OBSERVATION

Extracorporeal Photopheresis in Sézary Syndrome

No Significant Effect in the Survival of 44 Patients With a Peripheral Blood T-Cell Clone

Elisabeth Fraser-Andrews, MA, MRCP; Paul Seed, MSc; Sean Whittaker, MD, MRCP; Robin Russell-Jones, MA, FRCP

Background: Several retrospective studies have claimed that extracorporeal photopheresis (ECP) prolongs survival in patients with erythrodermic cutaneous T-cell lymphoma. In a retrospective study of 44 patients with Sézary syndrome, we compared survival in patients treated with ECP with that of patients treated conventionally at the same institute. All patients had genotypic evidence of a peripheral blood T-cell clone.

Observations: Twenty-nine patients received ECP (group 1); 15 patients did not receive ECP, 8 patients when ECP was available (group 2) and 7 before ECP was available (group 3). Forty-three of 44 patients received other conventional treatments. Median survival from diagnosis of Sézary syndrome was 39 months in group 1, 22 months in group 2, and 27.5 months in group 3 (Kaplan-Meier analysis). Cox regression analysis showed no significant difference between the 3 groups after correcting for age, sex, and initial Sézary cell count (hazard ratio, 0.56; 95% confidence interval, 0.26-1.17; $P = .12$).

Conclusions: This study does not support the contention that ECP prolongs survival in patients with Sézary syndrome. The median survival in the ECP-treated group is considerably less than that reported in other published series, possibly because genotypic evidence of clonality in the peripheral blood was required for inclusion in this study. We believe that a randomized trial comparing ECP with standard chemotherapy is urgently needed.

Arch Dermatol. 1998;134:1001-1005

From St John's Institute of Dermatology (United Medical and Dental Schools of Guy's and St Thomas' Hospitals) (Drs Fraser-Andrews, Whittaker, and Russell-Jones) and Department of Public Health Medicine (UMDS) (Mr Seed), St Thomas' Hospital, London, England.

SÉZARY SYNDROME (SS), a leukemic variant of primary cutaneous T-cell lymphoma (CTCL), is characterized by erythroderma, lymphadenopathy, pruritus, and the presence in the peripheral blood of atypical lymphocytes with characteristic cerebriform nuclei (Sézary cells).[1] These cells are usually $CD4^+$ T-helper lymphocytes.[2]

Extracorporeal photopheresis (ECP) was first described in 1987 by Edelson et al[3] as a treatment for erythrodermic CTCL. For this procedure, leukocyte-enriched blood is obtained 2 hours after ingestion of 8-methoxypsoralen, exposed to UV-A light, and subsequently reinfused. This is performed on 2 consecutive days to constitute 1 treatment cycle; treatments are usually given monthly but the frequency may be increased or decreased according to patient response to treatment. Extracorporeal photopheresis is thought to augment the host $CD8^+$ cytotoxic T-cell response to tumor cell antigens.[4]

Patients with SS generally have a poor prognosis; a study of 106 patients with erythrodermic CTCL found a median survival of 2.6 years in patients with 5% or greater circulating Sézary cells, compared with 6.8 years in patients with fewer than 5% circulating Sézary cells.[5] Both large and small variants of Sézary cells have been described,[6,7] and the small variant may be found in benign inflammatory dermatoses such as erythrodermic psoriasis and eczema.[7] This may result in diagnostic confusion, especially as diagnostic skin biopsy abnormalities are not seen in all cases of SS.[8] The neoplastic nature of the Sézary cells can be demonstrated using Southern blot analysis of the T-cell receptor (TCR) β gene to detect a discrete band in addition to the germline bands, indicating the presence of a monoclonal population of T lymphocytes.[9,10]

Follow-up data on the original cohort of 39 erythrodermic patients of Edelson et al[3] reported a median survival of 60.3 months from diagnosis of the erythrodermic state and 47.9 months from initiation of photopheresis.[11] Several smaller studies of the use of ECP in CTCL have since been published, commenting on clinical response.[12-14] Two recent articles reported median survivals of 96 months (20 patients)[15] and greater than 100 months from diagnosis (28 patients).[16] There have, however, been no controlled trials comparing ECP with conventional therapies.

