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Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network

S. Stacchiotti[1]*, E. Palassini[1], R. Sanfilippo[1], B. Vincenzi[2], M. G. Arena[3], A. M. Bochicchio[4], P. De Rosa[5], A. Nuzzo[6], S. Turano[7], C. Morosi[8], A. P. Dei Tos[9], S. Pilotti[9] & P. G. Casali[10]

[1]Department of Cancer Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale dei Tumori, Milano; [2]Department of Medical Oncology, University Campus Bio-Medico, Rome; [3]Department of Cancer Medicine, Ospedale Ignazio Toraldo, Tropea; [4]Department of Cancer Medicine, Istituto di Ricovero e Cura a Carattere Scientifico Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture; [5]Unit of Medical Oncology and Innovative Therapy, Istituto Nazionale Tumori Fondazione G. Pascale, Napoli; [6]Department of Cancer Medicine, Ospedale Renzetti, Lanciano; [7]Department of Cancer Medicine, Ospedale Mariano Santo, Cosenza; [8]Department of Radiology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori, Milano; [9]Department of Anatomic Pathology, General Hospital of Treviso, Treviso; [10]Department of Pathology and Molecular Biology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori, Milano, Italy

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Background: Angiosarcoma is a highly aggressive soft tissue sarcoma. Responses to anthracyclines plus/minus ifosfamide, and taxanes alone or in combination with gemcitabine are well documented. Very few data are available on gemcitabine as a single agent.

Patients and methods: We retrospectively reviewed all cases of advanced progressive angiosarcoma treated with gemcitabine as a single agent (1000 mg/m^2 i.v. every week for 3 weeks every 4 weeks), at Istituto Nazionale Tumori and within the Italian Rare Cancers Network from January 2008 to November 2010.

Results: Twenty-five patients [mean age: 52 years; radiation therapy (RT)-related: 8] received gemcitabine. Best tumor response by RECIST was as follows: complete response = 2, partial response = 14, stable disease = 2, progressive disease = 7 cases, for an overall response rate (PR + CR) of 68%. Six of eight post-RT angiosarcomas responded to treatment. Median overall survival (OS) was 17 months. Median progression-free survival (PFS) was 7 months (range 1–40 months). One patient with a locally advanced thyroid angiosarcoma became resectable after 5 months of gemcitabine, with <10% residual viable tumor cells seen on surgical specimen. Overall, gemcitabine was well tolerated.

Conclusions: Gemcitabine is active in both RT- and non-RT-related angiosarcoma, with dimensional and possibly long-lasting responses. A formal phase II study on gemcitabine as a single agent is warranted.

Key words: angiosarcoma, chemotherapy, gemcitabine, sarcoma

introduction

Angiosarcoma is a very rare sarcoma (incidence <0.1/100 000/year) of vascular or lymphatic origin, whose cells variably recapitulate the morphological and functional features of normal endothelium [1]. In fact, angiosarcoma expresses vascular antigens, including CD31, CD34, D2-40, FLI-1, and vascular endothelial growth factor [1, 2]. Skin is the most common primary site, followed by deep soft tissues, viscera, and bone [1, 3–7]. Etiology is unknown. Yet, several risk factors for angiosarcoma have been described, such as a previous exposure to vinyl chloride [8–12] or radiation therapy (RT) [3, 13–16], preexisting benign vascular lesions [17], chronic lymphoedema [18], chronic infection/inflammation [3, 19–21], and prolonged immunosuppression [22, 23]. Angiosarcoma is usually regarded as a high-grade tumor, aside from morphology [1], being marked by one of the highest metastatic potentials among sarcomas, with an overall median survival of <4 years and a cure rate of <40% at 5 years. Series with a more favorable outcome after wide surgery and RT have been reported [3–5, 24, 25]. In fact, wide surgery followed by RT is the treatment of choice [25]; however, if primary site and the multifocality of local disease are, considered negative margins are often difficult to achieve [4, 25]. Sometimes, a less aggressive behavior can be seen in skin and breast angiosarcomas. These are the only two locations where angiosarcomas could be classified histologically as low, intermediate, or high grade. Nevertheless, an unfavorable outcome has been recently reported even for skin and breast angiosarcomas, especially in presence of necrosis or of an epithelioid morphology or in post-RT cases, even if the primary tumor is small in size [5, 6, 26–28]. The prognosis of

