

Topical Targretin and Intralesional Interferon Alfa for Cutaneous Lymphoma of the Scalp

Jennifer T. Trent, MD; Paolo Romanelli, MD; Francisco A. Kerdel, BSc, MBBS; Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Fla

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 56-year-old man presented with multiple red-violaceous firm, nontender nodules and plaques on the left frontal and parietal areas of his scalp (**Figure 1**). There was no regional lymphadenopathy. The patient denied any fever or chills. His medical history was significant for diabetes mellitus and hypertension, for which he was taking metformin, troglitazone, glyburide, and enalapril maleate. There was no personal or family history of cancer. A skin biopsy specimen from a scalp lesion showed a dense atypical lymphocytic infiltrate suggestive of malignant lymphoma (**Figure 2**). Results of extensive investigation including a bone marrow biopsy, lymph node biopsy, and computed tomographic scan of the chest, abdomen, and pelvis were negative for systemic lymphoma. A specimen from a repeated biopsy was submitted for flow cytometric analysis and Southern blotting for B- and T-cell receptor rearrangement. Immunophenotypic analysis showed a mixture of B and T cells. The T cells showed expression of CD3, CD5, and CD7 with markedly reduced and almost absent CD2, while the B cells expressed CD19, CD20, and CD22 with no evidence of surface immunoglobulin light chain restriction (**Figure 3**). This was suggestive of an atypical T-cell population. There was no T- or B-cell rearrangement on the first Southern blotting examination of the specimen; however, another examination of the specimen, which was submitted for T- and B-cell gene rearrangement analysis with restriction enzymes, demonstrated the presence of a monoclonal B-lymphocyte population indicative of a follicle center B-cell lymphoma. The patient did not want to undergo surgery, radiotherapy, or systemic chemotherapy.

THERAPEUTIC CHALLENGE

The challenge was to find a noninvasive therapy for the patient. The combination of interferon alfa and bexarotene gel (Targretin) appears to be effective in treating primary cutaneous B-cell lymphoma of the scalp.

SOLUTION

The patient was initially treated with intralesional injections of triamcinolone (20 mg/mL), and the lesions improved with flattening and decrease in erythema. However, after 5 injections, 1 per month for 5 months, he reached a point where no further improvement was noted. At this time, his treatment was switched to intralesional interferon alfa. He received a total of 10 injections of 5 million units each of interferon alfa at 4-week intervals for 5 months. The patient's condition improved again with flattening of the lesions; however, the patient required monthly injections because the tumors would reappear. Topical bexarotene gel (Targretin, Ligand Pharmaceuticals Inc, San Diego, Calif), applied twice a day, was then added to the regimen. He responded very well to the combination and, within 2 months, the lesions were completely flat with no clinical evidence of recurrence (**Figure 4**). The patient has been applying the Targretin gel on an as-needed basis, and the need for interferon alfa injections has decreased to every 3 months. The patient has been followed up for 1 year without any recurrence.

COMMENT

There are many therapeutic modalities that can be used for the treatment of primary cutaneous B-cell lymphoma (CBCL).¹⁻⁶ Systemic chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone, as monotherapy or in combination as polychemotherapy, can be used. Fierro et al⁴ showed that the use of COP (cyclophosphamide, vincristine [Oncovin], prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) polychemotherapy resulted in response rates of 98% with a relapse rate of 33%. Santucci et al⁷ showed 100% remission rate, with two thirds of the patients having relapses. In a report by Wong and Weller,³ intralesional steroids were shown to be effective in controlling local skin relapses of CBCL. Furthermore, radiation therapy may be successfully combined with chemotherapeutic agents or administered alone. Berti et al⁸ demonstrated complete remission in 100% of their cases;



Figure 1. Multiple red-violaceous, nontender nodules and plaques on the left frontal and parietal areas of the patient's scalp.

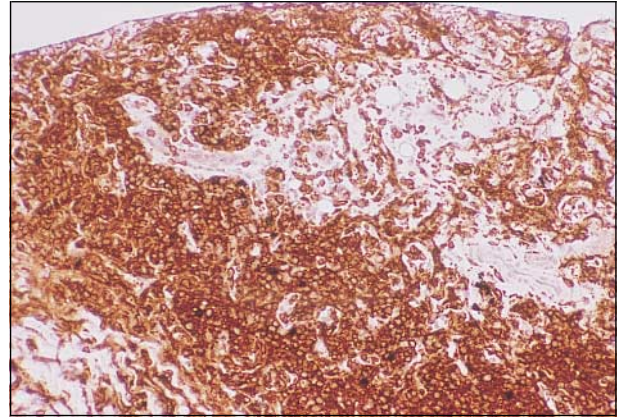


Figure 3. Immunophenotypic analysis of the scalp lesion showing strong positivity for CD20 (CD20 immunoperoxidase, original magnification $\times 15$).