We compared survival in patients with SS treated at St John's Institute of Dermatol-

PATIENTS AND METHODS

Forty-nine patients were identified as having a diagnosis of SS as defined by (1) erythroderma, (2) Sézary cells (atypical lymphocytes >10% of peripheral blood mononuclear cells), (3) clonal TCR β gene rearrangement detected in peripheral blood lymphocytes using Southern blot analysis,[13] and (4) skin histological findings consistent with a diagnosis of CTCL. Of these, 2 patients were unavailable for follow-up and the medical records were missing for 3 patients. Patients who were alive at the time of analysis had been diagnosed at least 24 months previously. The case notes of the remaining 44 patients were reviewed and the current clinical status determined by writing to the patients' general practitioner and hospital consultants as necessary. The following data were recorded: dates of symptom onset and diagnosis, Sézary cell count, white blood cell and lymphocyte counts at diagnosis or presentation to St John's Institute of Dermatology, histological results of lymph node biopsy if performed, treatments received, and outcomes.

The 44 patients were divided into 3 groups: group 1 consisted of patients treated with ECP between January 1991 and August 1996 (n=29; mean age, 61 years; 11 women and 18 men), group 2 consisted of patients not treated with ECP during the same period (n=8; mean age, 59 years; 4 women and 4 men), and group 3 consisted of patients who died before ECP was available (n=7; mean age, 65 years; 3 women and 4 men).

The ECP treatment was performed on 2 consecutive days at 4 weekly intervals in most cases; longer or shorter intervals were used in a minority of patients according to response to treatment. Leukapheresis was performed 2 hours after ingestion of methoxypsoralen (0.6 mg/kg) or methoxsalen (Uvadex, Therakos, Exton, Pa) (200 µg) was added directly to the leukocyte-enriched fraction (9 patients). The leukocyte-enriched fraction was then irradiated as it was pumped through a 1-mm thick UV-A transparent plate sitting between UV-A bulbs that delivered 1 to 2 J/cm^2 of UV-A (UVAR electropheresis system, Therakos). The treated blood was then reinfused.

Kaplan-Meier graphs were constructed to estimate median survival from diagnosis to death from any cause, enabling patients who had varying lengths of follow-up to contribute to the calculation of median survival. Cox regression analysis was used to compare survival in the different groups, correcting for age, sex, and initial Sézary cell count (Stata Statistical Software, release 5.0, Stata Corporation, College Station, Tex). A *P* value of less than .05 was considered significant.

ogy, London, England, who received ECP between January 1991 and August 1996 with survival of patients who did not receive ECP during the same period, and with a group of patients treated between 1987 and 1991. Of note, all our patients had T-cell clones in the peripheral blood as demonstrated by TCR gene analysis.

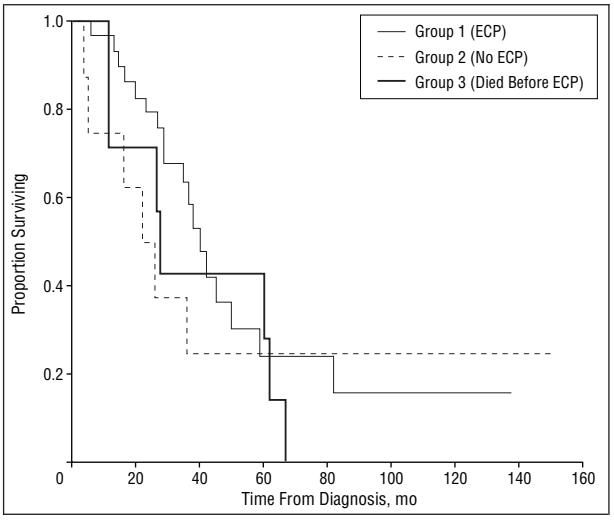

Figure 1. *Survival in groups 1, 2, and 3 (Kaplan-Meier analysis). The median survival rates in groups 1, 2, and 3 are 39 months, 22 months, and 27.5 months, respectively. Cox regression analysis showed no significant increase in survival in the patients treated with extracorporeal photopheresis (ECP), after correcting for age, sex, and initial Sézary cell count.*