Correspondence to: Dr S. Stacchiotti, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian 1, 20133 Milano, Italy. Tel: +39-02-23902803; Fax: +39-02-23902804. E-mail: silvia.stacchiotti@istitutotumori.mi.it

advanced angiosarcoma remains dismal [4]. Despite a strong need for systemic therapies, the rarity of angiosarcoma represents a major limitation to randomized trials and therefore only few prospective clinical studies are available. Most data are represented by retrospective case series analyses or case reports all suggesting that among soft tissue sarcomas, angiosarcoma appears to be more sensitive to cytotoxic chemotherapy [29]. In particular, the response rate to doxorubicin—the standard frontline chemotherapy for advanced sarcoma—as a single agent or in combination, is reported to the range between 40% and 65% [30, 31]. Beside anthracyclines, taxanes can be active, both as single agents and in combination with gemcitabine or with anthracyclines, with response rates between 20% and 65% [32–39]. Among new angiogenesis-related molecules, the activity of sorafenib, sunitinib, bevacizumab, and thalidomide has been reported, with response rates ∼15% [40–44].

In the past decade, convincing evidence of selective activity of gemcitabine, both as a single agent [45, 46] and in combination with docetaxel [37, 40, 47–51] or vinorelbine [52], has been generated in some sarcoma subgroups, including high-grade pleomorphic sarcomas as well as sarcomas featuring myogenic differentiation. Of interest, whereas a randomized phase II clinical study suggests the superiority of the combination of gemcitabine + docetaxel versus gemcitabine as a single agent [48], a pooled analysis of this study with another from the French Sarcoma Group would suggest that gemcitabine as a single agent is not inferior to gemcitabine plus docetaxel in leiomyosarcoma [51]. A plus of gemcitabine as a single agent is of course its favorable toxicity profile. In fact, tolerability of gemcitabine plus docetaxel is fair, with less cardiac toxicity compared with anthracyclines but still carrying a significant incidence of neutropenia and thrombocytopenia [47, 48]. To date, few anecdotal responses to gemcitabine in monotherapy have been reported in angiosarcoma [45, 46, 53]. Based on these data, since 2005, we have started using gemcitabine as a single agent in few patients with advanced angiosarcoma previously treated with anthracyclines and paclitaxel. Using the same schedule tested in leiomyosarcoma, we saw convincing responses, with beneficial effect on both symptoms and quality of life. In this article, report on a retrospective series of 25 patients with advanced angiosarcoma treated with gemcitabine as a single agent at our institution and within the Italian Rare Cancer Network. This is a collaborative network sharing clinical cases of rare cancers in Italy, with the goal of improving quality of care and decreasing health migration.

patients and methods

patient selection

We identified 25 patients with locally advanced or metastatic angiosarcoma consecutively treated at Istituto Nazionale Tumori, Milano (18 patients), and all those included in the database of the Italian Rare Cancer Network by other six institutions (University Campus Bio-Medico, Rome, 2 patients; Ospedale I. Toraldo, Tropea, 1 patient; IRCCS Rionero in Vulture, 1 patient; Istituto Nazionale Tumori Fondazione G. Pascale, Napoli, 1 patient; H Renzetti, Lanciano, 1 patient; Ospedale M. Santo, Cosenza, 1 patient), in the period between January 2008 and November 2010.

Histological diagnosis was centrally reviewed in all cases by two expert pathologists (SP and APDT). All patients had evidence of progressive disease before starting treatment. Eastern Cooperative Oncology Group performance status (ECOG PS) of three or less and an adequate bone marrow and organ function were required in all cases. All patients provided a written informed consent to data collection within the network and to the treatment: data were extracted from individual patients file and analyzed.

