A Novel Effective Therapy for Refractory Angiosarcoma of the Face and Scalp

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Case Report

An 85-year-old woman presented with an indurated rash that over the preceding 6 months had progressed to a well demarcated, violaceous lesion covering the majority of the right side of the cheek, temple area, and scalp. The rash was originally thought to represent angioedema from angiotensin-converting enzyme inhibitor medication prescribed for hypertension. Despite a change in this medication, the skin lesion persisted. The patient received a course of antibiotics followed by a course of oral prednisone without benefit. A skin biopsy was obtained and a diagnosis of angiosarcoma was made. The patient's medical history was significant for well-controlled hypertension, bilateral hip replacements due to osteoarthritis, and hysterectomy for dysfunctional uterine bleeding. Her medications included losartan and vitamins.

A limited staging evaluation was performed with a computed tomography scan of the head and sinuses, which revealed only indurated, dermal thickening widely dispersed over the areas noted above. There was no indication of metastatic disease.

The patient was initially treated with paclitaxel 90 mg/m^2 weekly. At the 6th week assessment, a partial response was noted, with resolution of the discoloration and reduced thickness of the facial lesions. The skin, however, remained indurated. Following a 2-week break, paclitaxel at 80 mg/m^2 was resumed for an additional 15 weekly doses. At the final visit, her skin appeared normal.

The patient then moved out of state to a warmer climate. Two months later, her skin lesions started to progress, with reddish discoloration and nodular lesions on the scalp. She received 1 dose of paclitaxel at 175 mg/m^2 with no response. She returned to our center for further care. At that point, she had nodular, violaceous lesions covering the entire right scalp and marked induration of the facial skin.

The patient was treated with gemcitabine at 1,000 mg/m^2 on days 1 and 8, repeated every 21 days. After 3 cycles, a new 1.5-cm violaceous nodule developed on the skin overlying her right mandible near her lip canthus. She was then given third-line treatment with weekly doxorubicin at 25 mg/m^2. Over 4 weeks of treatment, the nodule near the lip canthus grew dramatically to 4 cm in diameter with a necrotic center.

At this time, the patient was treated with concurrent paclitaxel (40 mg/m^2) and local irradiation. The involved submental, right cheek, and scalp regions were treated at 180 cGy daily to 5,940 cGy. The heavily involved right cheek area was then boosted to a total dose of 7,200 cGy. The patient manifested a complete clinical response within 2 weeks post-treatment. A small area of moist desquamation in the submental space and brisk erythema in other areas responded well to silver sulfadiazine ointment and aloe, respectively. Within 2 months, disease progression was again noted, with worsening edema and induration of the right eyelid that had been excluded from irradiation. The scalp lesions migrated across midline over the left vertex. An additional course of re-irradiation with concurrent paclitaxel was provided. The recurrent and new lesions plus a 1-cm margin were treated at 180 cGy daily to a total dose of 3,960 cGy. At the end of the radiation, the patient's lesions had largely resolved.

Unfortunately, the response was brief; 2 weeks after completion of the re-irradiation, the lesions on the right side of the scalp over the previously irradiated areas grew rapidly. She was subsequently treated with multiple lines of chemotherapies, including weekly doxorubicin for 5 additional doses; docetaxel at 35 mg/m^2 on days 1, 8, and 15, every 28 days for 2 cycles; and liposomal

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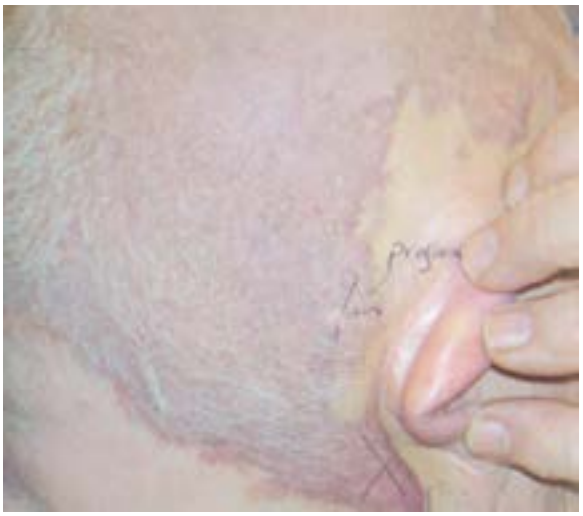

Figure 1. Disease progression after 5 lines of previous therapies.

