Bexarotene in Tumor stage Mycosis Fungoides

R Talpur, M Duvic

Citation

R Talpur, M Duvic. *Bexarotene in Tumor stage Mycosis Fungoides*. The Internet Journal of Dermatology. 2008 Volume 7 Number 3.

Abstract

Dr Rakhshandra Talpur has been a post-doctoral fellow, instructor and research scientist in the Department of Dermatology at The University of Texas, M. D. Anderson Cancer Center for the last eleven years and is a key member of our clinical research team in CTCL. She has worked on numerous clinical trials studying the immunology of T-cell mediated disorders and skin cancers, as well as clinical drug development in T-cell lymphomas, psoriasis, and various skin cancers.

Madeleine Duvic, MD, is Professor of Internal Medicine and Dermatology, and Deputy Chairman of the Department of Dermatology at The University of Texas, M. D. Anderson Cancer Center in Houston, Texas. She is a founding member of the United States Cutaneous Lymphoma Consortium (USCLC), a Board member of the International Society for Cutaneous Lymphoma, and also serves as Director of The Cutaneous Lymphoma Clinic at MD Anderson Cancer Center. Dr. Duvic has also served on the Board of Directors of the American Academy of Dermatology (AAD).

She is certified in Internal Medicine and Dermatology. She has been a principal and co-principal investigator on numerous clinical trials studying the immunology of T-cell mediated disorders and skin cancers, as well as clinical drug development and translational research in T-cell lymphomas, melanoma, and various skin cancers. A prolific author, she has written manuscripts, book chapters, abstracts, and over 300 peer-reviewed journal articles. She is co-author on a recent book on Retinoids and Carotenoids in Dermatology.

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL), including mycosis fungoides (MF) and Sézary syndrome (SS), are often responsive to treatment but current therapies have not been shown to increase survival and, in advanced stages, durable remissions are hard to achieve. There are no long-term studies to determine the optimal duration of bexarotene therapy or how best to taper the dose after a durable response.1 We present a patient who rapidly progressed from patch- to tumor-stage disease and responded rapidly to bexarotene and antibiotics.

INITIAL PRESENTATION

A 65-year-old Caucasian male with a one year history of red scaly patches on his trunk and extremities had a diagnostic biopsy of mycosis fungoides. The lymphocytic infiltrate in the biopsy contained CD3+ and CD4+ T-cells with a CD4 to CD8 ratio of 10 to 1 and a positive gamma gene rearrangement by polymerase chain reaction (PCR). The flow cytometry of the peripheral blood was normal. He had a past history of a serpentine rash on his scalp and biopsy showed erythema marginatum that cleared with intralesional corticosteroids.

TREATMENT COURSE

The patient was started on high and medium potency topical steroids without response. Topical mustargen was prescribed but the patient developed a cough and patches on his feet and lower legs progressed to ulcerated nodules.

In January 2009, he presented to our clinic with difficulty in ambulation due to ulceration of his right foot (Figure 1A) and leg (Figure 1B), papules on his temple, and plaques on his trunk with total body surface area involvement of 2.97% and skin weighted assessment (SWAT) score of 6.17%. A skin culture from a foot ulcer grew methicillin sensitive Staphylococcus aureus, and was treated with Dicloxacillin 500mg twice daily x 28 days. The biopsy showed epidermotropism and an atypical T-cell infiltrate with ulceration and perivascular infiltrate.

Figure 1. Clinical photos (A) ulcerated and nodular lesions (B) red yellow crusty ulcerated lesion on shin at baseline visit.

Figure 1

Figure 1a

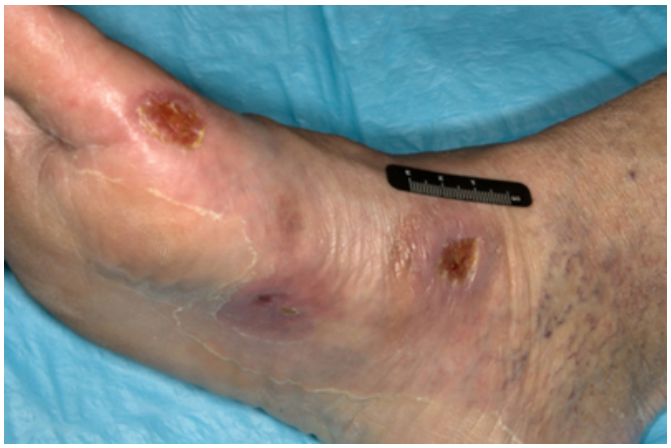
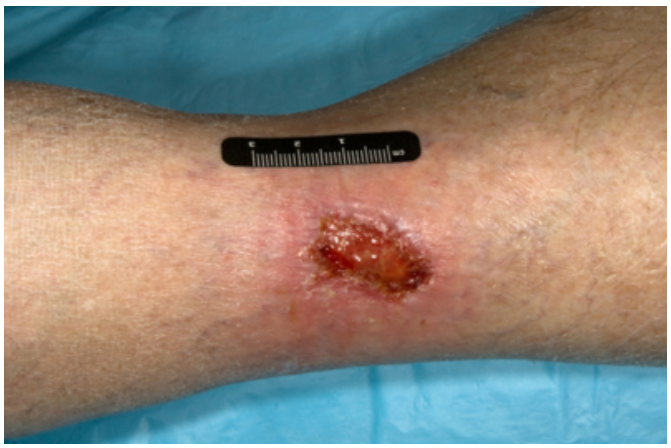