Patient characteristics are listed in Table 1: mean age/range 52/29–81 years; primary site: breast, 7; skin, 4; viscera, 4 (among which 3 heart), extremities, 2; other, 4; locally advanced/metastatic, 6/19; RT related, 8; human immunodeficiency virus (HIV) associated, 1; pretreatment with one or more medical treatment (anthracycline/paclitaxel/gemcitabine + docetaxel), 22 (7/19/5); and ECOG PS of three or more, 4. All patients had documented progression before starting treatment.

pathology

All patients expressed vascular antigens for CD31 and CD34 in all but two.

In angiosarcoma, tumor 'grade' has been shown poor correlation with outcome [4, 54, 55]. Here, we tried to categorize our case material taking into consideration the updated issues on the field. In detail, for the angiosarcoma of the esophagus, thyroid, lung, mediastinum, heart, retroperitoneum, and soft tissues, we followed the World Health Organisation (WHO) histological classification of sarcoma as recommended by each corresponding 'blue book' [1, 55–60]. Splenic angiosarcoma was graded according to the criteria proposed by Falk et al. [61]. As shown in Table 1, for breast angiosarcoma, we referred to both WHO classification[62, 63] and what was proposed recently by Nascimento et al. [64], who demonstrated that breast angiosarcoma shows a high propensity for metastases, irrespective of grade. For skin, we applied the two-tier system where necrosis and epithelioid features segregate with high-risk tumors [5].

Following this approach, all cases were classified as high-grade/high-risk angiosarcoma, as detailed in Table 1.

In particular, by WHO classification [63], cases of breast angiosarcoma were all classified as high grade but one (case 11, Table 1). All of them, however, were RT-related angiosarcoma, and thus to be considered high risk according to Nascimento [64]. Similarly, the three cases of skin angiosarcoma included in this series fell into the high-risk group according to what was recently proposed by Deyrup et al. [5] given the presence of necrosis and/or epithelioid features, and the tumor location (face, scalp) consistent with UV exposition (cases 1–3, Table 1).

Finally, three patients were metastatic at the onset, one to the lymph nodes (case 4, Table 1) and two to the lung (cases 15 and 25, Table 1).

treatment

Patients received gemcitabine 1000 mg/m^2 i.v. as a 30-minute infusion, on days 1, 8, and 15, every 28 days, together with steroids (dexamethasone 12 mg i.v. before gemcitabine infusion) and antiemetics (ondansetron 8 mg i.v. before gemcitabine infusion), until progression or toxicity. Treatment was withheld for hematologic grade ≥3 adverse events and for non-hematologic grade ≥2 adverse event (defined according to the National Cancer Institute—Common Toxicity Criteria, version 3.0) and restarted after recovery to grade <2 in case of hematologic or grade <1 in case of non-hematologic.

clinical assessment

Full blood cell count and biochemistry were assessed at baseline and before every gemcitabine administration. Adverse events were recorded. Disease status was assessed at baseline by a whole-body computed tomography (CT) scan, a CT, or a magnetic resonance imaging (MRI) of the sites of disease, and a whole-body bone scan. CT/MRI were repeated after 4–8 weeks of treatment and then every 2–3 months, but in case of problems.

