Psoralen Plus Long-Wave UV-A (PUVA) and Bexarotene Therapy

An Effective and Synergistic Combined Adjunct to Therapy for Patients With Advanced Cutaneous T-Cell Lymphoma

Karen S. McGinnis, MD; Michael Shapiro, MD; Carmela C. Vittorio, MD; Alain H. Rook, MD; Jacqueline M. Junkins-Hopkins, MD

Background: Multimodality biological response modifier therapy that includes photopheresis, interferon, and bexarotene is the standard of care in our institution for advanced cutaneous T-cell lymphoma with peripheral blood involvement. We added psoralen plus long-wave UV-A (PUVA) to this regimen in 5 patients with Sézary syndrome.

Observations: All patients responded with decreased Sézary counts, resolution of lymphadenopathy, and clearing of skin disease after the addition of PUVA. Adverse effects were well tolerated and managed via close clinical and laboratory follow-up.

Conclusions: The addition of PUVA to a multimodal immunomodulatory regimen in patients with Sézary syndrome can result in rapid and sustained remission of both skin and blood-borne disease. Further in vitro and in vivo studies are needed.

Arch Dermatol. 2003;139:771-775
A 65-year-old African American woman presented with stage IIIB Sézary syndrome. Total body 0.01% nitrogen mustard ointment and UV-B therapies were started, resulting in marked improvement in her skin and decrease in size of her lymph nodes. Her white blood cell count remained elevated at 16.3×10^3/µL with 91% circulating CD4+CD7− cells and a CD4/CD8 ratio of 48 by flow cytometry. She was started on monthly treatments of extracorporeal photopheresis, and interferon alfa-2a was administered subcutaneously 4 times per week. A year later, peripheral blood buffy coat analysis revealed 90% Sézary cells. Over the next 2 years, despite the addition of various retinoids (all-trans retinoic acid and later acitretin) and granulocyte-monocyte colony-stimulating factor injections administered after each photopheresis treatment, her disease continued to progress both clinically and in the blood, with an increase in the CD4/CD8 ratio from 47 to 95. Interferon alfa-2a was replaced by interferon gamma (1.6 million units subcutaneously 4 times weekly), and oral bexarotene (150 mg/d) was added. A second flow cytometry performed 7 months after the addition of interferon gamma and 3 months after the addition of bexarotene revealed an improved CD4/CD8 ratio of 27. However, the Sézary count remained high at 70% to 80%. Bexarotene dosage was increased to 225 mg/d. Ten months later, her Sézary count was essen-
tially unchanged, and her CD4+/CD8+ ratio was 22. Three-timess weekly PUVA was added, and within 1 month there was a dramatic decrease in her erythema and pruritus. At 2 months after the addition of PUVA, her Sézary count was 30% to 38% and her skin was clear. At 6 months after the addition of PUVA, the Sézary count was 5% to 10%, and the PUVA regimen was decreased to twice-weekly treatments. At 16 months after the addition of PUVA, her CD4/CD8 ratio was 1, her Sézary count was 1% to 3%, and her skin remained clear. Bexarotene-induced hypothyroidism and hyperlipidemia have been well controlled with the use of levothyroxine and fenofibrate, respectively.

CASE 3

A 53-year-old man presented with stage III B Sézary syndrome (folliculocentric-type with pruritus), extensive hair loss (Figure 1 A), and nonpainful cervical, axillary, and inguinal adenopathy. Findings from a skin biopsy (Figure 2) were consistent with follicular mycosis fungoides, and a peripheral blood buffy coat analysis revealed 20% to 30% Sézary cells. Flow cytometry revealed an elevated CD4/CD8 ratio of 6, with an expanded population of CD4+CD7- cells (45%). He was started on treatments with extracorporeal photopheresis, oral bexarotene (150 mg/d), and PUVA (3 times weekly). After starting PUVA (5 weeks) and bexarotene and photopheresis (8 weeks) therapies, the patient experienced hair regrowth in the affected areas as well as decreased lymphadenopathy. A second Sézary count was 7% to 10%. The PUVA regimen was decreased to 2 times per week. After starting PUVA (6 months) and bexarotene and photopheresis (7 months) therapies, there was continued hair regrowth (Figure 1B), and the Sézary count was 5% to 8%. Bexarotene-induced hypothyroidism and hypertriglyceridemia have been well controlled with levothyroxine and fenofibrate, respectively.

CASE 4

A 73-year-old white man presented with stage III B Sézary syndrome with a Sézary count in the 15% to 25% range. Over the following year, he experienced minimal re-
CASE 5

A 64-year-old white woman presented with stage IIIB Sézary syndrome. A Sézary count was 30% to 40%. Flow cytometry revealed a CD4/CD8 ratio of 5, with 19% cells displaying CD4+CD7− markers. She was started on treatments with extracorporeal photopheresis and oral bexarotene (150 mg/d), with only mild improvement at 3 months. Therapy with interferon alfa-2b (1.8 million units subcutaneously 3 times weekly) was started, and 2 months later the regimen was increased to 2.4 million units 3 times weekly, which was later substituted with interferon gamma owing to the development of peripheral neuropathy. The PUVA therapy was discontinued for personal reasons after 5 months of treatment. Since that time, there has been slow disease progression with worsening CD4/CD8 ratio, erythroderma, and pruritus. At present, his bexarotene-induced hypothyroidism has been controlled with levothyroxine, and bexarotene-induced hypertriglyceridemia has been controlled with atorvastatin and fenofibrate.