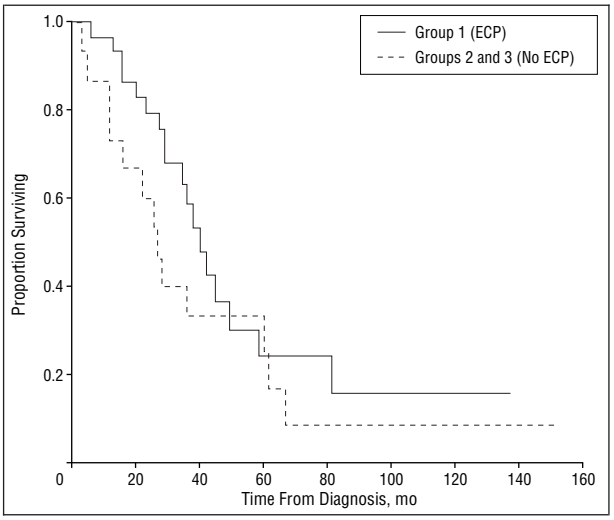

Figure 2. *Survival in group 1 compared with groups 2 and 3 combined (Kaplan-Meier analysis). The median survival is 39 months for the patients treated with extracorporeal photopheresis (ECP) and 26.5 months for those who did not receive ECP. Cox regression analysis showed no significant increase in survival in the ECP-treated patients (P = .12).*

RESULTS

SURVIVAL

Patients who died before the end of 1991 had a median survival from diagnosis of 27.5 months (range, 12-67 months). This compares with 39 months (range, 3-138 months) in patients treated with ECP and 22 months (range, 41-51 months) in patients who did not receive ECP (**Figure 1**). Cox regression analysis comparing the 3 groups did not show any significant difference in survival.

Groups 2 and 3 were combined to increase numbers in the non–ECP-treated group, and median survival in this group was 26.5 months. (**Figure 2**). Regression analysis comparing survival in group 1 with groups 2 and 3 combined did not show a significant increase in survival in the

Table 1. Systemic Treatment*

Treatment	Group 1: ECP (n = 29)	Group 2: No ECP (n = 8)	Group 3: Died Before ECP (n = 7)
Chemotherapy			
Chlorambucil	19	6	7
Chlorambucil with prednisolone	16	5	4
Fludarabine phosphate	3	0	0
Pentostatin	2	1	1
Methotrexate	3	3	2
PACEBOM	2	0	0
CHOP	6	0	1
Cyclophosphamide	0	0	1
Razoxane	1	0	0
Hydroxyurea	1	0	0
Radiotherapy			
Skin	6	2	1
Lymph nodes	6	0	1
Total skin electron beam	2	2	0
Photochemotherapy	16†	6	4
Immunomodulators			
Interferon alfa	12	1	5
Prednisolone	8	2	2
Azathioprine	3	1	1
Cyclosporine	2	0	0
Cosyntropin	0	0	2
Miscellaneous			
Retinoids	7†	1	1

**ECP indicates extracorporeal photophoresis; PACEBOM, prednisolone, adriamycin, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate; and CHOP, cyclophosphamide, vincristine, adriamycin, prednisolone.*

†Includes 1 patient who received a combination of retinoid therapy and photochemotherapy.

ECP-treated patients (hazard ratio, 0.56; 95% confidence interval, 0.26-1.17; $P = .12$). Fourteen of 29 patients in group 1 and 6 of 15 in groups 2 and 3 combined had lymph node biopsies. Dermatopathic changes were found in 2 patients in group 1 and 2 patients in groups 2 and 3 combined. The remainder all showed evidence of lymphoma, 12 in group 1 and 4 in the other 2 groups.