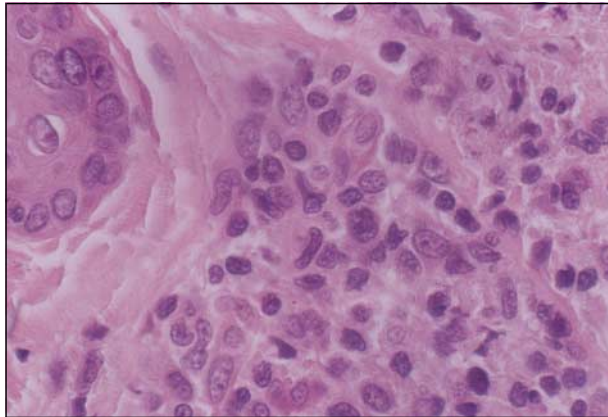


Figure 2. Histologic examination of the scalp lesion showing a dense atypical lymphocytic infiltrate suggestive of malignant lymphoma (hematoxylin-eosin, original magnification $\times 40$).



Figure 4. Complete clinical response to the combination therapy.

however, there were a large number of relapses (14/44). Piccinno et al⁹ also showed 100% complete remission rate with 68% relapse rate. There are also reports of intralesional cisplatin and intralesional interferon alfa as effective therapy. There are a couple of case reports regarding the use of intralesional interferon alfa for CBCL. Santucci et al⁷ reported that 1 of the 2 patients treated had complete remission. However, the dosage and frequency of treatments were not discussed. Zenone et al⁵ treated 1 patient who had complete remission with intralesional interferon alfa after failing 5 treatments of polychemotherapy and radiation. For the first 2 months the patient received 3 million units every week, then 5 million units was given every week for 4 months. Finally, the patient received 10 million units every month for 6 months. The patient had no recurrence 1 year after treatment. More recently, systemic and intralesional rituximab, an anti-CD20 monoclonal antibody, has produced excellent response rates. We know of no published reports regarding the treatment of CBCL with Targretin or topical alitretinoin gel (Panretin, Ligand Pharmaceuticals Inc). Therefore, when considering treatment options, it is necessary to select the drug that is safe, effective, and convenient.

The use of bexarotene (Targretin), a retinoid that selectively activates the retinoid X receptors, has been used in the successful treatment of cutaneous T-cell lymphoma (CTCL), has shown substantial results in acquired immunodeficiency syndrome–related Kaposi sarcoma, and has prolonged survival of patients with non-small cell lung carcinoma and advanced renal cell carcinoma (when combined with interferon alfa).¹⁰⁻¹⁸ Bexarotene is a member of a class of retinoids that selectively activate the retinoid X receptors. When these receptors are activated, they function as transcription factors that regulate gene expression.¹⁰⁻¹³ These genes cause apoptosis. Retinoids that activate the retinoid A receptors have been shown to control cell differentiation and proliferation.

Oral bexarotene has been used for the treatment of CTCL. However, its use is accompanied by important adverse effects. Bexarotene use can elevate triglyceride levels, leading to pancreatitis; can cause central hypothyroidism; and can elevate transaminase levels.^{10,11,13,14} Laboratory evaluation has to be undertaken prior to beginning therapy with bexarotene, then weekly for the first 4 weeks and every 8 weeks thereafter, as long as the laboratory values are stable. Its use is also contraindicated in pregnancy given its teratogenic effects.

Bexarotene has recently become available in gel form. It is the first Food and Drug Administration–approved topical agent for the treatment of refractory CTCL. Phase 1 and 2 trials with stage IA and IIA CTCL yielded complete clearing of 21% of the lesions and at least 50% improvement in 63% of lesions.^{19,20} In phase 3 clinical tri-

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in "Instructions for Authors." Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017. Reprints are not available.

als in patients with refractory or persistent stage IA, IB, and IIA CTCL, the overall response rate was 44% with a complete clearing of the lesions in 8% of the patients.²¹ When compared with Panretin, alitretinoin (a retinoid that can bind to both the retinoid A and X receptors) in the treatment of stage I CTCL, Targretin had an overall response rate of 77%, while Panretin had an overall response rate of 67%.²² From the standpoint of adverse effects, 97% to 98% of patients participating in the phase 1, 2, and 3 trials reported only pruritus (32%-33%), rash (72%-73%), and pain (22%-24%). It is not necessary to check laboratory values in patients using bexarotene gel because there has been no systemic absorption noted.

Since the patient described herein responded to interferon alfa, but did not have clearing of the lesion, Targretin was added as an adjuvant topical agent. Interferon alfa works through the modification of cytokine expression. Targretin gel may work through apoptosis and other yet to be defined mechanisms. In chronic diseases, oftentimes it is more effective to use complementary combination therapy than monotherapy. Our patient had marked improvement with complete clinical resolution of the lesions on his scalp after the addition of the Targretin gel. While the patient has had a remarkable response, he still requires occasional interferon alfa injections, indicating that neither the Targretin gel nor the interferon alfa alone could control his disease. It would appear, therefore, that the combination can be effective in localized low-grade primary CBCL.

Accepted for publication November 27, 2001.

