Sustained Remission of Treatment-Resistant Cutaneous T-Cell Lymphoma With Oral Bexarotene

Marilyn A. Mehlmauer, MD

Cutaneous T-cell lymphomas (CTCL) encompass a spectrum of clinical and histologic variants, characterized by malignant CD4+ T lymphocytes in the skin and visceral organs. This is a case report of a 74-year-old man with CTCL, including ulcerative lesions, resistant to multiple systemic therapies. Treatment with oral bexarotene resulted in rapid and sustained remission of both cutaneous and systemic symptoms.

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Cutaneous T-cell lymphomas (CTCL) include a group of extranodal non-Hodgkin lymphomas of T-cell origin with primary cutaneous involvement.[1-5] A chronic malignancy of CD4+ T lymphocytes, the disease may present initially a subtle to well-demarcated, atrophic, scaly, erythematous patches or plaques, usually on sun-protected areas.[1] The patch/plaque variant of CTCL, commonly called mycosis fungoides (MF), is the most frequent form.[2] Disease progression is slow, and CTCL may remain undiagnosed or misdiagnosed for years.[1,6] Established plaque/patch CTCL may progress to a more severe stage, erythrodermic CTCL (Sézary syndrome), which may present as exfoliating, diffuse, bright red cutaneous erythema; ulceration; secondary infection; and extracutaneous involvement.[1,2,4] Nearly all patients eventually exhibit signs and symptoms relating to skin lesions, including pruritus, ulceration, infection, or disfigurement.[5,7]

This report describes a patient with advanced skin involvement with CTCL and palpable lymph nodes. The disease was initially refractory to several systemic therapies. However, marked improvement followed therapy with oral bexarotene, a novel synthetic retinoid analog recently introduced for the treatment of cutaneous manifestations of CTCL refractory to at least one prior systemic therapy.[8,9]

Case Report

In 1990, a 74-year-old white man presented with a 2-year history of an evanescent pink rash, which first appeared on his right calf and progressed despite treatment with topical and parenteral corticosteroids. Disease flares occurred at 3- to 4-month intervals, with spontaneous remissions lasting up to 9 months. During one episode, the patient described spontaneous slow healing of a recurrent large ulcer on the left lateral thigh. The patient reported weight loss, fever, and chills before relapse of cutaneous symptoms, although these manifestations were not confirmed.

In 1991, the patient described himself as being "totally red." His chief complaint was itching. Results of skin biopsies in 1992 and 1993 revealed chronic dermatitis with eosinophilia and chronic dermatitis with epidermotropism, respectively. Findings from a third biopsy in November 1996 were interpreted as granulomatous dermatitis and were not diagnostic for MF. Extensive skin involvement subsequently developed, including scaling of the palms, soles, and scalp and fissuring on the lower extremities with erythematous patches, plaques, and ulcerating tumors. Axillary and inguinal lymph nodes were palpable. Although spontaneously healing ulcers are rare in MF, the overall clinical presentation prompted a diagnosis of granulomatous MF. After review of the patient's previous biopsy material—showing lymphocytes in the epidermis in clusters, focal spongiosis, neutrophils in the stratum corneum epidermidis, and an underlying lymphocytic band-like infiltrate, as well as granulomatous infiltrates

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Dr. Mehlmauer is in private practice in Pasadena, California, and is on the staff at Huntington Memorial Hospital, Pasadena.

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Reprints: Marilyn A. Mehlmauer, MD, 10 Congress St, Suite 320, Pasadena, CA 91105 (e-mail: mmehlmauermd@earthlink.net).

in the dermis—this diagnosis was considered most consistent with the biopsy findings and the clinical presentation. The diagnosis also was confirmed by an independent dermatopathologic review of the biopsy material and was supported by detection of clonal T-cell receptor γ chain gene rearrangements by DNA amplification of biopsy material in several repeated assays.

In February 1997, the patient began monthly photopheresis that continued for 7 months and was associated with steady improvement. The patient's condition ultimately worsened, and therapy was initiated with interferon alfa-2a (3 million IU administered subcutaneously 3 times per week). Treatment, which continued for 9 months, resulted in a partial response. Interferon alfa-2a therapy was discontinued. Although computed tomographic scans remained negative for obvious internal involvement, palpable axillary and inguinal lymph nodes and recurrent ulcerative lesions persisted. A brief course of oral chlorambucil was initiated; however, chlorambucil was determined to be of no benefit and was discontinued. Interferon alfa-2a therapy was then restarted.