Table 1. Patients characteristics

Patient ID	Age at the time of treatment with GEM (years)	Gender	Site of primary	Risk factor	Diagnosis	Primary tumor grading	Grade according to risk stratification scheme (Nascimento)	Disease extension at time of GEM	Pretreatment with TAX (response)	Pretreatment with ADM (response)	Pretreatment with GEM–TAX (response)
1	66	M	Skin (scalp)	UV radiation	Epithelioid angiosarcoma	NA	High risk	Locally advanced	Yes (PR)	Yes (PD)	No
2	60	M	Skin (scalp)	UV radiation	Epithelioid angiosarcoma	NA	High risk	M+	No	No	No
3	56	M	Skin (face)	UV radiation	Epithelioid angiosarcoma	NA	High risk	M+	Yes (PR)	No	No
4	62	F	Skin	RT	Epithelioid angiosarcoma	Metastatic at onset	–	M+	Yes (PD)	Yes (NV)	No
5	36	F	Breast	RT	Epithelioid angiosarcoma	High grade by WHO	High risk	M+	No	No	No
6	48	F	Breast	RT	Epithelioid angiosarcoma	High grade by WHO	High risk	Locally advanced	Yes (PD)	No	No
7	81	F	Breast (superficial)	RT	Epithelioid angiosarcoma	Low grade by WHO	High risk	M+	No	No	No
8	72	F	Breast	RT	Epithelioid angiosarcoma	High grade by WHO	High risk	M+	Yes (PR)	No	No
9	52	F	Breast (superficial)	RT	Epithelioid angiosarcoma	High grade by WHO	High risk	M+	Yes (PR)	No	No
10	74	F	Breast (superficial)	RT	Epithelioid angiosarcoma	High grade by WHO	High risk	M+	No	No	No
11	78	F	Breast (superficial)	RT	Well-differentiated, vasoformative growth angiosarcoma	Low grade by WHO	High risk	Locally advanced	Yes (SD)	No	No
12	63	F	Thyroid	UNK	Epithelioid angiosarcoma	High grade by FNCLCC	–	Locally advanced	Yes (SD)	No	No
13	43	F	Heart, right	UNK	Spindle angiosarcoma	High grade by FNCLCC	–	M+	Yes (PR)	No	No
14	36.	M	Heart, right	UNK	Epithelioid angiosarcoma	High grade by FNCLCC	–	M+	No	Yes (PR)	No
15	40	F	Heart, right	UNK	Epithelioid angiosarcoma	Metastatic at onset	–	M+	No	Yes (PR)	No
16	60	M	Pericardium	UNK	Epithelioid angiosarcoma	High grade by WHO	–	M+	Yes (PD)	No	No
17	42	F	Lung, left	UNK	Epithelioid angiosarcoma with extensive lymphangitic spread	High grade by WHO	–	M+	Yes (PD)	No	No
18	74	M	Lung, right	UNK	Epithelioid angiosarcoma with extensive lymphangitic spread	High grade by WHO	–	Locally advanced	Yes (SD)	No	No
19	35	M	Mediastinum	UNK	Epithelioid angiosarcoma	High grade by FNCLCC	–	M+	Yes (SD)	Yes (NV)	Yes (PR)
20	42	F	Esophagus	HIV infection	Epithelioid/solid angiosarcoma with extensive lymphangitic spread	High grade by FNCLCC	High risk	M+	No	No	No
21	44	F	Spleen	UNK	Spindle angiosarcoma	High grade by Falk	–	M+	Yes (PR)	Yes (PR)	Yes (PR)
22	40	M	Pelvis	UNK	Epithelioid angiosarcoma	NA	–	Locally advanced	Yes (SD)	No	No
23	66	M	Retroperitoneum	UNK	Epithelioid angiosarcoma	High grade by FNCLCC	–	M+	Yes (PR)	No	No
24	48	M	Thigh, right	UNK	Epithelioid angiosarcoma	High grade by FNCLCC	–	M+	No	Yes (SD)	No
25	29	M	Foot.	UNK	Epithelioid angiosarcoma	Metastatic at onset	–	M+	Yes (SD)	No	Yes (SD)

ADM, anthracyclines; F, female; FNCLCC, French Federation Nationale des Centres de Lutte Contre le Cancer; GEM, gemcitabine; GEM–TAX, gemcitabine + taxanes; M, male; M+, metastases; NA, not assessable; NV, non-evaluable PR, partial response; PD, progressive disease; RT, radiation therapy; SD, stable disease; TAX, taxanes; UNK, unknown; WHO, World Health Organisation.

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Response to treatment was assessed with the use of RECIST criteria [65].

