Adriamycin, Cisplatin, Ifosfamide and Paclitaxel Combination as Front-line Chemotherapy for Locally Advanced and Metastatic Angiosarcoma. Analysis of Three Case Reports and Review of the Literature

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Abstract. *Angiosarcoma represents 1 to 2% of soft tissue tumors. It originates from endothelial cells of small blood vessels and may affect a variety of organs, including the retroperitoneum, skeletal muscle, subcutis, liver, heart and breast. The outcome of angiosarcoma is poor for those patients in whom aggressive surgery cannot be considered. Chemotherapy, generally consisting of the combination of anthracyclines and ifosfamide, has little, but consistent effect. We report three cases of angiosarcoma in which first-line chemotherapy with adriamycin 40 mg/m^2 day 1, ifosfamide 3 g/m^2 day 1-2, cisplatin 35 mg/m^2 day 1-2 and paclitaxel 175 mg/m^2 day 3 led to clinically meaningful responses. The clinical relevance of incorporating paclitaxel in conventional soft tissue chemotherapy schedules in the light of both literature data and our experience is discussed. We emphasize the need for designing trials specifically dedicated to angiosarcomas, as this rare and severe condition may be a target for new antiangiogenic drugs.*

Angiosarcomas are very rare and aggressive tumors which are mainly localized in the head and neck (elderly men), breast (radiation-induced), pelvis and extremities. No prospective randomized trials have been conducted specifically on this subject and angiosarcomas are often included in the heterogeneous group of soft tissue sarcomas. In this report, we describe the results of a paclitaxel-based multidrug regimen through three cases reports and discuss treatment modalities from literature data.

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Case 1

A 62-year-old Caucasian male with a medical history of prior liver transplantation for NACH syndrome presented with a right L5 lumbago and sacroiliac pain. The patient had a right L5 radiculalgia, but there was no painful mass, cutaneous abnormalities, nor performance status decrease. Standard radiograms were normal, as were standard biochemistry and blood count.

CT scan, PET scan and MRI showed a heterogenous L5 vertebral tumor with osteolysis and extension to the right psoas muscle (Figure 1). Tumor biopsed to a diagnosis of epithelioid angiosarcoma (Figures 2 a and 2 b).

The patient underwent polychemotherapy according to the protocol shown in Table I. After 5 cycles, CT scan showed a 25% shrinkage of the mass and disappearance of the laterovertebral extension (Figure 3). Anemia grade III, nausea and diarrhea grade I/II were observed during therapy, but there was no febrile neutropenia, nor renal nor cardiac failure. A right L5 half vertebrectomy was performed with osteosynthesis from L3 to S1, after arterial embolization. Pathological findings confirmed a complete tumor response with 0% of viable cells.

The patient remained in complete remission for 14 months before bone metastases were diagnosed and being rechallenged with chemotherapy that is ongoing.

Case 2

A 24-year-old Caucasian male with a medical history of severe obstructive hypertrophic myocardiopathy was referred with chronic fever and a nonfunctional painful right knee. Standard radiograms of the right knee showed osteolysis, periosteal abnormalities and tumor extension to adjacent soft tissues.

Initial surgery diagnosed hemangioendothelioma, but lung metastases were shortly discovered concomitantly with local

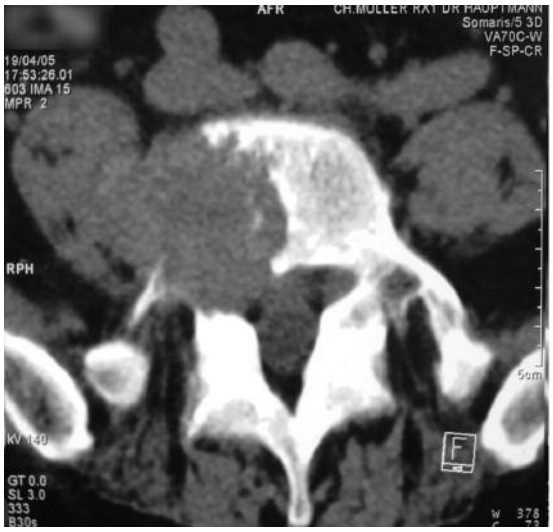

Figure 1. *CT scan at the diagnosis: osteolysis of L5 with foraminal and paravertebral extension.*

regrowth. A second surgery confirmed the final diagnosis of angiosarcoma as blood count and biochemical results revealed consumption coagulopathy.

