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Review

Chemotherapy in alveolar soft part sarcomas: What do we know?

P. Reichardt*, T. Lindner, D. Pink, P.C. Thuss-Patience, A. Kretzschmar, B. Dörken

Medizinische Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie, Robert-Rössle-Klinik, Helios-Klinikum Berlin, Universitätsklinikum Charité, Humboldt-Universität zu Berlin, Lindenberger Weg 80, D-13125 Berlin, Germany

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Abstract

Alveolar soft part sarcoma (ASPS) is a rare tumour. Published series about treatment and outcome are scarce. Conclusive data about the response to chemotherapy are not available. The aim of this study was to analyse the efficacy of palliative chemotherapeutic treatment options and the incidence and mode of presentation of brain metastases. We retrospectively analysed our own sarcoma data-base and reviewed the literature. From our registry containing 757 patients, we identified 8 patients with ASPS. From the literature, 47 cases of adult patients and 13 children with sufficient data about chemotherapy were identified. Response to first-line chemotherapy in 68 patients was: complete remission (CR) 4%, partial remission (PR) 3%, stable disease (SD) 41%, progressive disease (PD) 51%. 285 patients with stage IV disease were evaluable for the analysis of metastatic sites. The incidence of brain metastases was 30.5% (87/285). Brain metastases were detected at a median interval of 48 months (range 0–396 months) after the primary diagnosis. Median survival after the diagnosis of brain metastases was 12 months. The median survival for patients with stage IV disease treated by chemotherapy was 36+ months (range 10–132 months) (31 patients evaluable) with a median follow-up of 46 months (range 10–135 months). ASPS shows a high incidence of brain metastases, at least 3 times higher than that of other soft tissue sarcomas. Chemotherapeutic regimens used for the treatment of other soft tissue sarcomas lack efficacy in ASPS. Staging investigations for ASPS should routinely include imaging of the brain. ASPS patients should not be treated with chemotherapy outside of controlled clinical trials. New targets for specific biologically-directed therapies need to be developed.

Keywords: Alveolar soft part sarcoma; Chemotherapy; Brain metastases

1. Introduction

Alveolar soft part sarcoma (ASPS) is a rare malignant tumour representing 0.5–1% of all soft tissue sarcomas [1–3]. ASPS was first described as an entity and classified in 1952 by Christopherson and colleagues [4].

The tumour shows a characteristic histological appearance consisting of nests of cells loosely arranged along fibrous septs, surrounded by capillaries [1,5]. The histogenesis of ASPS remains unclear. Due to the immunohistochemical detection of muscle-associated proteins, especially desmin, current theories propose that the tumour originates from skeletal muscle [1,3,5–7].

ASPS usually presents as an indolent slow-growing malignancy at an early age between 15 and 35 years [6,8,9]. The most frequent tumour sites are the muscles of the lower extremities, but sometimes head and neck masses, especially at the tongue or orbita, are presenting signs [3,6,10]. Metastases often appear very late in the course of the disease, most frequently in the lungs, bone or brain [3,6,9,11–14].

Although slow-growing, ASPS has a fatal prognosis if complete surgical resection is not possible. Children have a better prognosis, perhaps due to the more frequent presentation in the head or neck which results in an earlier diagnosis [3,15,16].

Complete surgical resection is the therapy of choice [11]. If this is not feasible, chemotherapy is often used. Published case series contain little data about the response to chemotherapy. According to personal experience, objective remission following chemotherapy is rare, but conclusive data are missing. In a recently published case series in the *European Journal of Cancer* by Ruth and colleagues [17] 2 of 15 patients developed brain metastases. In our own experience, brain metastases

* Corresponding author. Tel.: +49-30-9417-1211; fax: +49-30-9417-1219.

E-mail address: reichardt@rrk-berlin.de (P. Reichardt).

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occur much more frequent in ASPS than in other soft tissue sarcomas. A pattern of metastases that differs from other soft tissue sarcomas is discussed in Ref. [18].

