Low-Dose Bexarotene and Low-Dose Interferon Alfa-2b for Adult T-Cell Leukemia/Lymphoma Associated With Human T-Lymphotropic Virus 1

Stephen Richardson, MD; Jeanne B. Budgin, DVM; Jacqueline M. Junkins-Hopkins, MD; Carmela C. Vittorio, MD; Jason Lee, MD; Wallace T. Miller, Jr, MD; Alain H. Rook, MD; Ellen J. Kim, MD; Departments of Dermatology (Drs Richardson, Junkins-Hopkins, Vittorio, Rook, and Kim) and Radiology (Dr Miller), University of Pennsylvania Health System; Department of Dermatology, University of Pennsylvania School of Veterinary Medicine (Dr Budgin); Department of Dermatology, Thomas Jefferson Medical College (Dr Lee), Philadelphia

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 48-year-old Iranian man with a history of hypercholesterolemia and panic attacks acutely developed hand pruritus and an abdominal rash that was unresponsive to antihistamines. The rash spread across his entire trunk, and he developed chills and fatigue. He was initially diagnosed as having a possible drug reaction to fluvoxamine maleate, rofecoxib, or atorvastatin, but the rash persisted despite discontinuation of medication and a 3-week course of oral prednisone. Subsequent skin biopsy results suggested a lichenoid hypersensitivity reaction; he was given topical corticosteroids for a month, but there was no improvement.

When he presented to our clinic, he had diffuse erythema of the trunk and proximal upper extremities with numerous overlying 2- to 4-mm papules (Figure 1A). There was a palpable 4-cm² lymph node in the right axilla. The results of a second skin biopsy showed an atypical lymphocytic lichenoid and perivascular infiltrate, consistent with cutaneous T-cell lymphoma (CTCL). He had an elevated white blood cell count of 18 100/µL (18.1 × 10⁹/L) and an elevated serum lactate dehydrogenase level of 836 U/L (normal level, 313-618 U/L). The results of blood-flow cytometry revealed a 60% CD4⁺CD7⁻ lymphocyte population (normal, <10%) and an elevated CD4⁺CD8 ratio of 7.4 (normal ratio, 2.0). The peripheral blood smear showed 15% to 25% abnormal lymphocytes with either irregular or cerebriform nuclei (normal, <5%). Typical “flower cells” were not noted. A computed tomographic scan of the chest, abdomen, and pelvis with intravenous contrast revealed extensive bilateral axillary and pelvic lymphadenopathy (Figure 2A). There was no evidence of other organ involvement or hypercalcemia. The serologic results were positive for human T-cell lymphotropic virus 1 (HTLV-1) by both enzyme-linked immunosorbent assay and Western blot analysis. This constellation of findings was consistent with acute HTLV-1-associated adult T-cell leukemia/lymphoma (ATL).

Figure 1. Resolution of patient’s erythroderma during treatment with low-dose bexarotene and interferon alfa-2b. Erythroderma of the trunk at baseline (A) and 2 months after starting therapy (B).

THERAPEUTIC CHALLENGE

Adult T-cell leukemia/lymphoma is associated with HTLV-1 and is extremely difficult to treat. Adult T-cell lymphotropic virus 1 is endemic in areas of Japan, Australia, the Middle East, sub-Saharan Africa, the Caribbean, South and Central America, and the southeastern United States. In most cases, HTLV-1 is transmitted vertically from the mother to the infant at birth or dur-
At the University of Pennsylvania Cutaneous Lymphoma Clinic, Philadelphia, we primarily treat mycosis fungoides (MF), the most common type of T-cell lymphoma of the skin. The underlying cause of most cases of MF in the United States is unknown. Although the Tax sequence of HTLV-1 has been reported to be found in malignant lymphocytes from patients with MF, most patients with MF typically do not have circulating antibodies to HTLV-1. Thus, the precise role of the virus in the pathogenesis of most MF cases remains unclear.

One of the current effective therapies for MF is bexarotene, a novel third-generation retinoid X receptor–specific retinoid approved by the Food and Drug Administration in December 1999 for this condition. In combination with low-dose interferon alfa-2b (1.5 × 10^6 U administered subcutaneously 3 times a week) for the treatment of MF, we frequently use it in low doses (150-225 mg orally daily) in combination with low-dose interferon alfa-2b (1.5-3.0 × 10^6 U administered subcutaneously 3 times a week) for the treatment of MF. In our experience, this combination may provide synergistic therapeutic effects for MF and is extremely well tolerated.