Eleven patients in group 1 and 2 patients in group 2 were alive at the time of analysis.

SYSTEMIC TREATMENT

Systemic treatments for the 3 groups are given in **Table 1**. In all 3 groups the majority of patients received chlorambucil (32/44), usually with prednisolone. Photochemotherapy was also used in most cases (26/44). CHOP (cyclophosphamide, vincristine, adriamycin, prednisolone) was the most common form of combination chemotherapy used, while fludarabine phosphate, pentostatin, methotrexate, and cyclophosphamide were used as single agents.

Eight patients were seen at St John's Institute of Dermatology and did not receive ECP at a time when it was available. Four responded clinically to other treatments: pentostatin and prednisolone (1 case), chlorambucil only (1 case), radiotherapy only (1 case), and chlorambucil, total skin electron beam therapy, and interferon alfa (1 case). Two patients died, having failed to respond to prednisolone and chlorambucil. One patient was considered too frail to receive ECP (83 years old) and 1 developed extensive visceral involvement 1 year after presentation and having received methotrexate, etretinate, and radiotherapy to the skin.

Two patients in this group are alive; 1 remains in complete remission after receiving pentostatin in 1992 and 1 patient has reasonable disease control while taking intermittent chlorambucil.

EXTRACORPOREAL PHOTOPHERESIS

The number of treatments given; reason for stopping ECP; the types of treatments received before, during, and after ECP; and outcome are shown in **Table 2**.

The mean number of ECP treatments received was 14.3 (range, 2-51). Only 3 patients received ECP as their first treatment; 1 remains alive with reasonable disease control after 2 years of monthly treatments and 2 have died of progressive disease having received 6 and 9 ECP treatments followed by combination chemotherapy and radiotherapy. Eighteen patients did not receive additional systemic therapy or radiotherapy while receiving ECP. Eleven patients received 0 to 7 ECP treatments and 18 patients received more than 7 ECP treatments.

In group 1, the mean time from diagnosis to the first ECP treatment was 20 months (range, 1-127 months), and in this group of 29 patients, 11 remain alive and 5 are still maintained on ECP. Six patients remain alive, having stopped ECP for several reasons (Table 2); 3 are maintained on chlorambucil (2 patients) and methotrexate (1 patient), 1 patient has progressive disease despite receiving total skin electron beam therapy, 1 is receiving CHOP, and 1 is receiving fludarabine.

Although the mean time from diagnosis to commencement of ECP treatment was 20 months, 5 patients started ECP more than 30 months after diagnosis. Of these, only 1 has died, 82 months after diagnosis, having received 22 treatments. The other 4 patients have a median survival from diagnosis of 82 months (range, 44-138 months) compared with the median survival of 39 months for this group as a whole.

Treatment with ECP was generally well tolerated and was not discontinued as a result of adverse effects of the procedure. Treatment was stopped in 10 patients who did not respond or had progressive disease and 5 patients died during the treatment (3 of CTCL and 2 of infection with active disease). Venous access was a problem in 3 patients. One patient found the traveling to the treatment facility too onerous, 1 developed a pulmonary embolism that required warfarin anticoagulation, and 1 developed cardiovascular disease.

ONSET OF SYMPTOMS

Diagnosis in almost all patients was preceded by symptoms of varying duration. In groups 1, 2, and 3, the median time from onset of symptoms to diagnosis was 28.5 months (range, 0-360 months), 27.5 months (range, 7-157 months), and 23 months (range, 11-117 months), respectively. An eczematous eruption was commonly the first symptom. One patient was diagnosed as having parapsoriasis en plaque 30 years before a diagnosis of SS was made.