In order to achieve a more rational approach with regard to the use of chemotherapy and to obtain conclusive data about the incidence and time of presentation of brain metastases, we analysed our own data-base for patients with ASPS and performed a search of the literature for data about ASPS chemotherapy and brain metastases.

2. Patients and methods

The sarcoma registry of our institution, which contains data since 1990, was screened for patients with ASPS. Case records were analysed for primary diagnosis, time of systemic spread, occurrence of brain metastases, chemotherapy, response to therapy and follow-up. Response was assessed by applying the response evaluation criteria in solid tumours (RECIST) [19].

A Medline search using the Pubmed National Library of Medicine was conducted for articles published up to July 2002 using the search terms ''alveolar'', ''soft'', ''part'' and ''sarcoma''. Publications in which the abstract contained either ''brain metastases'', ''review'' or ''chemotherapy'' were fully analysed. Publications about soft tissue sarcomas which contained case series were screened for cases of ASPS. References made in the articles retrieved were followed and publications analysed if they contained one of the search terms. To avoid multiple inclusion of the same patient in our analysis only those patients with obvious primary data were included.

3. Results

From our registry containing 757 sarcoma cases, we identified 8 patients with ASPS (=1.1%) who were treated at the Charité between 1990 and 2002. Patients' characteristics, treatment, response and follow-up are shown in Table 1.

7 of the 8 patients developed brain metastases with a median interval of 51 months (range 0–113 months) from the primary diagnosis. All patients with brain metastases are still alive with a median time of follow-up since the detection of brain metastases of 12 months (range 5–36 months). All patients had surgical procedures performed under curative intent or for palliation. 7 of the 8 patients received an anthracycline- or ifosfamide-containing first-line chemotherapy. There were no objective responses (complete remission (CR): 0, partial remission (PR): 0, stable disease (SD): 6/8 pts, progressive disease (PD): 2/8 pts).

Four hundred publications about ASPS or soft tissue sarcoma were screened for data concerning palliative chemotherapy and brain metastases, respectively.

3.1. Palliative chemotherapy

Of 33 publications related to chemotherapy in ASPS, 15 articles contained sufficient data about patients' characteristics, the type of chemotherapy and response to be included in our analysis.

Individual data on 47 adult patients and 13 children could be analysed (Table 2).

In adults, an anthracycline-containing regimen was used in 29 of 47 patients. 6 of 47 patients received 2nd- or 3rd-line chemotherapy. Best response to first-line chemotherapy for locally advanced or metastatic disease was as follows: 3 CR (one after thiotepa and 2 after an anthracycline-containing regimen), 0 PR, 17 SD and 27 PD. 2 of 6 patients treated with 2nd- or 3rd-line therapy achieved an objective remission [one patient after anthracyclines and one after interferon alpha (INF-α)].

12 of the 13 children were treated with an anthracycline-containing regimen. Best responses were 0 CR, 2 PR (one patient with anthracycline treatment, one with anthracyclines and ifosfamide), 5 SD and 6 PD.

Pooling the published data of adults and children and the patients treated at the Charité, there were 3 CR (4%), 2 PR (3%), 28 SD (41%) and 35 PD (51%) as best responses to first-line chemotherapy. If only anthracycline-containing regimens are considered, best responses were CR 2/40 (5%), PR 2/40 (5%), SD 23/40 (58%) and PD 13/40 (33%).

3.2. Brain metastases

Pooling the data of the patients treated at the Charité and patients of the reviewed publications, there were 285 patients evaluable for the analysis of the site of metastases. 87 of 285 stage IV patients developed brain metastases in the course of their disease (30.5%).

Patient data available for the analysis of the interval between first diagnosis of ASPS and the detection of brain metastases or survival after diagnosis of brain metastases are shown in Tables 1 and 3. In 33 patients (7 from Table 1 and 26 from Table 3), the median interval between first diagnosis of ASPS and detection of brain metastases was 48 months (range 0–396 months). The median survival of 35 patients evaluable for survival (7 from Table 1 and 23 from Table 2) after the diagnosis of brain metastases was 12 months with 17 patients still alive at their last follow-up. The median follow-up after the diagnosis of brain metastases was 12 months.