Figure 2

Figure 1b



CLINICAL LABORATORY FINDINGS

Serological studies, including HIV, HTLV, hepatitis panel, C-ANCA, P-ANCAA, ANA, rheumatoid factor, cryoglobulins, Borrelia titer, complement C3 and C4 were negative.

DIAGNOSIS AND STAGE

At initial diagnosis this patient was Stage IA (T1, N0, M0) and the biopsy had a negative gene rearrangement, suggesting a good prognosis. However, his skin lesions progressed from patches to tumors, i.e. stage IIB (T3, N0, M0) and a second biopsy of a tumor did have a positive gene rearrangement.

CONSIDERATIONS FOR DERMATOLOGIST/ONCOLOGIST FROM REFERRING PHYSICIAN

Treatment options for tumor stage Mycosis Fungoides include local skin electron beam therapy, oral bexarotene, denileukin diftitox, vorinostat - a histone deacetylase inhibitor, targeted monoclonal antibodies, or monochemotherapy with doxil or gemcitabine.

Tumors may be exacerbated by Staph aureus infection and improve when the infection is addressed with culture-driven antibiotic therapy and wound care. In this patient, an oncologist might consider giving the patient chemotherapy for his tumors, but the patient would be placed at greater risk for sepsis. Bexarotene, an RXR retinoid, is a first line systemic drug for early and advanced MF patients' cutaneous manifestations of CTCL with a response rate of 45% in advanced patients2. Many specialists are unfamiliar with the management of bexarotene-related side effects of hypothyroidism and hyperlipidemia. As bexarotene may take time to achieve a maximum response, there is an algorithm that recommends therapy should be continued for a sufficient period to allow for a delayed onset of action.

Due to the progressive nature of his disease we planned to add denileukin diftitox if he did not respond to bexarotene. Local skin radiation was also considered as a first line therapy but feet and lower legs have more risk of radiation-induced fibrosis and ulceration with radiation. Since he was colonized, we used a conservative approach of antibiotics, wound care and oral bexarotene.

CLINICAL EVIDENCE

We increased the dose of bexarotene from 150 mg to 450mg and then to 600 mg daily. Levothyroxine was started at 25 mcg and increased to 150 mcg daily. He was also given oral prednisone 20 mg for one month for possible vasculitis. Pravastatin sodium was discontinued due to CK elevated to the 200s and fenfibrate was started. He also used wound care with vinegar soaks and topical mupirocin and silvadene. Three months later, the patient had a dramatic improvement including healing of his skin ulcers. The ulcerated nodular lesion on his foot (Figure 2A) and shin (Figure 2B) resolved, his body surface area involvement reduced from 2.97% to .26% and the SWAT from 6.17% to 0.76% (Figure 1B, 2B).

Figure 2. Clinical photos (A) resolution of the ulcerated, nodular lesion on foot (B) resolution of lesion on the shin after three months of bexarotene therapy.

Figure 3

Figure 2a

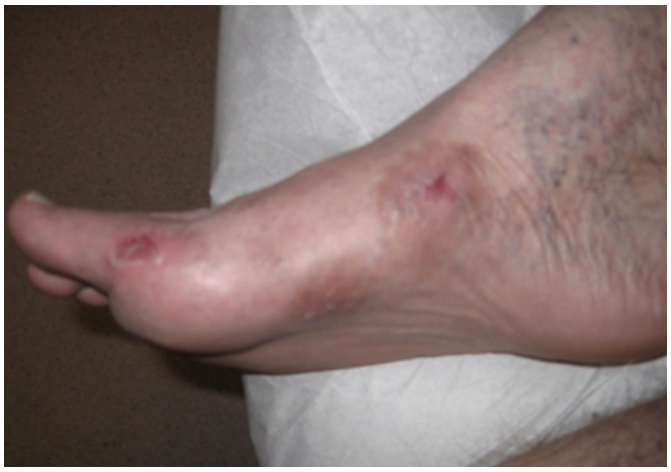
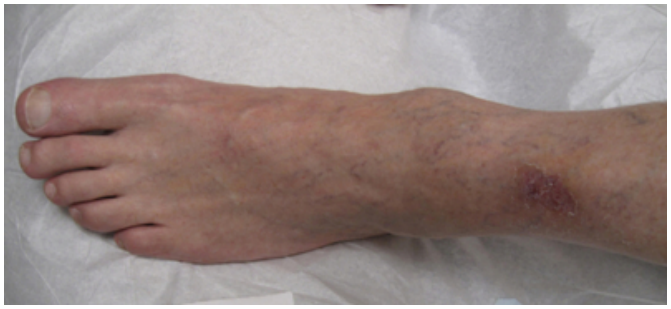


Figure 4

Figure 2b



We plan to continue the bexarotene 600mg/day (8 capsules) for at least six months. If he continues to stay in remission, the bexarotene can be tapered by one pill every other day every three months to 600mg/525mg (8/7 capsules).