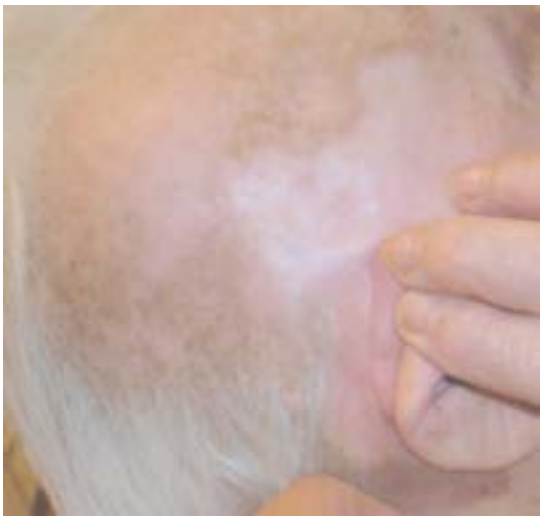

Figure 2. Complete response seen 3 weeks after the novel regimen.

doxorubicin at 45 mg/m^2 every 4 weeks for 2 cycles. It was apparent that her disease was in a refractory status (Figure 1).

At that point, hospice care was discussed, but the patient wished to continue treatment. Various nontested regimens were considered, including thalidomide, sorafenib (Nexavar, Bayer), bevacizumab (Avastin, Genentech), or a metronomic dosing of oral cyclophosphamide (CTX) plus oral methotrexate (MTX). The lack of financial support and concerns about off-label use for these expensive, newer drugs precluded their usage. Metronomic CTX 50 mg oral daily plus MTX 2.5 mg oral twice a day, 2 days per week was initiated.

Two weeks into this treatment, the lesions reddened, with an inflammatory appearance. Three weeks into treatment, complete resolution of the nodular violaceous lesions on the scalp and induration of the face (Figure 2) was noted. The patient was monitored monthly, and she did not experience any reportable adverse effects. She, however, had several episodes of facial skin infection with methicillin-sensitive *Staphylococcal aureus* within the previously irradiated areas, which responded to oral levofloxacin or doxycycline on different occasions. At the eighth-month evaluation, hyperpigmented, indurated skin lesions appeared over the left side of the face, submental chin area, and left temple region. Recurrence was also suspected on the right side of the face and scalp. A biopsy of a right-sided lesion was performed and confirmed recurrence of angiosarcoma. At that point, she requested hospice care, and died 2 weeks later after refusing oral intake.

Discussion

Angiosarcoma is a malignancy of endothelial origin. It is characterized by spreading through local invasion with high recurrence rates after initial local therapy, such as wide excision or irradiation. Chemotherapy, typically taxanes or anthracylines, is only transiently effective in disease control.[1,2] Here, we described a case of angiosarcoma of the face and scalp that followed a typical course of local invasion, initial response to therapy, rapid recurrence, and subsequent refractoriness, which then responded dramatically to a novel, nontoxic regimen. There were several interesting points observed during the disease course.

Among the chemotherapeutic agents given, paclitaxel provided the most benefit, with a 31-week progression-free survival (PFS) interval. Weekly paclitaxel was well tolerated and effective. Certainly, the effectiveness of weekly paclitaxel in this case could be attributed to its frontline usage. Weekly doxorubicin was also well tolerated, and provided temporary disease stabilization. Gemcitabine and docetaxel demonstrated limited activity likely due to their utilization late in the disease course. Radiation therapy with low-dose weekly paclitaxel was well tolerated and provided a dramatic but short-lived response of less than 2 months.

