5	NC	4 months
10	M	53	Lung	none	No	Primary	4	PR	7 months
11	F	58	Limb	none	No	Primary	6	PR	4 months
12	M	76	Spleen	ctx	Yes	Primary	8	PR	19 months
13	M	25	Heart	dox/ifo	No	Primary	1	PD	1 month
14	M	60	Scalp	rt	No	Relapse	4	PR	3 months
15	M	91	Face	none	No	Primary	6	PR	5 months
16	M	72	Scalp	none	No	Primary	4	CR	42 months
17	M	59	Scalp	none	No	Primary	4	PR	6 months
18	F	70	Trunk	none	No	Primary	2	PD	1 month
19	F	52	Trunk	none	No	Primary	4	NC	12 months
20	M	68	Face	none	No	Primary	3	PR	6 months
21	M	36	Trunk	none	No	Primary	6	PR	6 months
22	F	64	Heart	dox/ifo	No	Primary	4	PR	7 months
23	M	44	Heart	dox/ifo	No	Primary	3	PD	3 months
24	M	72	Scalp	rt	Yes	Relapse	4	PR	9 months
25	F	69	Scalp	rt	No	Primary	2	PD	3 months
26	M	26	Heart	dox/ifo	No	Primary	6	PR	8 months
27	M	78	Leg	surg	No	Relapse	2	PD	3 months
28	F	82	Trunk	rt/surg	No	Primary	4	PR	7 months
29	F	76	Trunk	rt/surg	No	Primary	4	PR	8 months
30	F	67	Trunk	dox/rt/surg	Yes	Relapse	14	PR	24 months
31	F	47	Trunk	rt/surg	No	Primary	2	PD	2 months
32	F	67	Trunk	dox/rt/surg	No	Primary	6	PR	5 months

dox: doxorubicin, ifo: ifosfamid, ctx: chemotherapy, rt: radiotherapy, surg: surgery.

location. Patients with face and scalp angiosarcomas demonstrate longer overall survival than the patients with angiosarcomas at the visceral sites. Secondary angiosarcomas after radiation therapy are associated with poor prognosis.[17] The standard treatment in localized disease is surgery, but due to the location in face and scalp radical resection without mutilation is seldom possible and the surgical removal of metastatic lesion is rarely feasible.

In the advanced disease setting, most patients will ultimately progress and die of their disease.

While in the past, most clinical trials on chemotherapy in advanced sarcomas included all histological subtypes, it has been recognised that specific sarcoma subtypes may be sensitive to some but not all agents: for instance, gemcitabine plus docetaxel is highly active in patients with uterine leiomyosarcomas, trabectedin was recently shown to be active against leiomyosarcomas and liposarcomas, imatinib and sunitinib are licensed for the treatment of patients with advanced gastrointestinal stromal tumours.[18–21]

Taxanes have shown no significant anti-tumour activity as single agent in advanced sarcomas failing standard systemic treatment options with doxorubicin and ifosfamide.[10,11,22] However, paclitaxel was first reported to have an interesting activity in angiosarcomas of face and scalp in a small retrospective single centre study.[15] Because angiosarcomas are rare tumours, a retrospective study on a larger number of patients requires a multicentre contribution. This was the goal of the present retrospective study, which was performed in centres of the STBSG of EORTC and included 32 patients from 10 centres.

In this retrospective study, the response rate for patients with angiosarcomas in face/scalp was 75%, while the response rate in tumours from other primary sites was 58%. Although response rates were remarkably better than the average response rates for other sarcoma subtypes, these results should be interpreted with caution given their retrospective nature. While the reported responses were of limited duration with a median time to progression of 7.6 months, most of them were obtained in a pretreated patient population, where such a result in general is considered worthwhile. Unfortunately the majority of these patients subsequently relapsed. Of note, a phase II trial of weekly paclitaxel predominantly in angiosarcomas other than face and scalp and using a lower dose intensity was recently reported in a series of 32 patients, yielding a response rate of 15% and a median PFS of 4 months.[23] Whether there is a different biologic behaviour between the angiosarcomas of the face and scalp and in other locations is not clear. These differences may also be related to

a more limited tumour bulk in face and scalp angiosarcomas or to superior delivery of drug to tumour. Nevertheless, these data suggest that treatment with paclitaxel may have a specifically high anti-tumour activity in angiosarcomas of face and scalp. In future antiangiogenic therapy may be a valid tool to add to antineoplastic therapy with paclitaxel in angiosarcomas.[24]

A number of questions remain, such as whether paclitaxel is superior to or equivalent to doxorubicin in the treatment of this disease; whether paclitaxel offers any particular advantage over standard therapy for angiosarcoma arising outside the scalp or face; what is the true difference in responsiveness to paclitaxel between scalp and face angiosarcoma and the disease arising elsewhere; are they biologically different diseases? Clearly randomised trials are a challenge to perform in such a rare disease, but ideally a prospective randomised trial to compare paclitaxel with doxorubicin in the treatment of angiosarcomas from all sites should be performed in order to provide an answer to these interesting questions.

Conflict of interest statement

None declared.

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