Progression-free survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier method [66]. Failure for PFS was progressive disease according to RECIST, or death. Patients who discontinued their treatment without evidence of disease progression, then progressed, and restarted gemcitabine with a new response were censored at the time of first progression or at the time of the last assessment of the tumor. Data for patients who interrupted their treatment without evidence of disease progression and underwent complete surgery and/or definitive RT were censored at the time of surgery or RT. Failure for OS was death due to any cause. Patients alive were censored at the time of the last contact.

results

Twenty-five were assessable for response. Among them, 10 are still on therapy.

treatment

Median treatment duration was 5 months (range 1–40+ months). Overall, treatment was well tolerated even in patients with the worse PS. The major non-hematologic toxic effects included liver toxicity (two patients, grade 2), fever (one patient, grade 3), and allergic reaction (one patient, grade 3). The most common hematologic toxic effects were anemia (two patients, grade 2) neutropenia (eight patients, four grade 3), and thrombocytopenia (five patients, one grade 3). Two patients had to definitely interrupt their treatment due to toxicity (grade 3 febrile neutropenia + thrombocytopenia; grade 3 allergic reaction). In four patients, responsive to treatment, who continued gemcitabine >6 months and experienced grade ≥2 hematologic toxic effects, treatment schedule was modified to gemcitabine 1000 mg/m^2 every 10 days without interruption. No dose reduction was necessary.

response

Twenty-five patients were assessable for response, as summarized in Table 2. The best response was RECIST complete response (CR) in 2 of 25 cases, partial response (PR) in 14 of 25 cases, a stable disease (SD) in 2 of 25 cases, and a progressive disease (PD) in 7 of 25 cases, for an overall response rate (i.e. RECIST CR + PR) of 17 of 25 (68%) cases. Responses were confirmed after 3 months in all patients but two, who progressed at 2 months. A subjective improvement consistent with response was observed in 12 of 15 patients who were symptomatic at baseline. Responses were observed irrespective of primary tumor response (PR) in 14 of 25 cases, SD in 2 of 25 cases, and PD in 7 of 25 cases, for an overall response rate (i.e. RECIST CR + PR) of 17 of 25 cases (68%). Responses were confirmed after 3 months in all patients but two, who progressed at two site and/or grading. Among RT-related angiosarcomas, a RECIST PR was detected in five of eight assessable patients (Figure 1). A PR was observed even in the HIV-related angiosarcoma. Four patients of this series were pretreated with gemcitabine + docetaxel before starting gemcitabine as a single agent, all with a response, and stopped their treatment after reaching the maximum tolerated dose of docetaxel. When progressing again, they were treated with gemcitabine as a single agent, with a new response in two of four patients, while the other two progressed. One 35-year-old patient, with lung and liver metastasis from a mediastinal angiosarcoma, achieved a CR after 9 months of treatment with gemcitabine and stopped his treatment after 12 months. Ten months after treatment interruption, there was a new progression. Response was reestablished upon restarting gemcitabine. This patient is still on treatment and progression free after 40 months from the first dose of gemcitabine

Table 2. Patients treated with gemcitabine: response to treatment

Patient ID	Best response RECIST	Symptoms at baseline/ improvement	PFS (months)	OS (months) (status)
1	PR	Yes/yes	7	8 (alive)
2	PR	No	3	3 (alive)
3	RC	Yes/yes	5	10 (alive)
4	PR	Yes/yes	7	17 (dead)
5	PR	No	9	8 (alive)
6	PD	Yes/no	2	3 (alive)
7	PD	Yes/no	3	6 (alive)
8	PR	Yes/yes	3	5 (lost to FU)
9	PR	Yes/yes	6	7 (dead)
10	PR	Yes/yes	3	10 (alive)
11	PR	No	18	15 (alive)
12	PR	Yes/yes	5	14 (alive)
13	PR	Yes/yes	3	5 (dead)
14	PD	No	3	5 (alive)
15	PR	Yes/Yes	6	10 (dead)
16	PD	Yes/No	3	3 (lost FU)
17	PR	No	4	4 (alive)
18	SD	Yes/Yes	7	14 (dead)
19	RC	No	40	40 (alive)
20	PR	No	1	1 (alive)
21	PR	Yes/Yes	10	23 (dead)
22	PR	No	5	11 (alive)
23	PR	Yes/Yes	7	11 (alive)
24	PD	No	2	11 (alive)
25	SD	No	6	6 (lost FU)

CR, complete response; FU, follow-up; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease.