Figure 3. Using flow cytometry, we found a decreased tumor burden in peripheral blood mononuclear cells during treatment with low-dose bexarotene and interferon alfa-2b. Two months after starting therapy, the CD4/CD8 ratio decreased from 7.4 to within normal limits (shaded bars) in the patient’s peripheral blood mononuclear cells. The serum lactate dehydrogenase (LDH) levels also normalized (solid line).

SOLUTION

The patient was prescribed an oral low dose of bexarotene, 150 mg daily, and a subcutaneous low dose of interferon alfa-2b, 3 × 10^6 U 3 times weekly. After 30 days of therapy, the patient experienced marked resolution of the diffuse skin eruption (Figure 1B). The node in the right axilla was no longer palpable. A second computed tomographic scan showed a significant decrease in the size of the axillary (Figure 2B) and pelvic lymph nodes.

During the course of therapy, the patient’s CD4/CD8 ratio and lactate dehydrogenase levels (Figure 3) improved. By day 60, his white blood cell count was normal at 6800/µL (6.8 × 10^9/L), and the percentage of malignant CD4+CD7− lymphocytes decreased to 46%. Thus, our patient’s symptoms responded rapidly and dramatically to treatment with bexarotene and interferon alfa-2b. Adult T-cell leukemia/lymphoma cells also typically express CD25, the interleukin 2 receptor. However, because there was no baseline CD25 assessment of lymphocytes, we did not monitor the CD25 results during the course of therapy.

To examine the potential mechanisms involved, we compared the percentage of apoptosis in the peripheral blood mononuclear cells (PBMCs) in healthy subjects with those of our patient with CTCL and HTLV-1 and after treatment with low-dose bexarotene and low-dose interferon alfa-2b. At baseline (no treatment), the PBMCs of the patient with CTCL and HTLV-1, although

alone has been reported to have an effect in ATL but at much higher doses (5 × 10^6 U administered subcutaneously 5 times a week).
the effect was less than that of bexarotene alone (Figure 5). The combination of bexarotene and interferon alfa-2b yielded a slightly higher level of apoptosis than treatment with bexarotene or interferon alfa-2b alone (40.3%), but the difference was not statistically significant.

The patient’s therapy has been maintained at the same low doses of bexarotene and interferon alfa-2b. On day 30, he began extracorporeal photopheresis, a well-established treatment for MF with leukemic involvement (Sézary syndrome). He has continued to do well with this treatment combination, with no recurrence of skin lesions or lymphadenopathy during the past 6 months.

**METHODS**

Peripheral blood mononuclear cells from the whole blood (prior to initiation of therapy) of a healthy volunteer and our patient were prepared as previously described for apoptosis assays. In addition, flow cytometric analyses were performed on the patient’s PBMCs at 0, 30, and 60 days after initiation of therapy. For the apoptosis assay, the PBMCs of the patient and the healthy subject were divided into 4 treatment groups: no treatment, in vitro bexarotene (10 μmol/L) alone, interferon alfa-2b (1000 U/mL) alone, and a combination of bexarotene (10 μmol/L) plus interferon alfa-2b (1000 U/mL). After in vitro treatment, the PBMCs were incubated at 37°C for 96 hours and evaluated for in vitro apoptosis using a modification of the terminal deoxyuridine triphosphate nick end labeling assay as previously described. Apoptotic cells were identified using a flow cytometer (FACScan; Becton Dickinson, Franklin Lakes, NJ). To detect cell surface markers, flow cytometric analysis was performed by the William Pepper Laboratory, University of Pennsylvania Medical Center, Philadelphia, utilizing commercial fluorescence-tagged antibodies against CD4, CD8, and CD7. The deletion of specific pan–T-cell surface markers is a common finding in T-cell malignancies. In cutaneous T-cell lymphoma, malignant cells are typically T-helper (CD4+) phenotype and exhibit the loss of the marker CD7. The tumor cells in HTLV-1–associated ATL generally are CD4−CD8−. The CD4−CD8 ratio and serum lactate dehydrogenase levels served as markers for circulating tumor burden.

