Therapeutic Efficacy of Interferon Alfa-2a and 13-cis-Retinoic Acid in Recurrent Angiosarcoma of the Head

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REPORT OF A CASE

A 77-year-old male patient presented with a 2-year history of recurrent angiosarcoma (AS) of the face and scalp. At the time of initial diagnosis, multifocal growth of the tumor was visible. On the left side of the scalp and forehead, several 1- to 5-cm² reddish-brown nodules were noticed, one of which was ulcerated and hemorrhagic. Another 5-cm plaquelike lesion was seen on the left cheek. The presumptive diagnosis of AS was confirmed by histological analysis. X-ray examination of skull and chest, magnetic resonance imaging of the neck, and abdominal ultrasound revealed no evidence of local or distant metastases. Due to the extent of the disease, radical surgery was not an appropriate option. It was thus decided to treat the AS by field electron beam therapy (cheek, 56 Gy; scalp and forehead, each 60 Gy; 2 Gy per fraction), leading to a complete response. Three months after electron beam therapy had been completed, a local recurrence developed in the nonirradiated frontoparietal region. Likewise, this area was successfully treated by field electron beam therapy (60 Gy; 2 Gy per fraction). Six months later, an apparent relapse of the tumor was observed in the electron beam–irradiated field (Figure 1). Examination showed a flat, sharply defined, 30-cm² dusky-red plaque involving the left tragus and preauricular region. Biopsy specimens taken from the cheek revealed typical histological findings of AS (Figure 2). No evidence of metastases in repeated staging procedures was observed.

THERAPEUTIC CHALLENGE

Since the relapse of AS developed in an area that had been pretreated by electron beam therapy, an alternative therapeutic approach was required. Facing rapid extension of recurrent AS in the absence of defined effective therapeutic regimens, a novel modality of systemic treatment for AS was considered.

SOLUTION

The patient was treated with subcutaneous interferon alfa-2a (6 × 10⁶ U/d) in combination with oral 13-cis-retinoic acid (1 mg/kg daily). During the following 8 weeks, further progression of the lesions was not observed. Subsequently, a manifest regression of the lesions became visible clinically. The bluish-red ecchymosillike plaque in the left preauricular region changed to a brown macular lesion and even resolved completely in the temporal areas (Figure 3). Three skin biopsy specimens were taken to confirm regression and clearance of the lesions. Histopathological examination revealed no evidence of AS. Solely hemosiderin deposits were detected (Figure 4). To monitor the drug toxicity, laboratory tests, including liver function tests, serum lipid profiles, and complete blood cell counts (to detect myelosuppression associated with interferon alfa-2a), were regularly performed, with results being normal. The treatment regimen was maintained for 4 months, during which no evidence of AS recurrence or progression was observed. Subsequently, after 6 months, the dosage was reduced to ease adverse effects (e.g., mucocutaneous dryness, fatigue, and myalgia). 13-cis-Retinoic acid was decreased to 0.5 mg/kg daily and interferon alfa-2a (6 × 10⁶ U) was given only 3 times per week. Twenty months after initiation of therapy, the state of disease remains stable with lack of any relapse or progression.

COMMENT

Cutaneous AS is an uncommon, malignant tumor presumably originating from endothelial cells. Angiosarcoma accounts for less than 1% of skin malignancies of the head and neck. Usually cutaneous AS presents on the scalp (>50%) of elderly patients but can also occur in any other region of the body and in internal organs. Initially, AS may be difficult to diagnose on the basis of clinical features, as it can resemble infectious or inflammatory processes. The clinical presentation includes red to dusky nodules, large diffuse spreading plaques, or ul-
Angiosarcoma is characterized by multifocal infiltrating growth, often extending far wider than its clinical appearance would suggest. Overall prognosis is poor, with a mean survival of about 20 months after diagnosis.

