



Long-Term Survival of a Patient with Angiosarcoma Treated with Tailored Paclitaxel – A Case Report

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Abstract

Background: Angiosarcomas are rare high-grade aggressive vascular malignancies of endothelial cell origin which account for approximately 1% of all soft tissue sarcomas and have a poor prognosis. The cornerstone of treatment is a large en bloc resection with negative margins, when feasible. However, the aggressive behavior, the diffuse pattern and the clinically undetectable spread of the disease makes a complete resection very difficult to achieve. At presentation, inoperable or metastatic disease is common. A phase II study has demonstrated clinical benefit and reasonable tolerance to treatment with paclitaxel.

Case presentation: A 68 year old man presented with facial angiosarcoma. After a multidisciplinary evaluation, the disease was considered locally advanced and not amenable to curative-intent surgery. Weekly paclitaxel was chosen as first-line treatment, starting on October 2009. Partial response was achieved after approximately 2 months of chemotherapy. Ten months later systemic treatment was stopped and the patient was evaluated by the radiation oncologist, a total dose of 60 Gy was delivered. Two months later, a rapidly progressing cutaneous recurrence in the irradiated area with nasal bleeding was noted. Due to the previous prompt and excellent response, treatment with paclitaxel was resumed, using the same weekly schedule. Again, partial response was achieved. At that point, it was reasonable to plan a long-term maintenance treatment with tailored schedule; paclitaxel was administered every 2 weeks. After more than 4 years of maintenance therapy, with an interval between consecutive administrations of no longer than 2 weeks, the patient is still in almost complete remission.

Conclusion: We report long-term survival of a patient treated with tailored paclitaxel regimen which enabled the improvement of the therapeutic index and reduced toxicities.

Keywords: Angiosarcoma; Paclitaxel; Long-term survival

Background

Angiosarcomas (AS) are rare high-grade aggressive vascular malignancies of endothelial cell origin (vascular or lymphatic) which account for approximately 1% of all soft tissue sarcomas and have a poor prognosis with an overall 5 year survival of about 35%. These tumors are most commonly diagnosed between the fifth and seventh decades of life, have a similar distribution among sexes and may arise from any anatomic site, most frequently detected on head, neck, extremities and breast [1].

AS displays clinical heterogeneity in terms of presentation and behavior. Various clinical forms have been described including primary AS of the scalp, AS associated with lymphedema, primary breast AS, AS arising from irradiated areas and vinyl-chloride induced liver AS. About 3% of all cases occur in genetic predisposing syndrome such as bilateral retinoblastoma and Recklinghausen neurofibromatosis [2]. These clinical presentations share an aggressive behavior, leading to a short median survival (15 to 30 months) [3].

In early stages, lesions are frequently confused with benign cutaneous diseases, infectious conditions or posttraumatic bruises and as a result, most patients have a significant delay in diagnosis. It is most commonly presented as a purplish-red papule and are usually painless; the increase in tumor size results in tissue infiltration, edema, tumor fungation, ulceration and intermittent or continuous bleeding; a capsule or a clear border separating normal from abnormal tissue are missing in AS [2,3].

The histological features of AS are abnormal pleomorphic malignant endothelial cells that can be rounded, polygonal or fusiform with or without epithelioid appearance. In areas of well differentiated tumor, vascular sinusoids formed by abnormal endothelial cells

associated with monocyte infiltration can be continuous with the normal vascular chain. In non-differentiated zones the architecture is more chaotic without defined vascular spaces, with multilayered cells forming papillary-like projections into the vascular lumen. The differentiation from melanoma or anaplastic carcinoma can be difficult in fields where the malignant endothelial cells form continuous sheets with hemorrhage and necrosis. In addition to histology, immunohistochemistry can be important to confirm the diagnosis since endothelial markers are typically expressed by AS – CD34, CD31 and VEGF [2].

