Extracorporeal Photochemotherapy: A Case Report and Update

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Extracorporeal photochemotherapy (ECP) was developed at Columbia Presbyterian Medical Center in the early 1980s for the treatment of cutaneous T-cell lymphoma (CTCL). ECP is now used primarily in the treatment of that disease at more than 100 centers worldwide. It also has been shown to be potentially effective in treating several autoimmune diseases. Most recently, it has been used in reversing solid-organ transplant rejection and graft-versus-host disease following bone-marrow transplantation. In this article, we present the case of one of the first patients treated with ECP and give an update on the current status of this therapy.

Extracorporeal photochemotherapy (ECP) was developed at Columbia Presbyterian Medical Center in the early 1980s.[1] Until recently, ECP was the only treatment approved by the US Food and Drug Administration (FDA) specifically for the treatment of cutaneous T-cell lymphoma (CTCL). In October 1994, at the International Consensus Conference on Cutaneous T-cell Lymphoma Treatment Recommendations, it was concluded that ECP should be considered first-line treatment for patients with erythrodermic CTCL.[2] Since its inception, ECP has been shown to be effective in treating various autoimmune diseases and in reversing solid-organ transplant rejection and graft-versus-host disease.[3-12] In this article, we present the case of one of the initial patients treated with ECP and give an update on the current status of this modality.

Development of Extracorporeal Photochemotherapy

ECP was developed as a modification of psoralen plus UVA (PUVA) photochemotherapy and leukapheresis, the removal of peripheral blood mononuclear cells (PBMCs). ECP involves oral administration of 8-methoxy-psoralen (8-MOP) followed by removal of PBMCs through leukapheresis. Collected PBMCs are then exposed to 2 J/cm^2 of UVA light and reinfused into the patient. Exposure to UVA light in the presence of 8-MOP activates the leukocytes because of the cross-linking of psoralen between DNA base pairs.[13]

In 1982, a pilot study was conducted of 5 patients with leukemic CTCL who were treated with ECP at Columbia Presbyterian Medical Center. ECP was performed on 2 consecutive days per month.[1] After 3 months of treatment, 2 of the 5 patients had complete clearing. With these encouraging results, a multicenter trail was launched.[14] Thirty-seven patients with treatment-resistant CTCL were studied. Of the 29 patients with erythrodermic CTCL, 83% (24) responded completely or partially to ECP, whereas only 38% (3) of the 8 patients with plaque and tumor-stage disease improved.[14] In 1988, one year after results of that study were published, the FDA approved ECP for cutaneous manifestations of CTCL. Subsequent studies have suggested that ECP also prolongs survival of patients with CTCL.[15]

Case Report

We report the case of a 90-year-old white woman who was one of the first to be treated with ECP at Columbia Presbyterian Medical Center as part of the original multicenter trial. The patient first presented in 1983 at age 75 years with a 6-month history of a diffuse, erythematous, scaly pruritic eruption. A skin biopsy was diagnostic of CTCL, as was a lymph-node biopsy. These findings were consistent with stage IVA disease. Peripheral T-cell marker data, available for the patient only as of 1988, were normal (CD4/CD8 ratio, <2.5; no loss of pan T-cell markers CD2, CD5, or CD7). The patient's medical history was significant for hypothyroidism, congenital hypogenesis of a kidney, hypertension, and stable abdominal aortic aneurysm. Initially, she responded well to PUVA