Cutaneous AS of the head and neck represents a therapeutic challenge. Due to the rarity of the disease, standard treatment strategies have not been established. Cure of AS by radical excision alone is scarce. Even surgery that respects adequate resection margins remains associated with a high rate of local recurrence due to multifocal growth and inapparent transdermal expansion of AS. In addition, most patients are diagnosed as having lesions too extensive to allow sufficient radical surgery, in particular on the head and neck due to anatomical restrictions. Thus, radiotherapy is often used as an adjunct to surgery to provide improved local control and survival. Yet standard
radiation protocols have not been defined due to incomplete documentation and lack of efficacy assessment. Typically, irradiation with high-energy electrons using doses of 60 Gy at 2 Gy per fraction is recommended.4 Even after a combined surgical and radiotherapeutic approach, only a few patients will be cured. In most patients, AS recurs at local and distant sites, frequently accompanied by lymphatic and organ metastases, thus underscoring the need for effective second-line systemic therapy.

Information and documentation on effective systemic chemotherapy of AS is limited. In a series of 9 patients, doxorubicin was given either alone or in combination with radiotherapy, resulting in a median survival of 18 months.5 Only recently, Casper and colleagues6 described encouraging results of regressions in 3 patients with AS after systemic paclitaxel therapy. A treatment alternative that has not been evaluated for AS therapy is the combination of subcutaneous interferon alfa-2a and oral 13-cis-retinoic acid. This regimen has been previously demonstrated to be effective in cutaneous T-cell lymphoma7 and in tumors of epithelial origin.8 Preliminary observations communicated by Burgess et al.9 in 1996 suggested efficacy of this combination treatment in AS, which prompted us to consider this regimen in our patient as well. The molecular mechanisms by which the combination therapy mediates its antitumor effects in AS are yet to be determined. A large body of in vitro data demonstrated increased responsiveness of genes stimulated by interferons (IFNs) through retinoid-induced cell differentiation.10 This effect is thought to be conveyed in part by induction or increase in IFN receptor expression.11 In addition, induced cell differentiation, itself as a principal effect of retinoids, is substantially potentiated by interferon alfa-2a.12 Thus, retinoids and IFNs may exert their established antiproliferative, differentiative, antiangiogenic, and immunomodulatory properties through molecular mechanisms that complement each other.8 This assumption is supported by preclinical and clinical data indicating that combinations of retinoids and IFNs have enhanced and synergistic activities in different cell and tumor settings.10 A further strength of the combination is the non-overlapping and reversible toxicity. Whereas retinoic acid mainly causes concentration-dependent mucocutaneous dryness, the adverse effects of interferon alfa-2a are dominated by flu-like symptoms and fatigue.12 In our patient, fatigue and myalgia were the leading symptoms (World Health Organization grade 2), which prompted us to reduce the dosage of treatment to maintain good patient compliance.

Together, we here describe the effectiveness of 13-cis-retinoic acid and interferon alfa-2a combination therapy in a patient with recurring cutaneous AS of the head after radical radiation treatment. In the follow-up period of 20 months, the patient has remained free of disease. However, it is unknown whether the AS has really been eradicated or has only been suppressed. We assume that treatment needs to be continued to prevent recurrence. Nonetheless, combination therapy of oral 13-cis-retinoic acid and subcutaneous interferon alfa-2a may represent an effective second-line treatment for recurrent AS. We intend to keep the current dosage for a total period of 2 years before lowering the dose of 13-cis-retinoic acid in small decrements, while maintaining the present interferon alfa-2a treatment. Whether this combination treatment may also serve as alternate adjuvant therapy for AS needs to be determined. We believe that our observed promising efficacy of combined 13-cis-retinoic acid and interferon alfa-2a treatment justifies further evaluation of this regimen in patients with AS, both in a second-line situation and in an adjuvant setting.

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REFERENCES


Editorial Comment: Subcutaneous interferon alfa-2a and oral 13-cis-retinoic acid may offer a ray of hope for patients with angiosarcoma, considering its dismal prognosis. However, larger patient series will have to be studied to determine if the remission observed in this patient is an isolated case or if the observed therapeutic effect is reproducible. Early detection and aggressive surgical intervention with careful surgical margin examination should still be considered the first-line treatment of angiosarcoma.

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