The patient underwent 6 cycles of the combination chemotherapy (Table I) and experienced a partial response (PR) of more than 75%. Toxicity consisted of grade III anemia – treated with blood support and erythropoietin, an episode of febrile neutropenia and grade III mucositis. Despite close cardiac monitoring with ultrasonography the patient died of cardiac failure, while still responding to therapy.

Case 3

A 69-year-old Caucasian female, with a medical history of left breast medullary carcinoma treated by surgery and adjuvant radiotherapy was referred 13 years later with a rapidly growing left breast mass. Clinical examination revealed a 15 cm-diameter tumor, with ulcerative, hemorrhagic and necrotic features, invading pectoral and intercostal muscles. Tumor biopsy showed fusiform cells, with atypic nuclei, mitosis and necrosis. Immunostainings were positive for vimentin, CD34, CD31 and factor VIII, but negative for cytokeratin, diagnosing angiosarcoma. The patient received 5 cycles of the combination regimen (Table I) and 2 additional cycles with carboplatin AUC 5 instead of cisplatin, in the setting of reversible acute renal failure. A good tumor clinical response was obtained as the tumor size decreased to 3×2 cm and the patient was able to undergo radical mastectomy with an additional external beam radiation therapy. The patient remained in complete remission for 14 months, before multi-metastatic relapse and death.

Table I. *Polychemotherapy schedule.*

Cisplatin 35 mg/m^2 day 1, day 2
Adriamycin 40 mg/m^2 day 1
Ifosfamide 3 g/m^2 day 1, day 2
Paclitaxel 175 mg/m^2 day 3
Every three weeks
Systematic administration of: Desrazoxane, MESNA and G-CSF from day 1 to day 5. Hematopoietic growth factor support.

Discussion

Angiosarcomas represent 1 to 2% of all soft-tissue tumors and are rare and aggressive tumors, with an usual presentation of high grade and multifocal disease (1, 2).

Diagnosis might be difficult in the setting of a necrotic and ulcerative tumor, as in case 2, where the first diagnosis was hemangioendothelioma. Differential diagnosis for angiosarcoma includes carcinoma, pleomorphic rhabdomyosarcoma, melanoma and epithelioid hemangioendothelioma. Angiosarcomas are divided into classic (well, moderately, and poorly differentiated) and epithelioid subtypes. The classic subtype is the most frequent, characterized by a variety of round to oval spindle-shaped and epithelioid cells, with a background of hemorrhagic and erythrophagocytosis cytoplasmic deposits. Mitotic figures and necrosis are also described. The epithelioid subtype is characterized by the lack of hemorrhagic background. Angiosarcomas are characterized by positive immunostaining with factor VIII-related antigen, CD31, CD34, Fli-1 and vimentin (3-5).

As angiosarcomas are generally included in the heterogeneous group of the soft tissue sarcomas, there have been no specific randomized trials aimed at this rare condition. Soft tissue sarcoma first-line chemotherapy with adriamycin plus ifosfamide has been the standard therapy since objective response rates of 45%, including 10% of complete response and a median survival of 15 months were obtained (6-9).