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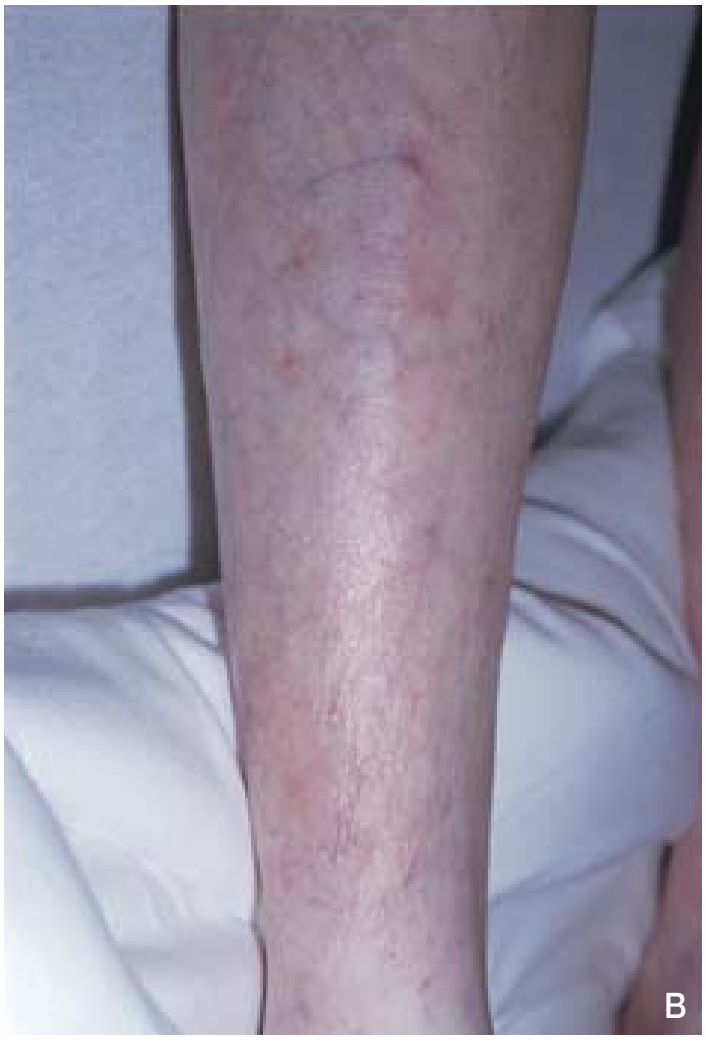

Patient's back (A) and lower right leg (B) 13 years after start of photopheresis shows normal skin without evidence of cutaneous T-cell lymphoma.

treatment. Upon recurrence of her disease in 1985, she was started on ECP. The patient improved steadily but still showed evidence of disease on skin biopsy 6 years after starting ECP. Treatment was transferred briefly to another institution, where she cleared completely, and then treatment was tapered. In 1992, the patient returned to Columbia Presbyterian Medical Center and was treated every 8 weeks. Since then, she has shown no evidence of disease either clinically (Figure, A and B) or histologically. Tapering of treatment has continued; currently, ECP is performed every 15 weeks. The patient has not experienced any significant side effects from treatment, and her quality of life continues to be high.

Comment

CTCL is caused by malignant proliferation of clonal helper T (T_H) cells. Initially, CTCL manifests in the skin as patches, plaques, or erythroderma with subsequent development of cutaneous tumors and involvement of the lymph nodes and blood. Prognosis of erythrodermic CTCL is poor; overall length of survival is expected to be 30 to 40 months from the time of diagnosis using conventional chemotherapy.[16] Kim et al[17] reviewed the medical records of 106 patients with erythodermic CTCL and Sézary syndrome to determine important prognostic factors. According to this classification, because of our patient's age and lymph-node involvement, she would have had an unfavorable prognosis and would have been expected to survive only approximately 1.5 years after diagnosis. In view of this, our patient, who is now in her 15th year postdiagnosis, has done extremely well, and her case represents one of the best examples of the effectiveness of ECP.

The original report by Edelson et al[14] has been confirmed by others. Although there is still no standard definition of "response," and these various subsequent reports have involved patients with CTCL at different stages, noting their results is important. In a follow-up study, Heald et al[15] showed prolonged median survival for ECP patients (60 months) versus historic controls (30 months). They also observed that patients who responded completely to ECP had lower CD4/CD8 ratios compared with nonresponders. In 1989, Heald et al[18] reported on a group of 32 patients with CTCL who received ECP. Of the 22 patients who had erythrodermic CTCL, 19 received ECP as first-line treatment; of these 19 patients, 79% (15) responded completely or partially, which correlated well with the results of the original study. The initial mean CD4/CD8 ratio was significantly lower in the 5 best responders (5.27) than in the 5 worst responders (39.6).[18]

Armus et al[19] reported on 5 patients with erythrodermic CTCL, 4 (80%) of whom responded completely or partially to ECP. They also reported the unusual case of a patient whose tumor-stage disease responded completely to ECP, with histologic clearance of the disease. In 1996, Duvic et al[20] reported a response rate (complete plus partial) of 50% in 34 patients studied; all responders except one had erythrodermic CTCL. Zic et al[21] reported on the long-term follow-up of 20 patients who had CTCL in various stages and who were treated with ECP. Overall response rate was 50%. Zic et al[21] concluded that early response to treatment (ie, within first 6–8 months) is the most valuable predictor of long-term outcome. Koh et al[22] reported a total response rate of 53% in 34 (31 erythrodermic) patients from 2 institutions. In line with previous results, a correlation was found between CD4/CD8 ratio and response. Prinz et al,[23] studying 17 patients with CTCL (3 with erythrodermic CTCL, 14 with patch/plaque or tumor-stage disease), reported no complete responders but 12 (71%) partial responders. They found no correlation between CD4/CD8 ratio and response.