3.3. Survival

Survival data were analysed of all patients who received chemotherapy and of whom data about the

Table 1
Clinical characteristics of patients treated at the Charité

Patient no.	Gender	Age at first diagnosis (years)	Site of primary tumour	Metastatic sites	Interval from first diagnosis to metastases (months)	Interval from first diagnosis to brain metastases (months)	Surgical treatment	First-line chemotherapy	Response to first-line chemotherapy	Additional lines of chemotherapy and response	Alive after diagnosis of brain metastases (months)	Follow-up since first diagnosis (months)
1	F	15	Left thigh	Lung	41	–	Rad-ex Loc-ex	mito	SD	CYVADIC—SD; HD-Ifo—SD; eto—SD; tro: NE	NE	118 Dead
2	F	23	Right thigh	Lung, liver, brain	53	53	Rad-ex Loc-ex Brain-op	epi/HD-Ifo	SD	–	>36	89 awd
3	F	29	Right thigh	Lung, brain	15	75	Rad-ex Loc-ex	epi/HD-Ifo	PD	adri/DTIC—SD	>5	80 awd
4	M	43	Right scapula	Lung, liver, LN, brain	0 (initial)	25	Rad-ex Loc-ex Brain-op	ifo/carbo/eto/hyperth	SD	epi/HD-Ifo—SD; tro—SD, adri/DTIC—PD	>9	34 awd
5	M	21	Left thigh	Lung, skin, brain	0 (initial)	0 (initial)	Loc-ex Brain-op Brain-radio	epi/HD-Ifo	PD	topo—PD, other — PD	>22	22 awd
6	F	29	Left calf	Lung, bone, brain	0 (initial)	5	Brain-radio	adri/DTIC	SD	–	>8	13 awd
7	F	47	Right poplitea	Lung, local, brain	113	113	rad-ex Loc-ex Brain-op Brain-radio	adri/DTIC	SD	–	>22	135 ned
8	M	27	Soft pallet	Lung, brain	15	51	Rad-ex Brain-radio	adri/DTIC	SD	tro—NE	>12	63 awd

F, female; M, male; rad-ex, radical excision of primary site; loc-ex, local excision of metastasis; brain-op, excision of brain metastasis; NE, not evaluable; HD-Ifo, high-dose ifosfamide; CYVADIC, Cyclophosphamide, vincristine, adriamycin (doxorubicin) DTIC; LN, lymph node; brain-radio, radiotherapy to brain metastases; epi, Epirubicin, ifo, ifosfamide; carbo, carboplatin; eto, etoposide; hyperth, hyperthermia; Adri, doxorubicin; mito, mitoxantrone; tro, trofosfamide; topo, topotecan; awd, alive with disease; ned, no evidence of disease; mets, metastases; SD, stable disease; PD, progressive disease; NE, not evaluated.

type of chemotherapy and response and the time of metastases were reported.

Median survival since the diagnosis of metastases for the 31 patients evaluable for survival (8 from Table 1 and 23 from Table 2) was 36+ months (range 10–132 months), with 17 of the 31 patients alive at their last follow-up. The median follow-up since primary diagnosis was 46 months (range 10–135 months).

4. Discussion

Alveolar soft part sarcoma is a rare subgroup of soft tissue sarcomas. In our sarcoma registry of 757 patients, we identified 8 patients with ASPS since 1990 (=1.1%). This frequency compares well with the published data [1,17].

Data about the efficacy of chemotherapy are rare. Pooling data from the literature search and patients treated at the Charité, efficacy data for first-line chemotherapy were available for 68 patients, including 13 children: CR 4%, PR 3%. SD 41% and PD 51% resulting in an overall response rate of 5/68 (=7.4%). The response rate did not seem to be significantly higher for the subgroup treated with an anthracycline-based regimen, compared with other regimens (consisting of ifosfamide, thiotepa, methotrexate or others); [CR+PR: 4/40 (10.0%) versus 1/28 (=3.6%)]. Ifosfamide-containing regimens, either alone or in combination with anthracyclines, did not lead to an increased efficacy in the subgroup of 15 evaluable patients: PR 7%, SD 60% PD 33%. In 2 of 13 children treated with chemotherapy a response was noted, but the numbers in this group were too small to draw any firm conclusions.