Many different anticancer drug combinations, including cisplatin with doxorubicin, cisplatin plus paclitaxel, cisplatin plus doxorubicin plus paclitaxel (10), have recently been tested. As the results of these trials have not shown a notable improvement, we have tested a new protocol (Table I). Pegylated liposomal doxorubicin has also shown activity, with PR after 2 cycles and a complete response (CR) after 6 cycles, in a radiation-refractory angiosarcoma case report (11) and a 90% regression with analgesic effect in a lymphangiosarcoma case report (12). Pegylated liposomal doxorubicin but similar is more expensive than standard doxorubicin in terms of efficacy, although direct comparisons focusing on sarcomas have not

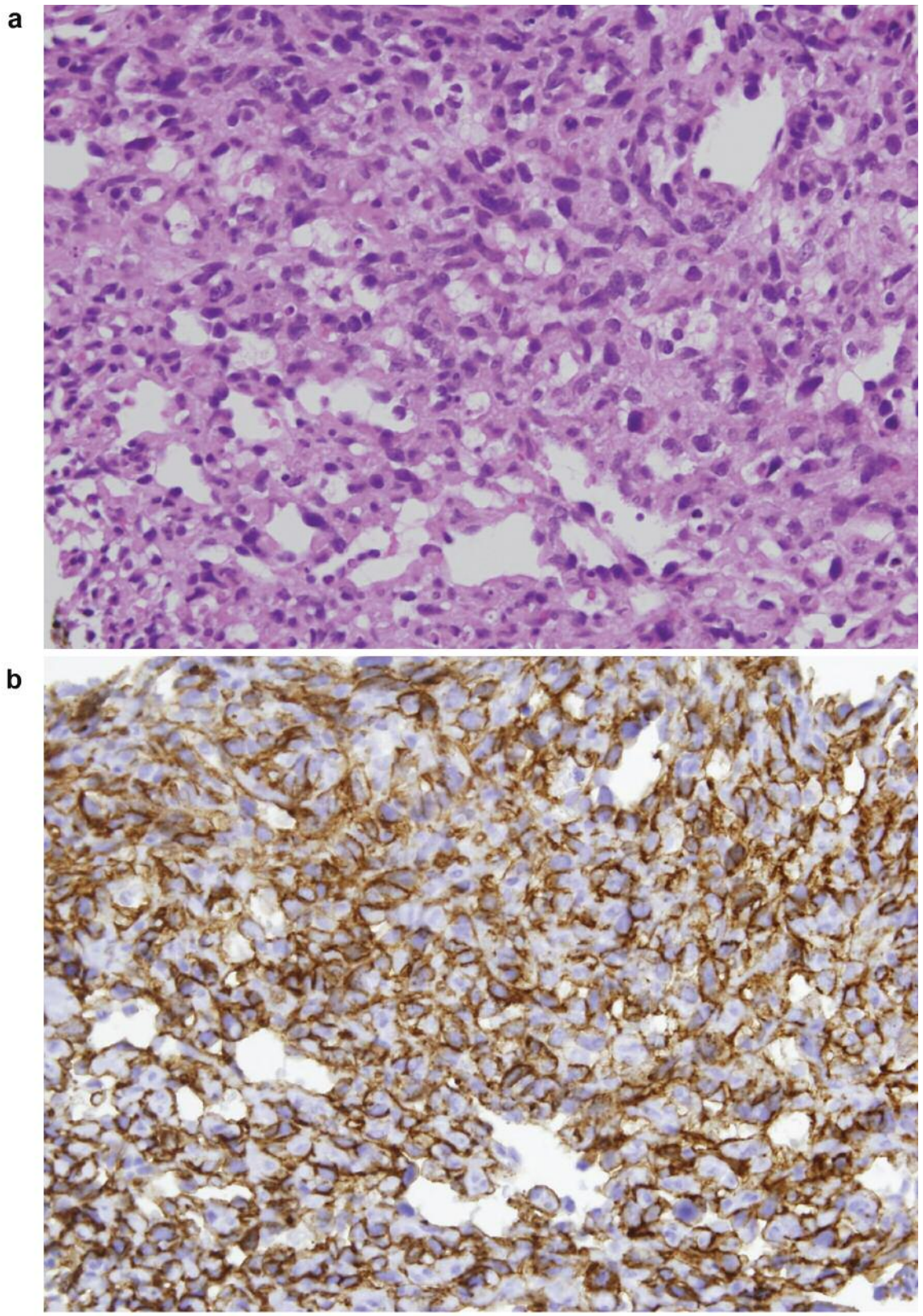

Figure 2. *a. Tumor biopsy: Hematoxylin-eosin ×40: Angiosarcoma invading the L5 vertebra. b. Tumor biopsy: Angiosarcoma invading the L5 vertebra: positive immunostaining for CD34 (×40) showing endothelial cells.*

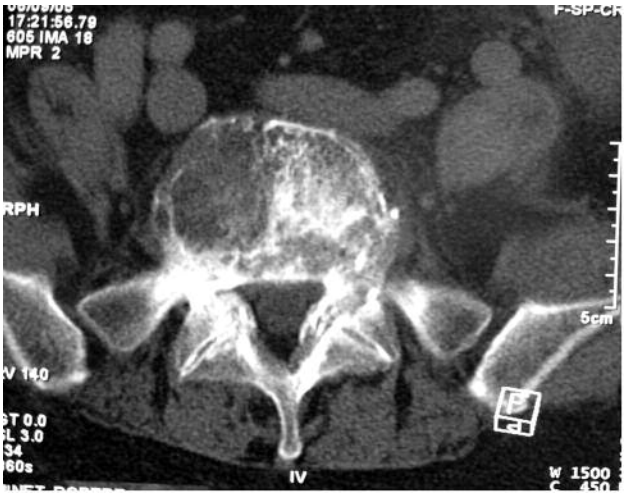

Figure 3. *Pre-op CT scan after 5 cycles of polychemotherapy: disappearance of the extension to the muscles, shrinkage of the mass and beginning of bone reconstruction.*

been carried out. Considering these data, we decided to design our combination with doxorubicin rather than use its pegylated liposomal form.

As angiosarcomas originate from endothelial cells, it is conceivable that the antiangiogenic and pro-apoptotic activities of paclitaxel contribute to its efficacy, as observed in our cases. *In vitro* and *in vivo* (mice models) data have shown that low-dose schedules of paclitaxel significantly inhibit endothelial cell