In our experience of using ECP for 6 months or longer to treat 20 patients with CTCL, the response rate for patients with erythrodermic CTCL (72%) was higher than the overall response rate of 50% (E. Knobler, MD, I. Warmuth, MD, unpublished data, 1998). Including all patients treated, we also found that the response rate was higher among those with an initial CD4/CD8 ratio less than 10 (67%) than among those with a ratio greater than 10 (14%).

An attractive feature of ECP, besides the clinical response, is the paucity of serious adverse effects. The most common side effect is mild transient nausea caused by ingestion of psoralen. There also have been reports of hypotension correctable with immediate administration of fluid, as well as a few reports (mainly at one center[24]) of cardiac effects (eg, exacerbation of congestive heart failure, development of arrhythmia), thrombophlebitis, transient elevation of liver enzymes, and catheter-related staphylococcal sepsis. Nehal et al[25] reported 2 cases in which patients developed aggressive squamous cell carcinomas while receiving ECP. These patients, however, had other risk factors for developing skin cancers (eg, prior PUVA treatments). In our experience, nausea is occasionally a problem, as is hypotension responsive to fluid administration. We have had one case of possible catheter-related staphylococcal sepsis. We also have had one patient with numerous basal and squamous cell cancers, as well as lentigo maligna melanoma. However, this patient had Fitzpatrick skin type II and admitted to having had many

blistering sunburns as a child and young adult. Nausea may soon become a nonissue because the FDA is considering approval for a new form of psoralen—a liquid that can be injected directly into the collection of PBMCs. This injectable psoralen has been used successfully in Europe since its introduction in 1993.[26] The side-effect profile of ECP is in sharp contrast to the far more debilitating effects of conventional chemotherapy, including bone-marrow suppression leading to opportunistic infections, severe nausea, and hair loss.

Not everyone with CTCL responds to monotherapy ECP, and those who respond completely are in the minority. Attempts to define the subgroup of patients who respond best point to patients who have erythrodermic CTCL with evidence of peripheral blood involvement and who have near-normal numbers of $CD8^+$ peripheral blood T cells at the start of therapy.[15,27] Elucidating the mechanism of action of ECP will help define the subpopulation of patients who should be treated with this modality. The constellation of events that have been found to result from ECP suggests an immunologic mechanism. In the murine mouse model, ECP has been shown to increase major histocompatibility complex class I surface antigen expression on $CD4^+$ cells, leading to heightened $CD8^+$ cytotoxic response specific for pathogenic CD4 cells.[24,28] ECP also has been shown to induce the release of tumor necrosis factor and cytokines interleukins 1 and 6. Release of these cytokines implicates the activation of monocytes.[29,30] Interaction of malignant T cells with PUVA also has been shown to lead to apoptosis of the cells.[31] It has been suggested that CTCL is a malignant proliferation of T_H subtype 2 cells, and studies have found that ECP increases T_H subtype 1 cell response and reverses the abnormally high level of T_H subtype 2 cells.[17,32] In view of these immunologic effects, which seem to result from ECP, ECP is classified as a biologic response modifier.

Since its initial use in the treatment of CTCL, ECP has shown promise in the treatment of some autoimmune diseases, including pemphigus vulgaris, systemic lupus erythematosis, systemic sclerosis, and rheumatoid arthritis.[3-6] ECP is now also successfully being used as an adjunct in the treatment of solid-organ allograft rejection—reversing acute rejection and allowing for lower doses of immunosuppressants such as prednisone.[7-9] The most recent and exciting use of ECP is in acute and chronic graft-versus-host disease resulting from bone-marrow transplantation.[10-12] Here again, ECP has been useful as an adjunct therapy for reversing graft-versus-host disease and for allowing for use of smaller doses of immunosuppressive agents.

Conclusion

ECP use has increased since development of the original treatment more than 15 years ago. Currently, ECP is being used in more than 100 centers worldwide, primarily for the treatment of CTCL. In addition, there have been anecdotal reports of the effectiveness of ECP in treating certain autoimmune diseases. Most recently, ECP was found useful in reversing solid-organ transplant rejection and graft-versus-host disease. Current evidence suggests an immunologic effect of ECP. Once the exact mechanism of action of ECP is elucidated, a more precise characterization of the treatment group and of other indications for this therapy will develop.

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