In soft tissue sarcomas, monotherapy with anthracyclines is reported to result in response rates of 18–25% [20]. Combination regimens of anthracyclines and high-dose

Table 2
Systemic chemotherapy of adult patients and children with measurable disease and evaluation of response (published data)

Patient No.	[Ref.]	First-line	Response	2nd/3rd Line	Alive since Dx of metastases (months)	Follow-up (months)
Adults						
1	[30]	AI	SD		98	98 ned
2	[30]	AI	SD		68	68 Death
3	[30]	A	SD		46	46 Death
4	[31]	A	SD		35	35 ned
5	[32]	A	SD	TT—SD	24	60 Death
6	[13]	A	PD		48	48 Death
7	[13]	A	PD		63	63 awd
8	[13]	Other	PD		NA	210 ned
9	[13]	Other	PD		64	64 Death
10	[33]	TT	CR	TT—SD	48	65 awd
11	[33]	Other	PD	Other PD TT—PD	35	36 Death
12	[34]	Other	PD	A—PR MTX—SD MTX—SD	36	36 awd
13	[35]	Other	PD		11	11 Death
14	[36]	Other	SD		108	108 Death
15	[36]	Other	PD		10	10 Death
16	[36]	MTX	PD		18	Death
17	[37]	I	SD		NA	NA
18	[10]	A	CR		132	132 ned
19–21	[10]	A	PD		NA	NA
22–37	[10]	A	9xSD &		NA	NA
38–45	[10]	Other	15xPD		NA	NA
46	[38]	AI	SD	INF-a—PR	NA	108 awd
47	[17]	A	CR	Other—PD	NA	112 Dead
Children						
1	[6]	A	PR		NA	42 Death
2	[6]	A	PD		16	16 Death
3	[6]	A	PD		30	30 Death
4	[6]	AI	PR		NA	86 ned
5	[6]	AI	PD		33	33 awd
6	[6]	AI	PD		43	43 awd
7	[6]	AI	PD		NA	139 ned
8	[12]	A	SD		NA	244 ned
9	[12]	A	PD	I—SD Other—PD	13	13 Death
10	[12]	I	SD		NA	24 ned
11	[12]	AI	SD		12	12 ned
12	[12]	AI	SD		NA	24 ned
13	[39]	A	SD		60	108 awd

Follow-up is given in months since primary diagnosis. Dx, diagnosis; NA, not available or not applicable; ref, reference; other, other chemotherapy; A, with anthracyclines; I, with ifosfamide; MTX, with methotrexate; TT, with thio-tepa; INF-a, interferon alpha; awd, alive with disease; ned, no evidence of disease; CR, complete remission; PR, partial remission.

Table 3
Brain metastases time of diagnosis and survival (published data)

[Ref.]	Dx of brain metastases (months)	Survival with brain metastases (months)
[5]	NA	34 Alive
[28]	NA	24 Dead
[28]	NA	4 Dead
[28]	NA	4 Dead
[27]	NA	15 Alive
[27]	NA	20 Alive
[40]	0 Initial	NA
[41]	56	72 Alive
[42]	NA	24 Alive
[43]	52	NA
[43]	24	NA
[44]	0 Initial	60 LOF
[14]	0 Initial	1 Dead
[14]	62	10 Dead
[36]	3	7 Dead
[36]	24	24 Dead
[45]	23	73 Dead
[45]	23	23 Dead
[18]	20	0
[18]	170	0
[18]	55	0
[33]	24	NA
[46]	26	0
[47]	84	12 Alive
[47]	96	NA
[48]	0 Initial	12 Alive
[49]	49	20 Alive
[25]	396	24 Alive
[50]	36	43 Alive
[51]	84	12 Dead
[51]	72	12 Dead
[51]	48	12 Dead
[17]	108	3 Dead

Column 2 shows the time interval between primary diagnosis and the diagnosis of brain metastases. Column 3 shows the survival time with brain metastases. Ref., reference; Dx, diagnosis; LOF, loss to follow-up; NA, not available.

ifosfamide can lead to response rates of up to 52% [21]. It has to be concluded that in terms of the objective tumour response, ASPS are generally much less responsive to any known chemotherapy than other soft tissue sarcomas. According to the tumour response rates obtained, chemotherapies currently used must be judged to be ineffective in ASPS.