We propose a novel combination therapy that may significantly affect HTLV-1–associated ATL, a fatal disease that has limited treatment options at present. Fewer than 5% of patients with HTLV-1 will develop ATL, which has 4 clinical types: acute, lymphomatous, chronic, and smoldering. In its acute and lymphomatous forms, ATL is rapidly progressive, with a median survival of 3 to 6 months.

The patient described herein experienced a rapid remission of acute ATL after initiating therapy with a combination of low-dose bexarotene and low-dose interferon alfa-2b, which, to our knowledge, has not been reported to have been used for this condition. Our data demonstrate that in vitro bexarotene alone induced increased apoptosis in the patient’s PBMCs compared with the healthy subject. A previous study has shown that other retinoids inhibit the growth and survival of ATL cells in vitro. This finding may be due to retinoid effects on the nuclear factor kappaB signaling pathway. We previously reported a case of ATL in which the symptoms underwent rapid regression in response to combination treatment using the older second-generation retinoid etretinate with interferon alfa and zidovudine. When exposed to therapeutic concentrations of bexarotene in vitro, MF-derived cell lines undergo apoptosis. Prior to therapy, the patient’s PBMCs were isolated and treated in vitro with diluent, bexarotene (10 μmol/L), interferon alfa-2b (1000 U/mL), or a combination of bexarotene (10 μmol/L) and interferon alfa-2b (1000 U/mL). Both bexarotene and interferon alfa-2b alone induced increased apoptosis of the patient’s cells compared with diluent-treated cells. Combination treatment with both bexarotene and interferon alfa-2b yielded a higher level of apoptosis than either individual treatment, but no synergy was appreciated.
published observations, 2005). In addition, interferon alfa-2b can enhance processing of apoptotic tumor cells by dendritic cells and can augment cell-mediated immunity, each of which are beneficial properties that may account for the synergism observed clinically when interferon alfa-2b is combined with bexarotene.

Based on our clinical observations and the laboratory analysis of the patient’s malignant T-cell responses, we report that combination therapy using low-dose bexarotene and low-dose interferon alfa-2b may be an effective treatment of ATL. Additional controlled, prospective studies are needed to validate the use of this combination. In addition, this treatment may also be effective in other serious medical conditions associated with HTLV-1, such as HTLV-1-associated myelopathy or tropical spastic paraparesis.

Acknowledgment: We are grateful to members of the Bexarotene Worldwide Study Group for their contributions:

Many members of the Bexarotene Worldwide Study Group, including: U. Tschachler, M. Z. Sing, V. Gruenwald, J. F. Jaffe, M. D. Larson, S. A. Kohn, J. S. Karim, J. L. O’Toole, N. L. Chernoff, W. M. Marghoob, J. A. DeCristofaro, D. J. de Kruif, M. A. Sachs, and M. J. Kirkwood, for their invaluable contributions and evaluations of the patient’s malignant T-cell responses, we acknowledge the contributions of the following individuals and organizations: Pauline G. Leung, RN, Barbara J. DeNardo, RN, William H. Macey, RN, for assistance in caring for the patient; William K. Witmer and Sam Dulay for preparation of the clinical photographs; and Michael Young and Ligand Pharmaceuticals for the kind gift of bexarotene for the in vitro studies.

Funding/Support: This work was supported by a grant from the National Institutes of Health (AI-45566) and the Center for Cutaneous Biology and Immunology at the University of Pennsylvania. We thank Helmut H. Mohr, MD, for editorial assistance.

Accepted for Publication: May 20, 2004.

Correspondence: Ellen J. Kim, MD, Department of Dermatology, University of Pennsylvania Health System, 2 Maloney Bldg, 36th and Spruce streets, Philadelphia, PA 19104 (ellen.kim@uphs.upenn.edu).

Support: Michael Young, MD, also provided the bexarotene used in the in vitro studies.

Clinical trials: The authors thank Patricia G. Bromley, RN, Barbara J. DeNardo, RN, William H. Macey, RN, for assistance in caring for the patient; William K. Witmer and Sam Dulay for preparation of the clinical photographs; and Michael Young and Ligand Pharmaceuticals for the kind gift of bexarotene for the in vitro studies.

References


Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapies to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins unjustified 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. Electronic submissions must have all figures in TIFF format. 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, 14377 Woodlake Dr, Suite 111, Town and Country, MO 63017 (cuttingedge@lasersurgeryusa.com).