

Multiple Keratoacanthomas Arising in the Setting of Sorafenib Therapy: Novel Chemoprophylaxis With Bexarotene

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Introduction

Sorafenib is a novel antineoplastic drug that targets multiple intracellular and cell-surface kinases, inhibiting tumor cell proliferation and angiogenesis. While it is currently approved to treat metastatic or unresectable renal cell or hepatocellular carcinoma, studies are underway to evaluate its utility in other solid organ tumors. We present a case of a 61-year-old woman with metastatic ovarian cancer and no history of skin cancer who developed multiple keratoacanthomas while on a clinical trial using sorafenib. Surgical excision was performed palliatively for large and symptomatic lesions. Because of the patient's terminal condition and unwillingness to undergo multiple surgical procedures, we instituted chemoprophylaxis with oral bexarotene. After two months of therapy, the patient has reported partial regression of some of the tumors and has not developed any new lesions.

This is the second known report of multiple keratoacanthomas arising in the setting of sorafenib therapy.¹ In addition, this is the first known report of using bexarotene for chemoprophylaxis or treatment of keratoacanthomas.

Case Report

In 2006 at another institution, a 60-year-old woman with no history of skin cancer was diagnosed with ovarian cancer of the papillary serous adenocarcinoma type. She underwent surgical debulking of the tumor as well

as two cycles of paclitaxel and carboplatin chemotherapy and four cycles of docetaxel and carboplatin. Subsequently, her serum CA-125 level returned to normal, indicating remission of the cancer. However, 5 months after completing chemotherapy, her serum CA-125 level again elevated to 95 from a nadir of 5, indicating that cancer had returned. A PET/CT scan confirmed multiple hypermetabolic peritoneal masses as well as right inguinal nodal activity. An excisional biopsy was performed on the right inguinal node, and histology disclosed metastatic adenocarcinoma. The patient was referred to our institute for consideration of a clinical trial. In late 2007, she began a clinical trial using a combination of carboplatin, paclitaxel, and sorafenib.

The patient continued her monthly follow-up meetings in the Gynecologic Oncology Program. Three months after beginning treatment with carboplatin, tamoxifen, and sorafenib, she reported a rapidly enlarging, non-healing erythematous papule on her left nares and presented to dermatology for evaluation. By this time, she had developed a similar lesion on the left leg (Fig 1). Histologic examination of these lesions revealed well-demarcated crateriform squamous proliferations with a central keratin plug consistent with ker-



Fig 1. — Keratoacanthoma on the lower part of the left leg.

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atoacanthomas (Fig 2). Both tumors were surgically excised. Within 2 months, she developed 2 more keratoacanthomas located on her left calf and right forehead. Due to the large size and rapid growth of the tumors, the patient elected to undergo surgical excision. In the next few months of dermatology follow-up, she developed 6 new erythematous papules with a central hyperkeratotic core on her lower extremities (Fig 3). Despite a previous report implicating sorafenib in the development of keratoacanthomas, the patient and her oncology team elected to continue on the clinical trial because the benefits of this treatment for her ovarian cancer were deemed to exceed the risks of developing new skin tumors.

Taking into consideration her metastatic ovarian cancer and the likely development of additional lesions, the dermatology team and the patient agreed that an alternative to multiple surgical procedures was necessary. Since oral retinoids have been successfully used to treat multiple keratoacanthomas, we discussed chemoprophylaxis utilizing an oral retinoid for systemic effect, specifically acitretin. Because of insurance coverage issues, she was unable to obtain this medication, but she was able to obtain coverage for bexarotene.