Table 2. Extracorporeal Photopheresis Treatment*

Patient No.	No. of ECP Treatments	Reason ECP Stopped	Outcome	Therapy Before ECP	Therapy During ECP	Therapy After ECP
1	18	PD	A	PUVA, MTX, CyA	. . .	TSEB
2	3	CVS disease	D	PUVA, etretinate	. . .	Not known
3	5	PD	D	PUVA, P&C, etretinate, AZA	. . .	P&C
4	5	Pulmonary embolism	A	PUVA, P&C	. . .	MTX
5	3	Venous access	A	IFN, UV-B, P	. . .	P&C
6	6	PD	D	None	DXT-LN, skin	CHOP, acitretin
7	4	Venous access	D	P&C, IFN	. . .	P&C, acitretin
8	5	PD	A	IFN	. . .	Fludarabine, P&C, razoxane
9	3	Travel	A	PUVA, C, DXT-LN	. . .	CHOP
10	2	Died	D	P&C	. . .	Died during ECP
11	5	Died	D	P, AZA, CHOP, PUVA, fludarabine	TSEB, DXT-LN	Died during ECP
12	22	PD	D	PUVA	P&C	DXT-skin, IFN
13	9	PD	D	Fludarabine	DXT-LN	CHOP
14	16	Ongoing	A	PUVA, P	DXT-LN	Ongoing ECP
15	51	Ongoing	A	P&C, PUVA, IFN	. . .	Ongoing ECP
16	18	No response	A	P&C	. . .	C
17	10	PD	D	P&C, UV-B, PUVA, IFN, pentostatin	. . .	P&C
18	24	Died	D	PUVA, P&C, mustine	P, IFN	Died during ECP
19	24	Ongoing	A	PUVA, UV-B	. . .	Ongoing ECP
20	46	Ongoing	A	P&C	P	Ongoing ECP
21	11	PD	D	DXT-skin, P&C, PUVA	DXT-skin, IFN	CHOP
22	9	PD	D	None	. . .	CHOP, re-PUVA, DXT-skin, PACEBOM
23	3	Venous access	D	P&C	. . .	IFN, MTX, acitretin
24	11	Died	D	IFN, P&C, pentostatin	. . .	Died during ECP
25	17	PD	D	C	. . .	P&C
26	13	Died	D	P	DXT-skin, IFN	Died during ECP
27	25	PD	D	C, PUVA, CyA	DXT-LN, skin	PACEBOM, PUVA
28	26	Not known	D	Etretinate, UV-B, AZA, IFN, PUVA, hydroxyurea, P&C	P&C, P	Not known
29	22	Ongoing	A	None	None	Current ECP

**ECP indicates extracorporeal photopheresis; PD, progressive disease; A, alive; D, dead; CVS, cardiovascular; TSEB, total skin electron beam therapy; P, prednisolone; C, chlorambucil; CyA, cyclosporine; MTX, methotrexate; AZA, azathioprine; IFN, interferon alfa; DXT, local radiotherapy; LN, lymph nodes; CHOP, cyclophosphamide, vincristine, adriamycin, prednisolone; PACEBOM, prednisolone, adriamycin, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate; PUVA, psoralen–UV-A; P&C, prednisolone and chlorambucil; and ellipses, no systemic treatment except ECP.*

COMMENT

Our data does not support the contention that ECP prolongs survival in patients with SS. Thus, a median survival of 39 months in 29 patients treated with ECP (group 1) was not significantly different from a median survival of 22 months in the non–ECP-treated group (group 2) or of 26.5 months in the historical controls treated before ECP was available (group 3). Because TCR gene analysis was used routinely at St John's Institute of Dermatology only 2 years before ECP became available, the number of patients in group 3 is small. Because most patients referred to St John's after 1991 were referred for consideration of therapy with ECP, the number in group 2 is also small. As this can affect the level of significance, the analysis was repeated with groups 2 and 3 combined. Again, the difference in survival between the ECP and non–ECP-treated groups failed to reach significance (P=.12). Retrospective data are often published but are subject to selection and confounding biases. These are eliminated as much as possible in a randomized, prospective study. This was a retrospective, nonrandomized study, and so most of the patients treated with ECP had already been treated with conventional therapy. Although an argument could be made that ECP would therefore be given to patients with a poorer prognosis, it could also be argued that ECP is given to those patients who survive long enough to receive other treatments before referral for consideration of ECP treatment, thus biasing this group toward patients with a better prognosis. The patients in our study who survived longest also had the longest time from diagnosis to the start of ECP treatment, which would tend to support this suggestion. Furthermore, the survival of patients treated before ECP was available (group 3) was longer than for group 2 patients, suggesting that the most severely affected patients had been allocated therapeutic modalities other than ECP. For these reasons, the differences that do exist between the ECP and non–ECP-treated groups may reflect selection bias rather than the impact of treatment on survival.