Corresponding author: Francisco A. Kerdel, BSc, MBBS, University of Miami Department of Dermatology, PO Box 016250, Miami, FL 33136 (e-mail: Dermatology.department@hcahealthcare.com).

- Sabroe RA, Child FJ, Woolford AJ, Spittle MF, Russell-Jones R. Rituximab in cutaneous B cell lymphoma. *Br J Dermatol.* 2000;143:157-161.
- Heinzerling L, Dummer R, Kempf W, Schmid MH, Burg G. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B cell lymphoma. *Arch Dermatol.* 2000;136:374-378.
- Wong KC, Weller PA. Primary cutaneous B cell lymphoma: outcomes and treatment. *Aust J Dermatol.* 1998;39:261-264.
- Fierro MT, Quaglino P, Savoia P, Verrona A. Systemic polychemotherapy in the treatment of primary cutaneous lymphomas: a clinical follow up study of 81 patients treated with COP or CHOP. *Leuk Lymphoma.* 1998;71:583-588.
- Zenone T, Catimel G, Barbet N, Clavel M. Complete remission of a primary cutaneous B cell lymphoma treated with intralesional recombinant interferon alpha-2a. *Eur J Cancer.* 1994;30:246-247.
- Pandolfino TL, Siegel RS, Kuzel TM, Rosen ST, Guitart J. Primary cutaneous B cell lymphoma: review and current concepts. *J Clin Oncol.* 2000;18:2152-2168.
- Santucci M, Pimpinelli N, Arganini L. Primary cutaneous B cell lymphoma: a unique type of low grade lymphoma. *Cancer.* 1991;67:2311-2326.
- Berti E, Alessi E, Caputo R, et al. Reticulohistiocytoma of the dorsum. *J Am Acad Dermatol.* 1988;19:259-272.
- Piccinno R, Caccialanza M, Berti E, et al. Radiotherapy of cutaneous B cell lymphomas: our experience in 21 cases. *Int J Rad Oncol Biol Phys.* 1993;27:385-389.
- Bexarotene (Targretin) for cutaneous T cell lymphoma. *Med Lett Drugs Ther.* 2000; 42:31-32.
- Henney JE. New drug for refractory cutaneous T-cell lymphoma. *JAMA.* 2000; 283:1131.
- Miller VA, Benedetti FM, Rigas JR, et al. Initial clinical trial of a selective retinoid X receptor ligand, LGD1069. *J Clin Oncol.* 1997;15:790-795.
- Bexarotene (Targretin) [package insert]. San Diego, Calif: Ligand Pharmaceuticals Inc; 2000.
- Duvic M, Cather JC. Emerging new therapies for cutaneous T cell lymphoma. *Dermatol Clin.* 2000;18:147-156.
- Millikan L, Mustafa M, Yocum R. RXR-selective oral retinoid bexarotene (Targretin) shows efficacy and safety in AIDS-related Kaposi's sarcoma. Abstract and poster presented at: Fifth Annual NCI AIDS Malignancy Conference; April 23-25, 2001; Bethesda, Md. Abstract 53.
- Wilding G, Carducci MA, Hwu WJ, Atkins MB, Reich SD. A multicenter phase I-II evaluation of oral bexarotene and interferon alpha 2B combination treatment in patients with advanced renal cell carcinoma. Presented at: Annual Meeting of the American Society of Clinical Oncology; 2001; San Francisco, Calif. Abstract 763.
- Rizvi N, Hawkins MJ, Eisenberg PD, Yocum RC, Reich SD. Ligand L1069-20 Working Group. Placebo controlled trial of bexarotene, a retinoid X receptor agonist, as maintenance treatment for patients treated with chemotherapy for advanced non small cell lung cancer. *Clin Lung Cancer.* 2001;2:210-215.
- Khuri FR, Rigas JR, Figlin RA, et al. Multi-institution phase I-II trial of oral bexarotene in previously untreated patients with advanced non small cell lung cancer. *J Clin Oncol.* 2001;19:2626-2637.
- Breneman D, Duvic M, Kuzel T, Stevens V, Yocum R. Phase I-II clinical trial demonstrates the safety and efficacy of bexarotene (LGD1069) topical gel for the treatment of cutaneous T cell lymphoma. Abstract presented at: 57th Annual Meeting of the American Academy of Dermatology, March 19-24, 1999; New Orleans, La.
- Kuzel T, Breneman D, Duvic M, Truglia J, Yocum R, Stevens V. Phase I-II trial of Targretin gel in the topical treatment of patients with cutaneous T cell lymphoma [abstract]. *J Inv Dermatol.* 2000;114:830.
- Heald P, Mehlmauer M, Martin A, Olsen E, et al. The benefits of topical bexarotene (Targretin) in patients with refractory or persistent early stage CTCL [abstract]. *J Invest Dermatol.* 2000;114:840.
- Whaley KL, Cather J, Walker D, et al. Topical retinoids improve stage I cutaneous T cell lymphoma lesions. Presented at: Society for Investigative Dermatology; April 1997; Washington, DC.