Since our treatment team was experienced with prescribing bexarotene to patients with cutaneous T-cell lymphoma, we started the patient on oral bexarotene 75 mg

twice a day. After 1 month of treatment, the patient noticed only minimal improvement. Therefore, her bexarotene dosage was increased to 75 mg every morning and 150 mg at night. Her thyroid function and lipids remained within normal limits for the first 2 months of therapy, but during the third month, her free T4 dropped to 0.51 ng/dL and her triglycerides increased to 294 mg/dL. She was subsequently started on levothyroxine and fenofibrate by her primary care physician. After 3 months of treatment with bexarotene, 5 of the 6 remaining keratoacanthomas completely resolved, leaving only postinflammatory hyperpigmentation. The 1 remaining lesion was less than half of its original size (Fig 4). The patient has not developed any new lesions, and she has continued the chemotherapy with sorafenib as well as the bexarotene for chemoprophylaxis of keratoacanthomas. It appears that bexarotene provided a nonsurgical alternative for management of her multiple keratoacanthomas.

Discussion

Sorafenib, a bisaryl urea, was approved by the US Food and Drug Administration in 2005 for the treatment of renal-cell carcinoma and has shown promising results against hepatocellular carcinoma. It is thought to have broad antitumor activity against colon, breast, and non-small cell lung cancers.² Sorafenib inhibits wild-type

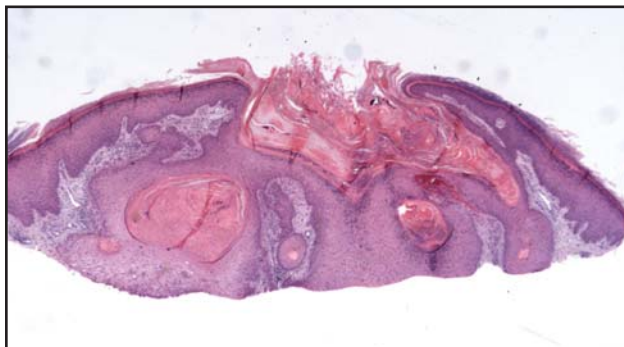


Fig 2. — Histology: keratoacanthoma on the lower part of the left leg.



Fig 3. — Large keratoacanthoma on left leg. Note smaller lesion visible on inferior anterior leg.



Fig 4. — Lower legs after treatment with bexarotene. Note one remaining lesion on left anterior lower leg and hyperpigmented macules at sites of regressed keratoacanthomas.

RAF gene products and several tyrosine and serine/threonine kinases, thus inhibiting tumor cell proliferation and angiogenesis.^{1,3} Sorafenib is fairly well tolerated; common side effects include fatigue, diarrhea, and hypertension. Multiple cutaneous effects have been reported including hand-foot skin reaction, alopecia, pruritus, dry skin, and flushing.³ Keratoacanthomas in the setting of sorafenib therapy is a known but rare adverse effect, having been reported only twice in the English literature.^{1,4}

Keratoacanthomas are controversial lesions in dermatology. The debate over whether keratoacanthomas are a variant of squamous cell carcinomas or benign tumors has yet to be resolved. These tumors are generally considered to be either squamoproliferative follicular-based tumors that resolve spontaneously or a variant of squamous cell carcinomas that can involute or invade.⁵ Clinically, keratoacanthomas are easily diagnosed as rapidly growing nodules with a central necrotic core.⁵ However, the histopathology is not clear cut, thereby creating the controversy in diagnosis and management. Proposed causes of keratoacanthomas include immunosuppression, photodamage, viral infection (human papilloma virus), genetic predisposition, and carcinogen exposure.¹ Eruptive keratoacanthomas of the Grzybowski variant are rare, generally appearing sporadically in middle-aged to older patients who may have hundreds of lesions in a generalized distribution. While the exact cause of the eruptive onset of these lesions is unknown, the Koebner phenomenon has been described, as well as a few cases associated with internal malignancy. This should be distinguished from multiple keratoacanthomas of the Ferguson-Smith type, which are inherited in an autosomal dominant manner, are present in young Scottish patients, and heal with scarring.