Although retrospective data are often the subject of debate, there is no ambiguity about the median survival of 39 months in our ECP-treated group. This is considerably less than that reported in other series in the literature. Thus, the cohort of 29 patients with erythrodermic CTCL originally reported by Edelson et al[3] had a median survival of 60.3 months.[11] This is contrasted with a median survival of 30 months in historical controls not treated with ECP. More recently, Gottleib et al[16] reported a median survival of more than 100 months from diagnosis in 28 patients with CTCL. Unfortunately, at least 4 of these patients had patch or plaque mycosis fungoides rather than erythroderma, so it is more difficult to compare these data with our own. Similarly, Zic et al[12] reported a median survival of 96 months in 20 patients treated with ECP, but again only 3 of these were erythrodermic and no controls were included in their study. Even so, such data are widely quoted as providing evidence for the beneficial effects of ECP on survival in patients with erythrodermic and other forms of CTCL. Our findings suggest that these claims should be treated with caution, particularly as these studies did not use clonality for diagnostic purposes.

The main advantages of our study are the large number of patients treated and the fact that the groups used for comparison were patients treated at the same institute with conventional therapy either contemporaneously or shortly before ECP became available. Additionally, all patients exhibited erythroderma and all had definite evidence of a neoplastic population of T cells in the peripheral blood using Southern blot analysis of the TCR β gene. We therefore had unequivocal evidence of lymphoma and were not treating patients with benign erythroderma. Other studies have not used clonality as a criterion for diagnosis. Thus, in the original study by Edelson et al,[3] only 11 of 39 patients were known to have a peripheral blood clone. Because they did not report how many of these patients were erythrodermic or the clonality status of the other 26 subjects, the number of erythrodermic patients without a T-cell clone cannot be estimated. Similar considerations apply to the study by Gottlieb et al[16] in which clones were detected in 9 of 15 patients tested while 13 patients were not tested. This may explain the shorter median survival of 39 months in our ECP-treated patients compared with 60.3 months in 29 erythrodermic patients reported by Heald et al[11] and greater than 100 months from diagnosis by Gottlieb et al.[16]

Those who are persuaded of the efficacy of ECP on survival in patients with SS might argue that the stricter diagnostic criteria used in our study mean that patients are being treated too late in their disease to derive any benefit from ECP. However, TCR gene analysis using Southern blot analysis has a detection sensitivity of 1% to 5%[10] and polymerase chain reaction–based analysis is even more sensitive.[17] Since a minimum of 10% of mononuclear cells in SS exhibit atypical, cerebriform nuclei, TCR gene analysis should, by definition, be at least as sensitive as conventional morphologic assessment. Furthermore, the rationale of treating patients who do not have a peripheral blood clone is questionable. Since it is generally accepted that ECP exerts its therapeutic effect in CTCL by rendering malignant T cells immunogenic,[18] how can it work if malignant cells are not detected in the peripheral circulation?

In this retrospective, nonrandomized study of 44 patients with SS and genotypic evidence of a T-cell clone in the peripheral blood we have been unable to demonstrate a significant influence of ECP on survival. A randomized controlled trial in which ECP is compared with standard chemotherapy is clearly needed. To recruit sufficient patients, the study will need to be international and genotypic evidence of a peripheral blood T-cell clone should be used as an entry criterion.

Accepted for publication March 5, 1998.