Of greatest interest was the rapid and complete response seen with the oral metronomic dosing of CTX and MTX. This treatment program had no side effects. It was convenient for the patient and the least expensive of any therapy received. Its effect was rapid and dramatic;

within 2 weeks the lesions had reddened with an inflammatory appearance mimicking disease progression but without extension of the existing lesions. By the end of the third week, all lesions had disappeared. The 32-week PFS interval achieved with CTX/MTX at the sixth line (including radiation therapy) setting was unexpected and extraordinary in that it produced a similar PFS to paclitaxel—which is known as one of the most active agents in this malignancy—given in the first-line setting.[1,2]

This low-dose metronomic program of CTX and MTX has no cytotoxic effects. The mechanism of action is believed to be via antiangiogenesis.[3] This approach was initially studied and has been used in the treatment of metastatic breast cancer, with some benefit in the frontline setting.[4] It is unclear whether such dramatic benefit, as seen in our patient, would have occurred with initial usage of metronomic CTX/MTX. It is possible that the first 5 chemotherapy programs and radiation treatments had a priming effect, rendering the malignancy vulnerable to the later antiangiogenesis effect.

Single-agent metronomic trofosfamide, an alkylating agent structurally related to CTX and ifosfamide, has been used in relapsing angiosarcoma with successful disease control.[5] It is therefore possible that a similar response to that seen herein could have resulted with omission of MTX.

This treatment program provides an economical, effective, and nontoxic therapy in the disease relapse setting, and may warrant further testing in the frontline treatment of this challenging malignancy.

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Review

Metronomic Chemotherapy for Advanced Cutaneous Angiosarcoma

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Therapeutic Challenges in Cutaneous Angiosarcoma

Jiang and colleagues[1] describe a typical presentation of cutaneous angiosarcoma, which most commonly affects the elderly and involves the face and scalp.[2,3] Angiosarcoma is a rare but aggressive subtype of soft-tissue sarcoma; prognosis is usually dismal. It can be further subclassified into cutaneous angiosarcoma, soft tissue angiosarcoma, primary breast angiosarcoma, lymphedema-associated angiosarcoma, and radiation-induced angiosarcoma, although the biologic difference between these subtypes has not been conclusively defined.

The case study illustrates several therapeutic challenges presented to the clinician in the management of patients with cutaneous angiosarcoma. Firstly, it may initially resemble benign skin pathologies, leading to delayed diagnosis. Often, with its infiltrative and multifocal nature, surgical resection is either not feasible at the time of diagnosis, or complicated by involved margins and high relapse rates.[2] In elderly patients with advanced disease, systemic therapy with cytotoxic chemotherapy or biologic agents may be associated with tolerability and safety concerns. Control of local complications including tumor fungation, ulceration, hemorrhage, or infection may also be difficult, with cosmetic implications. Finally, there is a lack of studies in the literature to guide clinical practice; most recommendations are based on retrospective case series or soft tissue sarcoma trials including heterogeneous subtypes.

Currently, conventional cytotoxic chemotherapy—with anthracyclines, ifosfamide or taxanes—is the mainstay of treatment in advanced angiosarcoma, but is

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limited by its modest efficacy, significant toxicities, and rapid emergence of drug resistance, as discussed by Young and colleagues.[4]

Metronomic Chemotherapy in Cutaneous Angiosarcoma

In an attempt to overcome these shortcomings of conventional chemotherapeutic regimens, metronomic chemotherapy, with its potential antiangiogenic effect, has attracted much interest in the treatment of angiosarcoma, an endothelial-cell–derived tumor particularly dependent on angiogenic signaling. Vascular endothelial growth factor (VEGF) and its receptors are highly expressed in angiosarcoma.[5]

Metronomic chemotherapy involves rescheduling of drug administration such that low doses of chemotherapeutic agent(s) is/are given continuously or frequently without extended treatment breaks.[6] This strategy primarily works by targeting genetically stable endothelial cells of tumor blood vessels rather than actively proliferating tumor cells, as with conventional chemotherapy schedules; immunomodulation has also been implicated in its mechanism of action.[7] The antiangiogenic effect of metronomic treatment was first observed in preclinical xenograft models.[8-11] As reviewed by Scharovsky and associates,[7] in the clinical setting, results of metronomic chemotherapy trials in various cancer types including breast, non-small-cell lung, lymphoma, melanoma, and prostate cancer are encouraging, some also showing reduced VEGF levels with treatment.[12,13] In addition to its antitumor efficacy, metronomic dosing is also associated with sustained tumor regression (as endothelial cells are genetically stable and less mutagenic than dividing tumor cells) and minimal acute toxicities, allowing prolonged treatment duration and use in patients with advanced age or comorbidities.