proliferation, motility and invasiveness (13, 14), with cytotoxic effects (15). In a report of 9 angiosarcoma patients treated with single-agent metronomic front-line paclitaxel, 4 CR, 4 PR and 1 stable disease (SD) lasting for 10 months were observed (16). Salvage metronomic paclitaxel in angiosarcomas originating from various sites also showed efficacy in 2/4 patients as they experienced long-lasting SD (4 years), and PR lasting for 5 months.

Combining weekly doxorubicin 20 mg/m^2 day 1 and paclitaxel 100 mg/m^2 day 2 with concurrent cisplatin 30 mg/m^2 day 3 in first-line treatment led to a persistant (2-year) CR in a patient with metastatic seminal vesicle angiosarcoma (10). In a similar study, nine patiens with locally advanced or metastatic angiosarcomas received metronomic paclitaxel leading to 3 CR, 3 PR and 3 SD (17).

Given these data, we administered a combination of adriamycin, cisplatin, ifosfamide and paclitaxel to our patients, to combine the well-established cytotoxic properties of the former drugs with the promising antiangiogenic effects of the latter. We show that this combination is active, as two patients experienced a PR of more than 75%, and one patient had CR lasting for one year.

Future trials are awaited to confirm the benefits of adding paclitaxel to standard soft tissue sarcoma chemotherapy in the subset of angiosarcomas. Maintenance chemotherapy with low-dose metronomic paclitaxel could be an option, as well as investigating recent antiangiogenic drugs such as bevacizumab to provide the best treatment options to our patients suffering from this rare and severe condition.

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