TJC Turkish Journal of Cancer
Volume 33, No.1, 2003

Extracorporeal photochemotherapy in the treatment of cutaneous T-cell lymphoma

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ABSTRACT

Extracorporeal photochemotherapy is a modality that has been established for the management of cutaneous T-cell lymphoma. In this treatment method leukocyte-enriched peripheral blood is exposed to ultraviolet-A in an extracorporeal system in the presence of psoralen. Today extracorporeal photochemotherapy is the treatment of choice especially for Sezary syndrome, in which the circulating phase of the cutaneous T-cell lymphoma dominates the clinical picture. [Turk J Cancer 2003;33(1):23-26]

KEY WORDS:

Extracorporeal photochemotherapy, cutaneous T-cell lymphoma, procedure, complications, mechanisms of action, predictors of outcome

INTRODUCTION

Extracorporeal photochemotherapy (ECP), is a form of apheresis therapy that permits the direct targeting of psoralen-mediated photochemotherapy to circulating pathogenic T cells. Cutaneous T-cell lymphoma (CTCL) is a low-grade non-Hodgkin's lymphoma characterized by the malignant proliferation of helper T lymphocytes that infiltrate the skin. ECP is the treatment of choice especially for Sezary syndrome and erythrodermic CTCL, in which the circulating phase of the CTCL dominates the clinical picture. First introduced for the treatment of CTCL, ECP has since been evaluated in studies and randomized trials as a potential treatment for autoimmune diseases, solid organ transplant rejection, and graft-vs-host disease. This article focuses on the current use of ECP in CTCL, procedure and complications, possible mechanisms of action, and predictors of clinical response.

CTCL was the first disease for which ECP was evaluated. In the first study by Edelson et al. published in 1987 (1), 27 of 37 patients with otherwise resistant CTCL responded with an average 64% decrease in cutaneous involvement. The responding group included 8 of 10 patients with lymph-node involvement, 24 of 29 with exfoliative erythroderma, and 20 of 28 whose disease was resistant to standard chemotherapy. One year after this clinical study the use of ECP for the treatment of Sezary syndrome had FDA approval. Heald et al. (2) provided long-term follow-up on the original

29 erythrodermic CTCL patients reported by Edelson et al., compared the results with historical controls and declared that ECP may also increase survival time from a median of 30 months to over 66 months. Even in the view of existing controversy and statistical validity associated with comparing results to historical controls, the influence of ECP on the natural history of erythrodermic CTCL by inducing remissions and prolonging survival appeared to be of significance.

Later studies appeared to confirm the initial impressions of efficacy. Zic et al. (3,4) described a response rate reaching up to 75% with possible complete remissions of up to 25% and a median survival time of 96 months. Zachariae et al. (5) treated 7 patients with the red man (pre-Sezary) syndrome. Of these 7 patients, 6 had been on systemic steroids and 3 had also received steroids without sufficient effects, all were initially treated with topical nitrogen mustard but no longer tolerated this treatment. With ECP all signs of erythroderma disappeared in 6 of 7 patients.

The effectiveness of ECP for CTCL patients with generalized patch/plaque and tumor stage has also been evaluated. Armus et al. (6) published data from 8 ECP treated patients. Four of 5 patients with erythrodermic CTCL and all 3 patients with patch/plaque or tumor stage responded.

Contrasting with these results, there have also been investigators who did not support the contention that ECP prolongs survival. Comparing survival in patients treated with ECP with that of patients treated conventionally, Fraser-Andrews et al. (7) were unable to show any significant difference in a retrospective study. In another 9-year retrospective study performed by Bisaccia et al. (8) complete and partial response were achieved by 14% and 41%, respectively, giving an overall response rate of 54%, which was underscoring the potential value of ECP in treating CTCL. Duvic et al. (9) reported their experience with 34 patients, 28 of which had erythroderma and 26 had extracutaneous disease. The overall response rate was 50%. Although found effective, ECP neither improved the remission rate nor shortened the response time in this study. We believe that, a randomized trial comparing ECP with standard therapies would clarify the effect of ECP on the survival of patients with CTCL.

ECP is likely to be more useful when combined with other modalities. Numerous therapies have been combined with ECP in past studies with apparent clinical benefit (2,4,6,9-12). Possibly because of its synergic effects, interferon seems to be the most commonly used combination with ECP. It was noted in one study that interferon-2α as an adjuntive therapy to ECP almost doubles the number of patients with a complete response for the combined treatment versus for ECP alone (4). For patients with a partial response or who does not improve, who presented with Sezary syndrome, tumoral stage or rapidly progressive disease at the pretreatment evaluation, combination treatment with ECP and interferon- should be considered (11).