Beginning in November 1998, the patient received 20 Gy of electron beam radiation to his left thigh lesion, a therapy that resulted in nearly complete healing. In March 1999, spot radiation therapy (30 Gy in daily fractions of 2.5 Gy) was delivered to a progressive, deep tendon–exposing, necrotic lesion in the right pretibial region. At that time, the patient's largest ulceration measured 18×7.5×0.4 cm. The CD4/CD8 rose from 22 to 27, an increase commensurate with a clinical decline. Interferon alfa-2a therapy was discontinued, and from August to November 1999, psoralen plus ultraviolet A (PUVA) therapy was added (32 treatments, cumulative dose of 293 J).

In January 2000, other treatments were stopped, and treatment with oral bexarotene (200 mg/m^2 per day) was initiated. The clinical presentation of lesions on the patient's buttocks before bexarotene therapy is shown in Figure 1. After 6 weeks of treatment, closure of large ulcerations on the buttocks, arms, and legs was noted. There was clinical resolution of facial and scalp tumors as well. Lymph nodes were no longer palpable; CD4/CD8 dropped to 2.5. The drug was generally well tolerated. A lipid panel revealed elevated serum cholesterol (303 mg/dL) and fasting serum triglyceride concentrations (332 mg/dL). Atorvastatin sodium was prescribed in March 2000.

Figure 2 shows the patient's buttocks after approximately 20 weeks of bexarotene therapy. At that time, the patient reported that he was feeling well and that his hair was beginning to grow in thicker and darker. By July 2000, the patient's skin showed only mild erythema of the face and scaling of the soles. CD4/CD8 was 4.2 as of September 2000, 9 months after the initiation of treatment with oral bexarotene. At the time of this report, the patient had continued treatment with bexarotene with near-complete clinical response.

Comment

Depending on stage of disease, CTCL may be treated with one of a variety of modalities, including topical corticosteroids (complete response [CR] rate, 25% in T1 disease, 60% in T2 disease), topical mechlorethamine hydrochloride or carmustine (CR rate, 70%–80% in T1 disease, 30%–60% in T2 disease), spot radiation therapy, and PUVA (CR rate, ≤90% in T1 disease, ≤70% in T2 disease).[4] More advanced cases may be treated with total body electron-beam therapy; photopheresis; interferon alfa; systemic retinoids (including oral bexarotene); or denileukin diftitox, an injectable recombinant fusion protein targeted to the IL-2 receptor.[10] Systemic chemotherapeutic agents are used only in end-stage disease, if at all.

The retinoids, a class of biologic response modifiers, are derivatives of natural and synthetic vitamin A analogs that bind to and activate intracellular retinoid receptors.[11] Both retinoic acid receptors and retinoid X receptors are found in human skin.[11,12] Once activated, these receptors function as transcription factors to regulate expression of genes controlling cellular differentiation and proliferation in both normal and neoplastic cells.[13] Retinoid acid receptor agonists (eg, isotretinoin [13-*cis*-retinoic acid]) have been used for CTCL both as monotherapy[14] and in combination with PUVA,[15] interferon alfa,[16] and cytotoxic chemotherapy.[17,18]

Bexarotene is the first retinoid X receptor–selective retinoid agonist studied in humans. In patients with early-stage CTCL who are no longer tolerant of previous therapy or whose disease has become refractory to previous therapy, overall response rate to oral bexarotene is approximately 50% (CR rate, 7%) at the recommended dosage, with higher response rates at higher dosages.[8] In patients with refractory, advanced-stage CTCL, overall response rate to oral bexarotene is approximately 45% (CR rate, 2%) at the recommended dosage, also with higher response rates at higher dosages.[9] Extensive or recurrent CTCL may be treated with a combination of skin-directed and systemic regimens.[4]

The patient described here had multiple lesions that remitted and recurred after early local