COMMENT

Multimodality biological response–modifier therapy is the standard of care in our institution for advanced CTCL. While no therapy thus far has been shown to be curative, combinations of therapies may work together to correct the immune abnormalities of this disease and to induce sustained remissions, and thereby improve both quality and quantity of life. Recently, a new medication, bexarotene, has been added to our armamentarium of immunomodulators. A so-called “rexinoid,” bexarotene, is selective for the retinoid X receptors (RXR), unlike traditional retinoids (ie, isotretinoin and all-trans retinoic acid), which have a predilection for the retinoic acid receptors (RAR). Bexarotene’s mechanism of action in CTCL is believed to be multifold and may work by inducing differentiation and enhancing apoptosis of the malignant T cells1 while inhibiting inflammation and decreasing abnormal proliferation of the surrounding keratinocytes.4

In contrast with the recent introduction of bexarotene, the treatment of CTCL with PUVA was first reported in 1976 by Gilchrest et al8 Its mechanism of action is believed to be via the binding of the UV-A–activated psoralen to DNA, resulting in apoptosis of neoplastic T cells in the skin and superficial capillaries. It may also effect lymphocyte function and migration.9 The use of re-PUVA (the addition of oral retinoids to the PUVA regimen) in CTCL was first reported by the Scandinavian Mycosis Fungoides Group7 in 1984. In 69 plaque-stage patients who were treated with PUVA or oral retinoids plus PUVA, the response rates were the same. However, the response was achieved with fewer PUVA treatments and lower cumulative UV-A dose in the setting of systemic retinoids. Moreover, the duration of remission was longer when maintenance retinoids were given. This apparent synergistic effect may be attributed to retinoid-induced reductions in epidermal thickness, enhancement of PUVA penetration, or retinoid-specific augmentation of immune functions.8 We believe that retinoids may “prime” the malignant T cells, sensitizing them to UV-A–induced apoptosis (A.H.R., unpublished data, 2001).

Psoralen plus UV-A has also been used in combination with interferon alfa-2a in advanced stages of CTCL. Among 15 patients treated with PUVA and interferon by Roenigk and colleagues,8 at doses ranging from 6 to 30 million units 3 times weekly, 12 achieved complete responses, while 2 achieved partial responses, with a median duration of response of 23 months.

In our series, 3 (60%) of 5 patients had a complete remission with the addition of PUVA to a multimodality, immunomodulatory regimen. It is notable that of these 3 patients, 1 had large cell transformation and rapidly progressive lymphadenopathy, 1 had a highly elevated Sézary count, and 1 had a folliculotropic variant. Given the worse prognosis associated with these factors, we believed that the complete and sustained remissions that ensued were highly promising.10 In the 2 patients with partial remission, PUVA was discontinued because of personal reasons (case 4) and PUVA burn (case 5). However, it is possible that additional treatment could have resulted in further improvement.

With respect to adverse events, 1 patient developed in situ melanomas after 14 months of PUVA treatment. Although there was no family history or personal history of melanoma prior to his PUVA therapy, this pa-
tient did have a history of extensive sun exposure over his lifetime, with multiple sunburns as a child. Nevertheless, it is possible that other factors related either to the primary disease resulting in suppression of the skin immune surveillance system or to a specific interaction between PUVA and bexarotene resulting in increased melanocyte carcinogenesis occurred.

The addition of PUVA resulted in neutropenia (defined as an absolute neutrophil count of ≤1000/µL) in 1 patient, which necessitated a decrease in bexarotene, interferon, and PUVA dosage. Of note, no serious infections (viral, bacterial, or fungal) occurred during the period of neutropenia. Possible reasons for this neutropenia include decreased bone marrow production or increased peripheral destruction via a mechanism similar to that proposed for the destruction of the malignant T cells.

Finally, 1 patient experienced a PUVA burn, resulting in discontinuation of therapy despite a dramatic response. Though it is possible that bexarotene may potentiate PUVA resulting in burns at lower doses, this has not been our experience. Indeed, recent resumption of PUVA has not resulted in additional burns in this particular patient.

In summary, the addition of PUVA to a multimodality immunomodulatory regimen including extracorporeal photopheresis, bexarotene, and interferon in patients with Sézary syndrome can result in dramatic and sustained remission of both skin and blood-borne disease. While the mechanism for this effect requires further in vitro as well as in vivo investigation, we propose that bexarotene may act as a biological “primer,” sensitizing the malignant T cells to PUVA-induced apoptosis. Finally, adverse effects of this combined regimen exist, but thus far they have been well tolerated and managed via close clinical and laboratory follow-up.

Accepted for publication November 13, 2002.

We acknowledge William Witmer for his assistance with photographic material.

Corresponding author: Jacqueline M. Junkins-Hopkins, MD, 2 Maloney, 3600 Spruce St, Philadelphia, PA 19104-4283 (e-mail: hopkinsj@uphs.upenn.edu).

REFERENCES