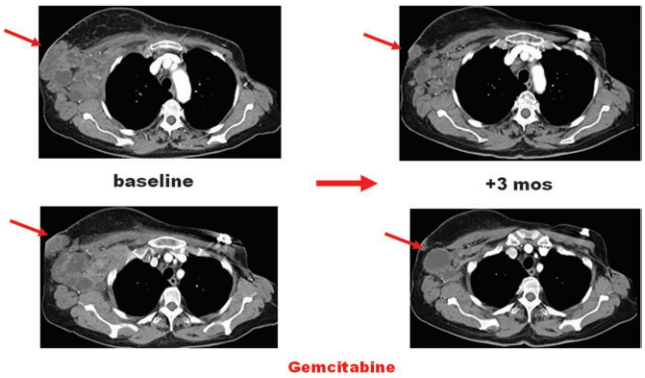

Figure 1. Post-radiation therapy breast angiosarcoma treated with gemcitabine: computed tomography scan (arterial phase after contrast medium). A RECIST partial response after 3 months of treatment with gemcitabine was obtained and patient underwent complete surgical resection.

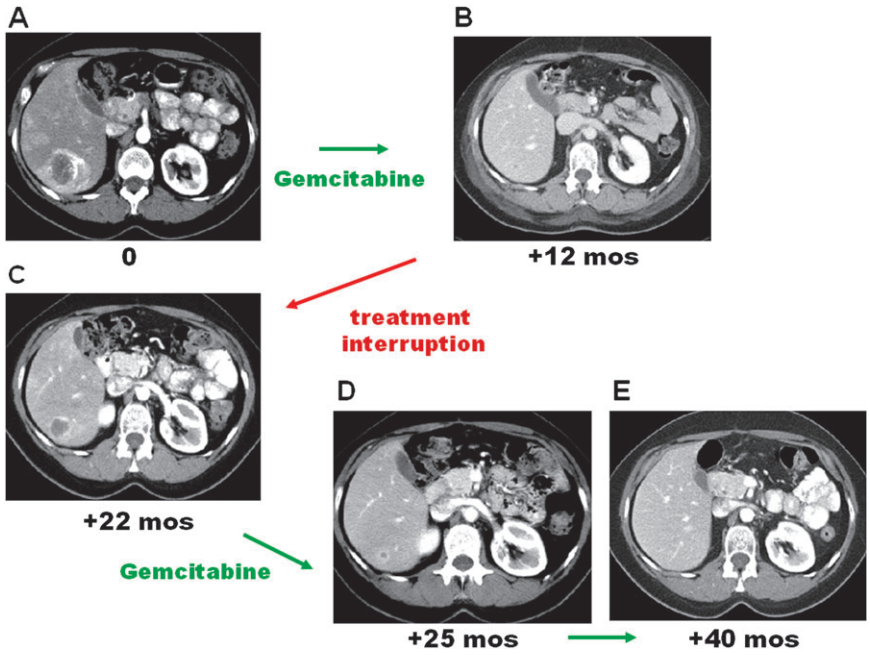

Figure 2. Liver metastasis from mediastinal angiosarcoma treated with gemcitabine: computed tomography scan (arterial phase after contrast medium). (A and B): Almost complete response after 12 months of treatment with gemcitabine; (B and C): interval progression observed at 22 months, i.e. 12 months after treatment interruption; (C, D, and E): new response after restarting gemcitabine observed at 25 months and maintained at 40 months.