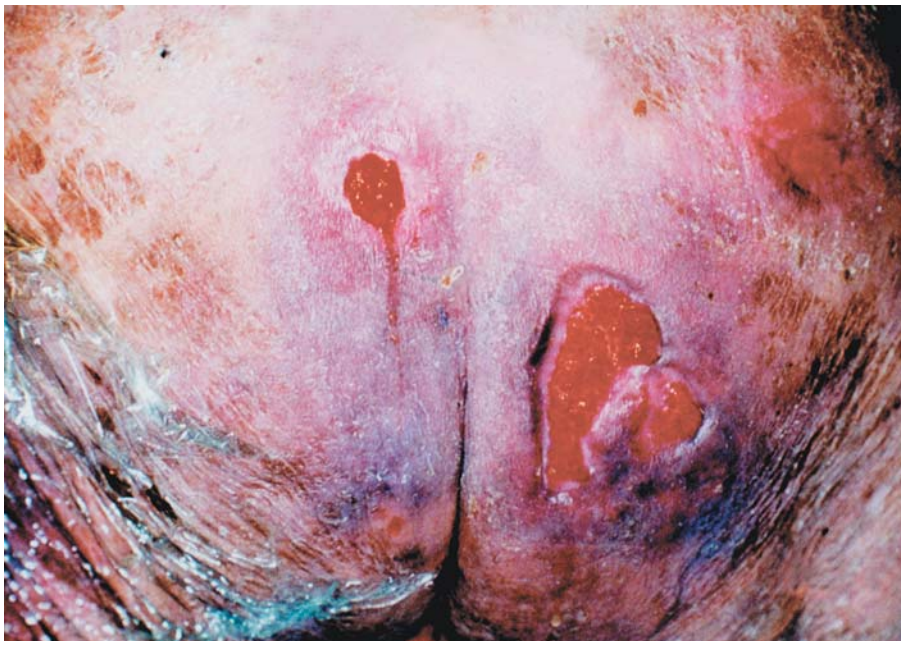

Figure 1. Three ulcerative lesions on the patient's buttocks. Nearby inflamed areas are also in the process of ulceration.

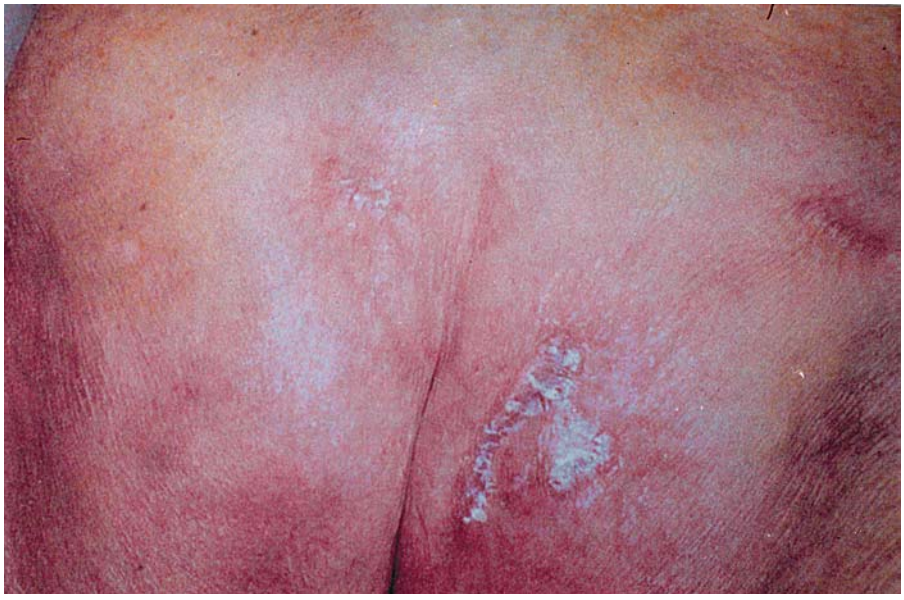

Figure 2. The patient's buttocks after approximately 20 weeks of oral bexarotene therapy.

treatment with topical and parenteral corticosteroids. Topical chemotherapy with mechlorethamine was not considered because the patient had open wounds. The patient's lesions relapsed despite a prolonged course of photopheresis therapy, then became refractory to interferon alfa-2a. The patient initially refused radiation therapy but later consented to local electron-beam treatment for thigh and pretibial lesions. Worsening of other cutaneous symptoms necessitated consideration of an alternative treatment.