TREATMENT GUIDELINES

SKIN DIRECTED CARE

Erythematous or opened ulcers in MF patients are often colonized with Staphylococcus aureus. Topical and oral antibiotics are an important element of the treatment regimen for Mycosis fungoides and SS patients. We recommend rinsing skin with 1:4 parts white vinegar to water or using Lachydrin 5 lotion to lower skin pH and reduce Staph aureus colonization. Cetaphil (glycerin based) or Ceravé (lipid based) are also excellent emollients, as are aquaphor or vasoline for very scaly skin. After moisturizing, topical mupirocin should be applied to open ulcers, triamcinolone cream to patches, and hydrocortisone Eucerin for groin, axillae, and face.

TEACHING POINTS

Bexarotene is an active single agent with a high response rate for the treatment of recurring or refractory CTCL. Bexarotene is the first RXR selective retinoid approved and shown to have an overall response rate of 45-55% in both early and advanced CTCL patients. In the advanced study, 44% of the patients with erythroderma and SS had partial responses to bexarotene as a single agent.2

Hypertriglyceridemia, the most frequent side effect, occurred in 79% patients, and was associated with pancreatitis in a few patients. Central hypothyroidism occurred in 69% of the early stage patients and 35% of the late stage patients.2, 3 Leukopenia and neutropenia are other possible rare side effects of bexarotene.2, 3

Although the recommended dose is 300 mg/m2/day, we suggest starting with 1-3 capsules (75-225 mcg), increasing as tolerated. Thyroid hormone replacement is needed for nearly all patients on bexarotene, and should be adequate to keep the free T4 in the normal range. Thyroid stimulating hormone levels remain suppressed while patients are on bexarotene. We generally use 25 mcg of levothyroxine for each 75 mg capsule starting as soon as bexarotene is administered. Failure to correct the hypothyroidism makes the triglycerides harder to control. Synthroid should be decreased or stopped if bexarotene is discontinued.

Hypertriglyceridemia can be anticipated and thus avoided or minimized by giving concomitant fenofibrate 145 mg with atorvostatin 20-80 mg and omega 3 fatty acid capsules. Low-dose bexarotene (1-3 tablets) can be initiated and the dose gradually increased as tolerated. In order to minimize the bexarotene-associated hyperlipidemia it is important to identify patients with familial hypertriglyceridemia, an individual or family history of myocardial infarction or cardiovascular disease (CV), or a history of diabetes. Many patients with a history of CV will have hypertriglyceridaemia that will need to be treated before starting bexarotene therapy with both fenofibrate at 145mg daily and atorvastatin at 20-40 mg, if there is high cholesterol. Fenofibrate and atorvastatin together should be used with caution since there is a small risk of rhabdomyolysis. Muscle symptoms and creatinine phosphokinase levels should be monitored.

Baseline free T4, thyroid stimulating hormone (TSH), and fasting triglyceride and cholesterol levels (HDL and LDL) should be obtained at baseline at one week of therapy, monthly until stable, and then every three months in all

patients at baseline being considered for bexarotene treatment.

CONCLUSIONS

Bexarotene is effective in the management of CTCL, has the advantage of an oral route of administration, and is generally well tolerated. Our patient was started at a lower dose of bexarotene, and responded when the optimum dose of 600 mg per day was reached. An increase in dose (provided triglycerides remain within acceptable limits) is an option that should be considered before switching to a different therapy.

References

1. Gniadecki R, Assaf C, Bagot M, et al. The optimal use of bexarotene in cutaneous T-cell lymphoma. Br J Dermatol 2007;157(3):433-40.
2. Duvic M, Hymes K, Heald P, Martin AG, Myskowski P, Crowley C, Yocum RC and the Worldwide Bexarotene Study Group: bexarotene is effective and safe for the treatment of refractory advanced stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncology 2001;19:2456-2471.
3. Duvic M, Martin AG, Kim Y. Phase 2 and 3 clinical trial of oral bexarotene (Targretin Capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch. Dermatol 2001; 137: 581-593

Author Information

Rakhshandra Talpur, MD
Division of Internal Medicine, Department of Dermatology, The University of Texas M.D. Anderson Cancer Center

Madeleine Duvic, MD
Division of Internal Medicine, Department of Dermatology, The University of Texas M.D. Anderson Cancer Center