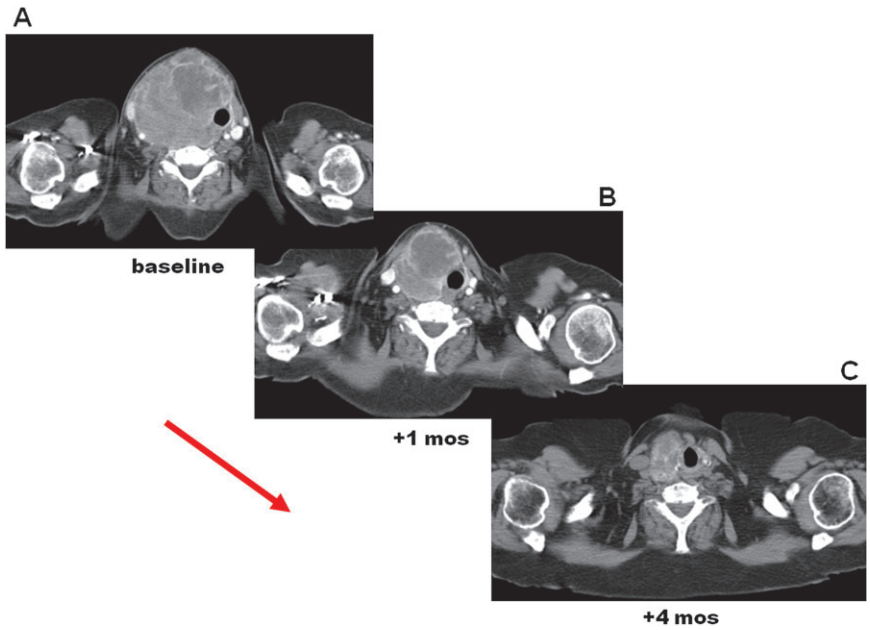

Figure 3. Locally advanced thyroid angiosarcoma treated with gemcitabine: computed tomography scan (arterial phase after contrast medium). (A, B, and C): Progressive dimensional response to gemcitabine, with evidence of best response achieved at 4 months. At that time, tumor resectability was obtained.

(15 months after gemcitabine resumption). He is well tolerating gemcitabine save for G1 transaminitis and G2 thrombocytopenia (Figure 2). Among the seven patients who started gemcitabine for a locally advanced unresectable tumor, one (Figure 3) with a thyroid angiosarcoma had an impressive dimensional response, thus becoming resectable after 4 months of therapy. She received complete surgery followed by RT and is disease free 10 months later. The pathological analysis of the surgical specimen confirmed the response to treatment, with <10% viable tumor in the surgical specimen. Another patient with a locally advanced pelvic angiosarcoma involving both rectum and bladder had an almost complete response after 5 months of treatment. At that time, the patient was offered surgery, but refused. Then, he stopped gemcitabine and received exclusive RT. He is disease free at 8 months.

The median OS was 17 months (range 1–40 months), with six patients dead at the time of the present analysis. The median PFS was seven months (range 1–18+ months), with 54% patients progression free at 6 months (Figure 4). With respect to the patient on gemcitabine since 40 months, we

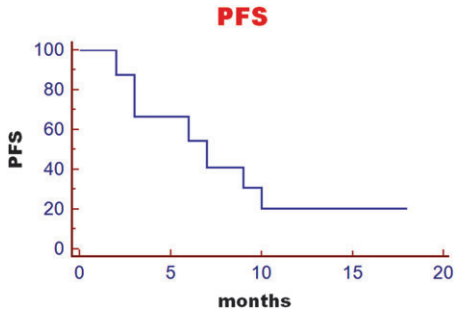

Figure 4. Progression-free survival.

have truncated the PFS curve at 18 months because this is the case of only one patient of this series.

discussion

Despite the rarity of the disease, in a collaborative clinical setting we could retrospectively collect 25 patients with progressing advanced angiosarcoma treated with weekly gemcitabine as a single agent on a 2-year span. Among 25 assessable patients, we observed 68% RECIST responses, including two CR, along with subjective improvement in symptomatic patients. Median PFS was 7 months, with some long-lasting responses (one patient is still responsive after 40 months).