Current discussions suggest that progression-free survival might be a better primary endpoint to assess treatment efficacy in sarcomas. 41% of patients with ASPS had stable disease following chemotherapy. However, from the data available, it is unclear how many of those patients actually had progressive disease before chemotherapy and subsequent disease stabilisation due to chemotherapy. The staging result "stable disease" could just be a result of the slow-growing nature of this disease.

Due to the slow rate of tumour growth and the late time of systemic spread, a different tumour biology (compared with other soft tissue sarcomas) is often proposed for ASPS. In 12 patients, a very long interval between primary diagnosis and the occurrence of systemic spread was reported, ranging from 99 to 252 months [18,22–25]. The median survival after diagnosis

of metastases of 36+ months calculated in this study and 40 months reported for ASPS [3] compares favourably with a 12 months median survival in soft tissue sarcomas in general [26].

Another argument suggesting a different underlying biology for ASPS is the high overall rate of brain metastases (30.5%). Case series from single institutions, including consecutive ASPS patients, have reported brain metastases in stage IV patients in 7/8 (Charité), 2/10 (van Ruth and colleagues [19]), and 9/48 (Portera and colleagues [10]).

Therefore, brain metastases are at least 3 times more frequent in ASPS (30.5%) than in other soft tissue sarcomas with a reported incidence of 1–9.7%) [27,28].

The higher frequency of brain metastases in ASPS compared with soft tissue sarcomas is also confirmed by Medline analysis, retrieving articles using "sarcoma + brain metastases" as search terms. Of 89 pooled patients from case series about brain metastases in soft tissue sarcomas, 11 patients (12.4%) had an ASPS, although ASPS accounts only for 0.5–1% [1] of all soft tissue sarcomas.

The median time of detection of brain metastases after the primary diagnosis of ASPS was 48 months. This high rate of cerebral seedlings may (in part) be due to the slow-growing nature of ASPS. Patients with other soft tissue sarcomas may die due to visceral spread before they could develop brain metastases. Currently, it remains unclear whether the high incidence of brain metastases in ASPS is due to a disease-specific pattern of metastatic spread or the result of the long duration of the disease.

The long interval between primary diagnosis and systemic spread, the high incidence of brain metastases and the low efficacy of well established chemotherapies indicate that ASPS represents a distinct entity amongst the soft tissue sarcomas. Recently, the *ASPL* gene was cloned [29]. Mutations in this gene may play a role in the development of ASPS. Future research may lead to a better understanding of the biology of ASPS. Possibly the detection of *ASPL* is the first step in helping improve knowledge about the biology of ASPS and may lead to the identification of tumour-specific targets and cell-directed therapy, as has been seen recently with the development of imatinib-mesylate (Glivec™, STI-571) for the targeted treatment of gastrointestinal stromal tumours (GIST).

5. Conclusions

Alveolar soft part sarcoma is a rare tumour which has a different tumour-biology compared with other soft tissue sarcomas. ASPS show a high incidence of brain metastases (30.5% of cases), at least 3 times higher than that of other soft tissue sarcomas. The interval between first diagnosis and cerebral metastases is long. Chemotherapeutic regimens used for the treatment of other soft tissue sarcomas lack efficacy in ASPS.

Consequences

1. Staging investigations for ASPS should routinely include imaging of the brain.
2. As recurrences may occur very late, follow-up should be for at least 10 years.
3. ASPS should not be treated with chemotherapy outside of controlled clinical trials.
4. Multicentric, multinational, prospective clinical trials should be initiated to obtain meaningful results about possible treatment options.
5. Special effort should be put into the development of new targets for specific new therapies.

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