Generally well tolerated by most patients, oral bexarotene can produce lipid abnormalities (elevated triglyceride, elevated total and low density lipoprotein cholesterol, and reduced high density lipoprotein cholesterol concentrations), hypothyroidism, leukopenia, and elevations in liver function tests, all of which are reversible on cessation of therapy. The increased serum cholesterol and triglyceride concentrations that developed in this patient were controlled by treatment with a 3-hydroxy-3methylglyaryl coenzyme A reductase inhibitor (atorvastatin sodium).

Blood lipid determinations should be performed before oral bexarotene therapy is initiated and weekly during the first 2 to 4 weeks; subsequently,

if hyperlipidemia does not develop, determinations can be performed less frequently. White blood cell count with differential determination should be performed at baseline and periodically during treatment. Liver function tests also should be performed at baseline and carefully monitored after 1, 2, and 4 weeks of initiating therapy. If liver function remains stable, liver function tests should be performed periodically thereafter during treatment. Baseline thyroid function results should be obtained and thyroid function monitored during therapy, as indicated.

In summary, this patient showed classic worsening CTCL, advancing to widespread, severe, recurrent, and disfiguring cutaneous ulceration; infection; and lymphadenopathy. His disease progressed despite several local and systemic palliative treatments, including photopheresis, oral PUVA, interferon alfa-2a, chlorambucil, and local radiation therapy. The cutaneous and systemic manifestations responded to oral bexarotene in rapid and dramatic fashion. The near-complete remission persisted for 17 months and appears to be continuing.

REFERENCES

1. Girardi M, Edelson RL. Cutaneous T-cell lymphoma: pathogenesis and treatment. *Oncology*. 2000;14:1061-1070.
2. Siegel RS, Pandolfino T, Guitart J, et al. Primary cutaneous T-cell lymphoma: review and current concepts. *J Clin Oncol*. 2000;18:2908-2925.
3. Rook AH, Heald P. The immunopathogenesis of cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am*. 1995;9:997-1010.
4. Kim YH, Hoppe RT. Mycosis fungoides and the Sézary syndrome. *Semin Oncol*. 1999;26:276-289.
5. Diamandidou E, Cohen PR, Kurzrock R. Mycosis fungoides and Sézary syndrome. *Blood*. 1996;88:2385-2409.
6. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood*. 1997;90:354-371.
7. Axelrod PI, Lorber B, Vonderheid EC. Infections complicating mycosis fungoides and Sézary syndrome. *JAMA*. 1992;267:1354-1358.
8. Duvic M, Hymes K, Heald P, et al, for Members of the Bexarotene Worldwide Study Group. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol*. 2001;19:2456-2471.
9. Duvic M, Martin AG, Kim Y, et al, for the Worldwide Bexarotene Study Group. 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.
10. Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol*. 2001;19:376-388.
11. Mangelsdorf DJ, Umesono K, Evans RM. The retinoid receptors. In: Sporn MB, Roberts AB, Goodman DS, eds. *The Retinoids: Biology, Chemistry, and Medicine*. 2nd ed. New York, NY: Raven Press; 1994:319-349.
12. Elder JT, Fisher GJ, Zhang Q-Y, et al. Retinoic acid receptor gene expression in human skin. *J Invest Dermatol*. 1991;96:425-433.
13. Chambon P. The molecular and genetic dissection of the retinoid signaling pathway. *Recent Prog Horm Res*. 1995;50:317-332.
14. Kessler JF, Jones SE, Levine N, et al. Isotretinoin and cutaneous helper T-cell lymphoma (mycosis fungoides). *Arch Dermatol*. 1987;123:201-204.
15. Thomsen K, Hammar H, Molin L, et al. Retinoids plus PUVA (rePUVA) and PUVA in mycosis fungoides, plaque stage. a report from the Scandinavian Mycosis Fungoides Group. *Acta Derm Venereol*. 1989;69:536-538.
16. Knobler RM, Trautinger F, Radaszkiewicz T, et al. Treatment of cutaneous T cell lymphoma with a combination of low-dose interferon alfa-2b and retinoids. *J Am Acad Dermatol*. 1991;24:247-252.
17. Duvic M, Lemak NA, Redman JR, et al. Combined modality therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 1996;34:1022-1029.
18. Zachariae H, Grunnet E, Thestrup-Pederson K, et al. Oral retinoid in combination with bleomycin, cyclophosphamide, prednisone and transfer factor in mycosis fungoides. *Acta Derm Venereol*. 1982;62:162-164.