The primary lesion is multifocal in about 10-15%. Lymph node involvement is present at the initial diagnosis in about 10-15% of soft tissue AS, in about 5% of scalp AS and rarely in primary breast AS. Approximately 15% of patients present with metastatic disease at the time of diagnosis. There is a tendency for metastasis by lymphatic or hematogenous routes, and late local recurrences and metastasis after years of apparent remission and successful local control are well documented. It is estimated that around 50% of the cases will develop distant metastatic disease [1].

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Received June 20, 2016; **Accepted** July 27, 2016; **Published** July 31, 2016

Citation: de Melo AC, Dias MF, Feijoo M (2016) Long-Term Survival of a Patient with Angiosarcoma Treated with Tailored Paclitaxel – A Case Report. J Tumor Res 2: 112.

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Treatment must involve a multidisciplinary team. The mainstay of treatment is a large en bloc resection with negative margins, when feasible. However, the aggressive behavior, the diffuse pattern and the delay to diagnose makes complete resection very difficult to achieve [2].

Radical resection with negative margins and low morbidity may preclude surgery, especially in certain anatomic sites, for example, head and neck region. Similarly to other soft tissue sarcomas, treatment is challenging and for resectable disease, a multidisciplinary approach combining surgery, radiation and/or systemic chemotherapy is usually advocated. In most cases, adjuvant radiotherapy is recommended, studies have shown a significant statistical benefit in median overall survival after adjuvant radiotherapy when compared with surgery alone (36 months versus 9 months, $p=0.033$). Despite these treatments, it is expected that 75% of recurrences will occur within 24 months locally and systemically, leading to a shorter median survival. In spite of the enhanced propensity for local and systemic failure, currently there is no consistent data supporting adjuvant chemotherapy [4].

At metastatic stage or for unresectable disease, as with other histological subtypes of soft tissue sarcoma, classical systemic treatment is based on doxorubicin containing regimens. Many reports suggest a high rate of objective response with doxorubicin-based regimen, but the responses seem to be transient [2]. Anthracyclines and taxanes are the single agents possessing the most effective anti-tumor activity against AS with response rates ranging between 15 and 40% [4-6].

Paclitaxel is an anti-tumor drug with proven activity in solid tumors. Its mode of action involves the stabilization of microtubules through the inhibition of the depolymerization process observed during the metaphase/anaphase transition of mitosis, blocking the normal mitotic spindle formation resulting in mitotic arrest in the late G2/M phase. Additionally paclitaxel exhibits anti-angiogenic activity [4,7,8]. Weekly paclitaxel seems to have a wide spectrum of antitumoral activity including vascular-derived tumors as AS and Kaposi's sarcomas [3].

Paclitaxel was found to be an active agent in retrospective series, as in the report by Schlemmer et al., which analysed 32 patients and described a response rate of 62% and a median time to progression of 7.6 months [7].

The ANGIOTAX study is a multicenter, phase II trial which assessed the efficacy and toxicity of weekly paclitaxel regimen (80 mg/m² on days 1, 8 and 15 every 4 weeks) in patients with metastatic or unresectable AS. The weekly administration of paclitaxel is thought to induce a clear increase in dose-intensity, without significant enhancement of toxicity, for fragile or heavily pretreated patients. The progression-free survival rates after 2 and 4 months were 74% and 45% respectively. The median time to progression was 4 months and the median overall survival was 8 months. The progression-free survival rate was similar in patients pre-treated with chemotherapy and in chemotherapy-naïve patients (77% versus 71%). Overall survival rates at 6, 12 and 18 months were 56%, 38% and 21%, respectively [3].

Onycholysis after prolonged paclitaxel is hypothesized by direct toxicity to the nail bed, inhibition of angiogenesis, a higher dose density and cumulative doses reached with weekly schedules. Overall, onycholysis was reported in 15–25% patients after prolonged paclitaxel treatment [9].

Here we report long-term survival of a patient treated with tailored paclitaxel regimen which enabled the improvement of the therapeutic index and reduced toxicities.