A recently published retrospective study evaluated metronomic oral cyclophosphamide and prednisolone in 26 advanced soft tissue sarcoma patients aged 65 or older with contraindications for doxorubicin, including 3 patients with angiosarcoma.[14] An overall response rate of 26.9% was reported; approximately half of the patients had stable disease for at least 12 weeks. The regimen had a favorable toxicity profile, and out-patient treatment was possible. In another pilot study involving 5 patients with angiosarcoma and 1 with hemangioendothelioma progressive or recurrent after first-line treatment, metronomic trofosfamide combined with pioglitazone and rofecoxib until progression achieved high efficacy and tolerability.[15] Specifically, of the 2 patients with cutaneous angiosarcoma of the facial skin, 1 had complete response for 6 months and the other died after 4 months of pneumonia unrelated to treatment or disease. Finally, case reports have described complete remissions achieved by metronomic trofosfamide in metastatic angiosarcoma[16] and by metronomic docetaxel in inoperable angiosarcoma of the scalp, with a progression-free survival of 2 years in one particular patient.[17]

Concordantly, in the current case study, Jiang and colleagues report the use of metronomic cyclophosphamide and methotrexate in a heavily pretreated elderly patient with cutaneous angiosarcoma, resulting in complete resolution maintained for 8 months. In addition to the antiangiogenic effect of metronomic schedules, both cytotoxic agents were shown in the laboratory to intrinsically inhibit vascular proliferation.[18,19] The combination was the first regimen to test the concept of metronomic therapy in the clinical setting,[12] mainly in metastatic breast cancer,[12,20-22] and was shown to be significantly cost-effective.[23] In the management of vascular tumors, this combination represents a logical treatment strategy that warrants further evaluation.

Future Directions

Metronomic chemotherapy is notable not only for its efficacy and tolerability, but also for sustained tumor response. In physically fit patients, this raises the possibility of initial induction of response by conventional intravenous chemotherapy, followed by continuous low-dose oral treatment as maintenance. Moreover, while metronomic chemotherapy exerts its antiangiogenic effect by targeting endothelial cells, biologic agents such as bevacizumab (Avastin, Genentech), sorafenib (Nexavar, Bayer), and sunitinib (Sutent, Pfizer) inhibit specific signaling factors in the angiogenesis pathway. Early-phase clinical trials have demonstrated their single-agent activity in soft-tissue sarcomas including angiosarcoma,[24-27] while newer molecules, including pazopanib (Votrient, GlaxoSmithKline) and axitinib (Pfizer), are under evaluation. The combination of metronomic chemotherapy with various new targeted agents, such as bevacizumab, may maximize angiogenesis blockade and improve clinical outcome. Particularly in cutaneous forms of angiosarcoma where local tumor control is essential for patient well-being, metronomic chemotherapy, especially with radiosensitizing agents, may synergize with radiotherapy.

However, a few practical issues have to be clarified before metronomic chemotherapy can be recommended as an established treatment. The choice of agents and their effective dose have to be better defined. Given the heterogeneity of angiosarcoma patients, the development of predictive and prognostic biomarkers, possibly circulating angiogenic cytokines, is helpful to assist patient selection and response assessment.

In conclusion, the management of advanced cutaneous angiosarcoma is challenging, and current treatment options are limited. Metronomic chemotherapy is a promising treatment modality, and larger scale prospective studies are necessary.

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ERRATUM

Christopher Twelves, MD, did not approve his sections of the printed version of the clinical roundtable monograph "Novel Treatment Options in the Management of Metastatic Breast Cancer," which appeared in the May 2011 issue of *Clinical Advances in Hematology & Oncology*. His approved version of the monograph is available at www.clinicaladvances.com.