This work was presented at the annual meeting of the British Association of Dermatologists, Harrogate, England, July 1997, and at the meeting of the Cutaneous Lymphoma Project Group, European Organisation for Research and Treatment of Cancer, Munich, Germany, December 1996.

Reprints: Elisabeth Fraser-Andrews, MA, MRCP, Skin Tumour Unit, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, England.

REFERENCES

1. Sézary A, Bouvrain Y. Erthrodermie avec presence de cellules monstreuses dans le derme et le sang circulant. *Bull Soc Fr Dermatol Syphiligr.* 1038;45:254-260.
2. Haynes B, Hensley L, Jegasothy B. Phenotypic characterisation of skin infiltrating T-cells in cutaneous T-cell lymphoma: comparison with benign cutaneous T-cell infiltrates. *Blood.* 1980;60:463-473.
3. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. *N Engl J Med.* 1987;316:297-303.
4. Schmitt IM, Moor AC, Patrignelli R, et al. Increased surface expression of class I MHC molecules on immunogenic cells derived from the xenogenization of P815 mastocytoma cells with 8-methoxypsoralen and long-wavelength ultraviolet radiation. *Tissue Antigens.* 1995;46:45-49.
5. Kin YH, Bishop K, Varghese A, Hoppe RT. Prognostic factors in erythrodermic mycosis fungoides and the Sézary syndrome. *Arch Dermatol.* 1995;131:1003-1008.
6. Lutzner MA, Emerit I, Dupepaire R, Flandrin G, Grupper C, Prunieras M. Cytogenetic, cytophotometric and ultrastructural study of large cerebriform cells of the Sézary syndrome and description of a small cell variant. *J Natl Cancer Inst.* 1973;50:1142-1162.
7. Duncan SC, Winkelmann RK. Circulating Sézary cells in hospitalized dermatology patients. *Br J Dermatol.* 1978;99:171-178.
8. Trotter MJ, Whittaker SJ, Orchard G, Smith NP. Cutaneous histopathology of Sézary syndrome: a study of 41 cases with a proven circulating T-cell clone. *J Cutan Pathol.* 1997;24:286-291.
9. Weiss LM, Wood GS, Hu E, Abel EA, Hoppe RT, Sklar J. Detection of clonal T-cell receptor gene rearrangements in the peripheral blood of patients with mycosis fungoides/Sézary syndrome. *J Invest Dermatol.* 1989;92:601-604.
10. Whittaker SJ, Smith NP, Russell-Jones R, Luzzatto L. Analysis of beta, gamma and delta TCR genes in mycosis fungoides and Sézary syndrome. *Cancer.* 1991; 68:358-366.
11. Heald P, Rook A, Perez M, et al. Treatment of erythrodermic cutaneous T-cell lymphoma with extracorporeal photochemotherapy. *J Am Acad Dermatol.* 1992; 27:427-433.
12. Zic J, Arzubiaga C, Salhany KE, et al. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 1992;27:729-736.
13. Armus S, Keyes B, Cahill C, et al. Photopheresis for the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 1990;23:898-902.
14. Prinz B, Behrens W, Hölzle E, Plewig G. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma: the Düsseldorf and Munich experience. *Arch Dermatol Res.* 1995;287:621-626.
15. Zic JA, Stricklin GP, Greer JP, et al. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol.* 1996;35:935-945.
16. Gottlieb SL, Wolfe JT, Fox PE, et al. Treatment of cutaneous T-cell lymphoma with extracorporeal photopheresis monotherapy and in combination with recombinant interferon alfa: a 10-year experience at a single institution. *J Am Acad Dermatol.* 1996;35:946-957.
17. Bourguin A, Tung R, Galili N, Sklar J. Rapid, nonradioactive detection of clonal T-cell receptor gene rearrangements in lymphoid neoplasms. *Proc Natl Acad Sci U S A.* 1990;87:8536-8540.
18. Lim HW, Edelson RL. Photopheresis for the treatment of cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am.* 1995;9:1117-1126.