The procedure

ECP consists of placing an intravenous line into the patients arm. Peripheral blood is drawn into the instrument where the white cells or buffy coat and a small amount of plasma are isolated and mixed with a steril 8-methoxypsoralen solution, a photoactivatable drug. The buffy coat is exposed to ultraviolet light to activate the drug and then returned to the patient. The entire procedure takes about 4 hours depending on the hematocrit level of the patient. This procedure is performed on 2 consecutive days at 4-week intervals with clinical evaluation at 6 months to determine response. Those who show clinical improvement are maintained on this treatment schedule until maximum clearing. Afterwards an additional 6 months of treatment is given and the patient is then gradually weaned off therapy.

Complications

Complications of ECP are minimal. Some patients may have nausea or an accentuation of erythema. About 10% may experience a transient fever after reinfusion of cells and less frequently hypovolemic hypotension can occur (1). Complications associated with other treatment modalities for CTCL such as myelosuppression, liver toxicity, renal toxicity, neural toxicity and radiation dermatitis have not been reported with ECP.

Mechanism of action

The mechanism of action of ECP is not well understood. Malignant lymphocytes may be directly killed by this approach. Marks et al. (13) showed that the lymphocytotoxic effect of ECP in CTCL is appearently mediated by DNA damage. UVA light is cytotoxic on its own, but is potentiated by methoxsalen.

The reinfused photomodified cells may provide a potent immunogenic stimulus leading to the onset of CD8+ cell-mediated anticlonotypic immune responses. It has been postulated that ECP may induce cytokine production (14). In advanced CTCL and in Sezary syndrome (perhaps through interleukin 4 and interleukin 10) a Th2 environment exists. This downregulates suppressor cell function and thus malignant clone can proliferate. ECP restores Th1/Th2 imbalance in CTCL and normalizes Th2 response, which in return normalizes CD8+ T cell response (15).

Alternatively there is evidence that ECP alters the soluble interleukin-2 receptor (sIL-2R) levels. It was known that the serum concentration of sIL-2R correlates with tumor burden in CTCL, which is necessary for the clonal expansion of the malignancy. Vonderheid et al. (16) showed that during ECP, serum concentrations of sIL-2R correlated with changes in clinical status.

Another possible mechanism may be induction of apoptosis. In vitro studies demonstrated that UVA-induced apoptosis is mediated by CD95-Fas expression and inhibited by Bcl-2 up-regulation and that UVA irradiation is able to down-regulate Bcl-2 expression. Osella-Abate et al. (17) evaluated Bcl-2/CD95-Fas expression on circulating clonal T cells from 7 patients with CTCL before and during ECP, and found that a Bcl-2 normal phenotype before ECP or a normalization in Bcl-2 expression during ECP were related to a better clinical response, whereas a persistent Bcl-2 high expression was a negative prognostic factor. On the other hand, no response was found in patients with a CD95-Fas negative phenotype, whereas the expression of CD95-Fas was associated with hematologic remission.

Predictors of clinical response

A normal CD4/CD8 ratio and a normal absolute count of CD8+ cells in the peripheral blood at the start of therapy are among the generally accepted criteria that appear to help predict a better outcome (2).

The presence of circulating Sezary cells seem to be another predictor of a satisfactory clinical response to ECP. It is reported that patients with circulating Sezary cells had a significantly better response to ECP than patients without circulating Sezary cells (11).

It is a common finding that patients with erythroderma respond best (1,6,9). A short interval from diagnosis to entrance into ECP is related with a better responce. Heald et al. (2) reported that patients with erythroderma who were heavily pretreated and received ECP late in the course of their disease did not respond as well as those who received ECP early. Thus they suggested that ECP should be considered the first line of therapy for erythrodermic CTCL. Zic et al. (5) revealed that early response after 6 to 8 months of ECP had a sensitivity of 100% and a specifity of 90% for predicting long-term (>4 years) outcome.

An increase in the serum IgG values during ECP was also reported to be a meaningful response marker (9).

Still, these factors are not always sufficient for predicting response, responders and non-responders can be found at both extremes.

CONCLUSION

Experience with ECP since 1987 suggests that this therapy is effective for advanced CTCL, particularly when compared with alternative therapies. Because of the potential for prolonged survival, including long-term complete response, in addition to the paucity of side effects associated with this treatment ECP should be considered first-line therapy for patients with circulating Sezary cells and favorable prognostic parameters (11).

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