Case Report

A 68 year old white man presented to a dermatologist in 2009 with a 2 months history of a painless livid red color patch like an ill-defined bruise located on the nose which rapidly spread through the nasal pyramid (Figure 1); a skin biopsy was done. The patient was referred to the oncologist four weeks later. He had a diffuse macule in the midface deeply infiltrative, involving the gingival tissue, the jugal mucosa, ulceration on the nose leading to an intermittent bleeding and an echymotic area in the neck surface (Figure 2); absence of cervical lymphadenopathy, despite that he had a very good clinical condition, ECOG performance status (PS) 1.

The initial biopsy showed atypical vascular proliferation with extravascular erythrocytes (Figure 3). The immunohistochemical stain was positive for CD31 (platelet-endothelial cell adhesion molecule) (Figure 4) which substantiated the diagnosis of AS.

An initial imaging evaluation with Computed tomography (CT) of the neck, thorax, abdomen and pelvis was done to delineate the extent of the primary lesion and to rule out the presence of distant metastasis. A laboratory workup which included a complete blood count, the basic metabolic profile and liver function tests were within normal limits. Imaging after a multidisciplinary evaluation, the disease was considered locally advanced not amenable to curative-intent surgery.



Figure 1: Lesion aspect during the first dermatological evaluation. A painless livid red color patch like an ill-defined bruise located in the nose which rapidly spread through the nasal pyramid.



Figure 2: Lesion aspect four weeks after the dermatological evaluation. A diffuse macule in the midface deeply infiltrative, involving the gingival tissue, the jugal mucosa, ulceration on the nose with intermittent bleeding and an echymotic area in the neck surface.

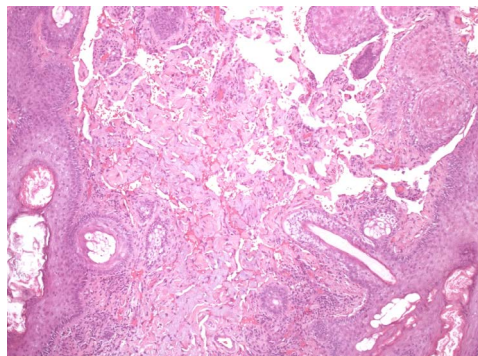


Figure 3: Initial biopsy, hematoxylin and eosin. Atypical vascular proliferation with extravascular erythrocytes suggesting angiosarcoma.

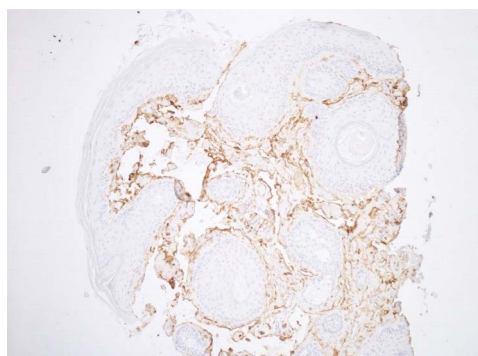


Figure 4: Immunohistochemical stain for CD31. Positive for CD31 (platelet-endothelial cell adhesion molecule) corroborating the diagnosis of cutaneous angiosarcoma.

Paclitaxel 80 mg/m² on days 1, 8 and 15 of a 4 week cycle administered intravenously as a 60 min infusion on an outpatient basis was chosen as a first-line treatment, starting on October 2009. Partial response was achieved after approximately 2 months of chemotherapy. Ten months later systemic treatment was stopped and the patient was evaluated by the radiation oncologist.

Initially, the patient underwent a facial magnetic resonance imaging (MRI) to better outline the area of injury followed by CT planning with conformational image fusion to the MRI for delineation of organs and gross tumor volume (GTV). Treatment planning consisted of anterior and lateral oblique fields in the nasal and oblique fields in the malar region (Figures 5 and 6). A total dose of 60 Gy in 30 fractions (200 cGy/fraction) with 4MV linear accelerator and physical filters was delivered. The patient tolerated radiotherapy well with only grade 1 erythema and dry desquamation assessed according to the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC 3.0). A clear response to treatment was seen from the beginning, leading to nearly complete disappearance of the lesion, classified as partial response in accordance with RECIST 1.0.