Several options for the treatment of keratoacanthomas exist such as surgical excision, radiation, or medical therapy.⁶ Medical chemoprophylaxis for keratoacanthomas includes the oral retinoids. The mechanism by which oral retinoids treat keratoacanthomas is not clearly understood. One theory is that retinoids inhibit keratinization by modulating the terminal differentiation of epidermal cells.⁷ Historically, isotretinoin and acitretin have been used successfully for this purpose, as has etretinate, which is no longer commercially available in the United States.⁷ In our patient, we instituted off-label treatment with oral bexarotene.

Bexarotene is an RXR-selective inhibitor approved for the treatment of cutaneous T-cell lymphoma. Hypertriglyceridemia and hypothyroidism are known common adverse effects of bexarotene; rare side effects include leukopenia and neutropenia.⁸ Baseline laboratory studies are recommended and include complete blood counts, liver function tests, creatine phosphokinase (CPK), lipid panel, thyroid-stimulating hormone (TSH), free T₄, and a pregnancy test. Laboratory work

should be monitored weekly on any dose of bexarotene until all values are stable, then once a month is sufficient.⁹ Of note, because bexarotene centrally depresses thyroid function, free T₄ is more accurate than TSH for monitoring thyroid function. Bexarotene is available in 75-mg capsules, and the recommended initial starting dose for treatment of cutaneous T-cell lymphoma is 300 mg/m² body surface area per day according to the manufacturer. However, increasing the dose will result in higher incidence of adverse effects.¹⁰ In our experience in treating cutaneous T-cell lymphoma, lower doses are often effective. Therefore, we often prescribe starting doses of 150 mg/day.

In an algorithm suggested by Talpur et al,⁹ patients can be started as high as 300 mg/day if their laboratory values are within normal limits. If a patient has baseline abnormalities in thyroid function or modestly elevated triglycerides (< 250 mg/dL), the authors recommend that the patient begin levothyroxine 0.025 mg/day or a low-dose lipid-lowering agent 1 week before beginning bexarotene.⁹ If the patient's triglycerides are > 250 mg/dL, they recommend that the lipids be normalized before initiating a low dose of bexarotene at 100 to 200 mg/day.⁹ If during the course of therapy triglycerides rise to between 400 and 800 mg/dL, bexarotene can be continued and the lipid lowering agent increased, but if the triglycerides rise to more than 800 mg/dL, then the bexarotene should be discontinued, at least temporarily.⁹ The authors of this study found that combining statins with fenofibrate resulted in the best control of patients' lipids, but they acknowledge that this creates the risk of myopathy and rhabdomyolysis. None of the patients in their study developed myopathy or rhabdomyolysis while taking atorvastatin, fenofibrate, and bexarotene.⁹ Combining gemfibrozil with bexarotene increases the risk of toxicity due to impaired hepatic metabolism and should therefore be avoided.

In summary, to minimize the adverse effects in our patient, we prescribed a regimen of 150 mg/day. At this dose, the keratoacanthomas partially regressed, but new lesions still appeared. When the dose was increased to 225 mg/day, no new lesions occurred and the remaining ones regressed. As expected, this treatment induced hypothyroidism and hypertriglyceridemia, but these effects were controlled with medical management.

Kong et al¹ reported that discontinuation of sorafenib should be considered if multiple keratoacanthomas requiring surgical procedures continually occur. Yet, the authors also note that the harm of the keratoacanthomas must be weighed against the possible benefit of treatment with sorafenib. In the above case, because of the limited options to treat the patient's metastatic ovarian cancer, she chose to continue taking the sorafenib and treat her keratoacanthomas. After palliative surgery, bexarotene was chosen for chemoprophylaxis and thus far has had promising results. Since it

is thought that the natural progression of these lesions may sometimes include spontaneous regression, the initiation of bexarotene cannot be confidently stated to cause this. However, the authors suggest that bexarotene be considered as a treatment option in patients with non-resolving keratoacanthomas.

Disclosures

Dr Glass has served as a consultant to Eisai, Inc. The other authors report no significant relationship with the companies/organizations whose products or services may be referenced in this article.

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