Angiosarcoma represents an exceedingly rare disease and very few prospective studies focusing on the medical treatment are available. Indeed, vascular malignancies are among the most aggressive histological sarcoma subtypes, with <30% patients being cured and a median OS in metastatic patients of ∼12 months [4]. In the advanced disease, cytotoxic chemotherapy is the treatment of choice, with anthracyclines, ifosfamide, and taxanes as possible options. Even if the response rate of angiosarcoma to these treatments is high compared with other sarcomas, their dose-limiting toxic effects (mostly cardiac and neurological) do not allow to prolong these therapies for >6–7 months in most cases. Furthermore, secondary resistance after response is frequent. Moreover, the combination of anthracyclines plus ifosfamide can be difficult to administer in many angiosarcoma patients, given their age and PS. By the way, RT-related angiosarcoma patients are often pretreated with anthracycline-based chemotherapy, with a limited bone marrow reserve, and they are likely to carry DNA repair mechanism defects that can underlie increased chemoresistance to cytotoxics like the alkylating agents. Thus, new and nontoxic drugs are strongly needed. For these reasons, gemcitabine seems to be a very promising therapeutic option.

Few anecdotal responses to gemcitabine in monotherapy have been reported in angiosarcoma [45, 46, 52]. In this series of pretreated and progressive patients, we could confirm an encouraging response rate, matching the best data on response to anthracyclines and taxanes. Responses were mostly dimensional, with some major or even complete response. In one patient carrying a bulky thyroid angiosarcoma not surgically amenable at baseline, the striking response to gemcitabine allowed an otherwise unfeasible surgical resection. Of interest, even if early secondary progression after response were observed (two patients responding at 2 months were progressing at the third month), in some patients responses lasted for long, with two patients on treatment for >1 year. Responses were observed irrespective of primary tumor site and tumor aggressiveness. It is well known that in angiosarcoma, histological grading shows poor correlation with outcome. Furthermore, clinical parameters such as lymphedema and prior exposition to risk factor such as RT or vinyl chloride have been found to impact over clinical behavior [4, 54]. Thus, rather than using conventional parameters for soft tissue sarcoma risk definition (i.e. tumor grade, depth, and size) [1, 5, 55, 57–61, 63, 64], we decided to classify our cases by incorporating those clinical and histological findings that recently proved more accurate in establishing angiosarcoma prognosis. As a consequence, all cases included in this series were eventually classified as high-grade/high-risk angiosarcomas.

Of interest, responses were observed even in the majority of the post-RT angiosarcoma (six PR out of eight).

In this retrospective analysis, toxicity could not be assessed at best. However, toxicity was limited overall, as expected with a drug with a well-known toxicity profile. Only two patients had to interrupt their treatment due to side-effects. On the other side, symptomatic improvement was reported by all responsive patients with symptoms at baseline. Treatment was well tolerated even in patients receiving gemcitabine for long. In particular, in four responding patients, treatment was maintained by lengthening the interval between drug administrations.

An interesting question in advanced angiosarcoma is whether gemcitabine as a single agent is a better option than the combination of gemcitabine plus paclitaxel. Contrary to what happens in leiomyosarcomas, indeed, in angiosarcoma both gemcitabine and taxanes can be active *per se*. This may be a major issue in an adjuvant or neoadjuvant setting. Yet, in a palliative setting, where the goal is to prolong survival and to preserve quality of life, the sequential use of taxanes and gemcitabine could be, probably in most cases, more advisable than their combination.

Of course, this could be the subject of clinical studies, which however are hardly feasible in such a rare sarcoma subgroup. This adds to the value of case series analyses like the one presented in this article. Even acknowledging the bias represented by the retrospective nature of the series, we can confirm that gemcitabine as a single agent is an active therapeutic option for angiosarcoma patients.

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disclosure

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