However, two months later, a rapidly progressing cutaneous recurrence in the irradiated area with bleeding was noted. Due to the previous prompt and excellent response to systemic therapy, paclitaxel was resumed on February 2011 using the same dose and weekly schedule. After less than 2 months of chemotherapy, a partial response was achieved (almost complete response, only a small nodule inside nasal cavity was left). Due to the clear sensitivity of the disease

to taxane, it was reasonable to plan a long-term maintenance treatment with a tailored schedule in order to reduce toxicity; paclitaxel was administered at the same dose, every 2 weeks and is currently ongoing.

After approximately 4 years of maintenance therapy, with an interval between consecutive administrations of no longer than 2 weeks, the patient is still in partial remission (Figure 7). A locoregional recurrence was documented thrice during this period - the first as a consequence of treatment interruption and two others because of treatment delay when patient was submitted to cataract surgery. Nonetheless, in both instances, a rapid response was achieved as the same treatment was restarted.

The prolonged therapy with paclitaxel was well tolerated, without evidence of any significant adverse effects. He experienced only grade 1 fatigue, grade 1 neuropathy, and nail changes grade 2 (Figure 8). Good quality of life was maintained throughout the treatment as well as patient's daily and social activities.

Conclusion

Angiosarcomas of the skin are aggressive tumors with high rates of recurrence, metastasis and poor overall prognosis [1-7]. Here we report long-term survival of a patient treated with the omission of day 8 of the paclitaxel regimen which enabled the improvement of

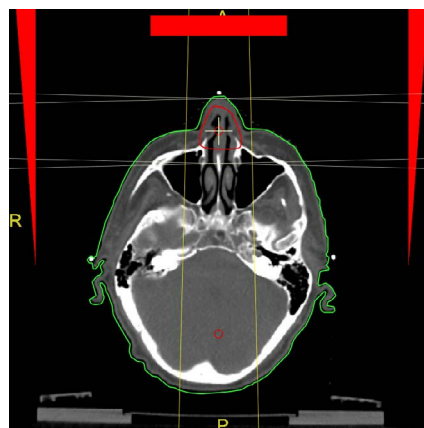


Figure 5: Radiotherapy planning. Treatment planning consisted of anterior and lateral oblique fields in the nasal region.

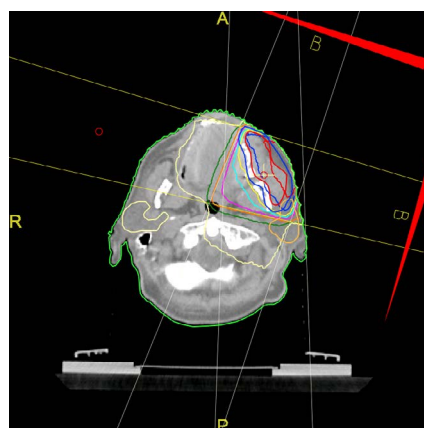


Figure 6: Radiotherapy planning. Treatment planning consisted of oblique fields in the malar region.

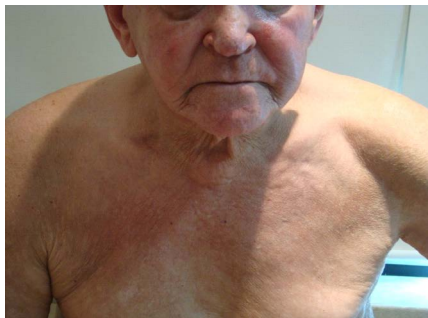


Figure 7: Almost complete remission. After approximately 4 years of maintenance therapy, with an interval between consecutive paclitaxel administrations of no longer than 2 weeks, the patient is still in almost complete remission.



Figure 8: Nail changes grade 2 according to CTCAE 3.0. Onycholysis after prolonged paclitaxel hypothesized by direct toxicity to the nail bed, inhibition of angiogenesis, higher paclitaxel dose density and cumulative doses reached with weekly schedules.

the therapeutic index, reasonable tolerance, clinical benefit and good quality of life. This schedule can represent an alternative, especially for good responders and long-term survivors.

Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Acknowledgement

We thank Doia Jeunon, MD and Thiago Jeunon, MD who have provided the biopsy review and its pictures.

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