



Extracorporeal photochemotherapy in cutaneous T-cell lymphoma

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Abstract

Extracorporeal photochemotherapy was originally conceived for the treatment of cutaneous T-cell lymphoma (CTCL) and as well as other T-cell mediated diseases. Evidence collected in the past 17 years has demonstrated that this treatment modality can have a very significant effect on the course of a subset of CTCL patients. The evidence available is positive but for a variety of reasons has been controversial within the medical community. A number of very well-designed multi-center trials which have been lacking since the first publication by Edelson et al. are being carried out so that hopefully a number of open questions will be resolved with greater clarity in the coming years. The fact remains that this innovative approach for the treatment of CTCL and T-cell mediated diseases has certainly opened new avenues of therapy and thought in photoimmunology and photomedicine. Clearly the very low side effect profile of this therapy has made it more attractive than the chemotherapeutic and immunosuppressive substances that are presently available or in experimental protocols. If and when the mechanisms of action are fully understood and appropriate studies investigating different treatment schedules and different combination therapies and modifications of its present form are performed the place of photopheresis in the therapeutics of CTCL as well as other T-cell mediated diseases and oncology will be better placed.

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1. Introduction

Twenty years ago the first encouraging experiences with extracorporeal photoimmunotherapy (ECP, photopheresis) were made. The then novel therapeutic modality has since been documented to be of significant value and above

expectations, in the treatment of cutaneous T-cell lymphoma (CTCL) as well as other T-cell mediated diseases in and outside of clinical dermatology.

The results of the first multi-center (USA and Europe) clinical trial suggesting that ECP may be of significant value in the treatment of CTCL were published by Edelson and co-workers in 1987 [1]. The subsequently established centers proceeded to explore the limits of its use both as monotherapy as well as in combination with more traditional but proven treatment modalities and in various stages (II–IVa) of the disease. ECP received FDA

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(Food and Drug Administration, USA) approval in 1988 for the palliative treatment of CTCL. As of 2002 it is being administered in over 150 centers in the United States, Europe, Latin America and the Near East with an expanded spectrum of T-cell mediated diseases beyond its original indication. ECP has also been shown to be efficacious in the management of acute and chronic graft versus host disease (GvHD) after allogeneic bone marrow transplantation, progressive systemic sclerosis and control of rejection after solid organ transplantation including heart, lung, and kidney [2].

Derived from the known psoralen and ultraviolet-A light (PUVA) treatment for dermatological diseases ECP involves the extracorporeal exposure of peripheral blood mononuclear cells (PBMC) to 8-methoxypsoralen and ultraviolet-A irradiation and subsequent return to the patient. The most commonly used machine for this treatment integrates an initial discontinuous leuka/plasma pheresis step with subsequent ultraviolet-A exposure in either a single unit or two separate units. Previously the drug 8-MOP was administered orally in a dose previously determined to produce a minimum of 60 µg/ml (suggested range: 60–200 ng/ml) of drug in the plasma ≈1.5 h after ingestion; presently following approval by the FDA in 1999 and the corresponding European Community regulatory agency the drug is delivered directly into the collected buffy-coat/plasma fraction prior to radiation and re-infusion. During the treatment procedure; the patient reclining in bed, blood is obtained from a cubital vein; anti-coagulated blood is then leucapheresed in a predetermined number of between three and six cycles (depending on the type of instrument used and patient's weight) through a continuously spinning centrifuge bowl. 240 ml of leukocyte-enriched blood is usually removed in this fashion and then pooled with up to 300 ml of plasma obtained during the same procedure. Between 100 and 200 ml of sterile normal saline are added in the process, yielding, under optimal conditions a targeted final hematocrit of approximately $2.5 \pm 1\%$. Higher values are considered to decrease the efficacy of the procedure as red blood cells are capable of interfering with and blocking the radiation of the mononuclear cells. In order to activate the 8-MOP con-

tained in the plasma and the nucleated blood cell fraction the total obtained volume is circulated through a 1 mm thick pathway in a sterile disposable cassette and exposed to UVA radiation, prior to re-infusion. As described and in order to completely circumvent problems in obtaining consistent reproducible psoralen levels in the to be irradiated fraction the new generation of instruments use extracorporeally administrable 8-MOP exclusively; a modification which, as shown by Knobler and Edelson [4], eliminates the known side effects of oral 8-MOP administration as well as need for pre-medication and drug level monitoring. Based on the various protocols which are still under scrutiny this treatment is, usually, repeated on 2 successive days at 2–4-week intervals. It can, in selected non responsive patients, be repeated for limited periods of time with much shorter intervals between treatments. During one treatment approximately 5–10% of the circulating T-cell pool is treated; the total UVA dose delivered has been targeted to be 2 J/cm².

As mentioned above the first clinical application of ECP was in the treatment of CTCL, with its efficacy and low side-effect profile being confirmed in numerous subsequent studies [1–5].

ECP is thus considered by leading authorities as a first line treatment for patients with erythrodermic stage disease CTCL [2] both alone or in combination with other proven treatment modalities. As reported, ECP has a remarkable low side-effect and toxicity profile; an additional motivating factor which has led to the evaluation of ECP for multiple other non-dermatological and dermatological indications. The rational basis for the additional treatment spectrum was supported by a number of experimental studies evaluating the effect of ECP on the immune system [6–15]. Under the assumption that ECP can suppress pathophysiologically relevant T-cell clones and relevant associated peptides a number of studies have been performed in order to evaluate the efficacy of ECP in inflammatory diseases other than CTCL where auto-reactive T-cells play a key role. Experience has been gained in selected disease entities such as systemic sclerosis, pemphigus vulgaris, rheumatoid arthritis, psoriasis arthritis,

systemic lupus erythematosus and, to a lesser extent atopic dermatitis and inflammatory bowel disease [16]. Data of the last two years shows that ECP may also have a major impact in the treatment of acute and chronic rejection in organ transplantation as well as GvHD after allogeneic bone marrow transplantation [2]. Carefully prospective randomized studies presently being performed in the later indication should help further expand the presence of this therapy in the area of hemato-oncology.

Understanding of key elements related to the mechanism of action and subsequent incorporation into improving the basic procedure should lead to a higher acceptance and decreased treatment costs which have been, from the start, a major point of criticism by those less familiar with the procedure and its efficacy; at issue are shorter treatment times and improved drug delivery associated with lower side-effects [3]. New research efforts are being concentrated on trying to precisely identify the molecular biological effects of this therapy, hopefully the final knowledge gained will contribute concurrently to a

better understanding of the pathomechanisms of the diseases treated and improvement in therapy [13–21].

Since CTCL was the first disease for which ECP was evaluated it is the area where the longest periods of observation are available. Enough evidence in clinical studies (Table 1), as well as FDA approval for use of ECP for the palliative treatment of the Sezary syndrome variant have helped to establish its value as a treatment of choice for this disease.

In the original study by Edelson and co-workers published in 1987 [1] 27 of 37 patients responded either with a partial or a complete remission. Subsequent published data appear to confirm the initial impressions of efficacy [2,21]. These studies, which showed that ECP is efficacious in CTCL describe a response rate that can reach 75% with possible complete remissions of up to 25% and no response in 25% of treated patients. Based on clinical, immunological and laboratory data the attempt has been made to better characterize those patients that are more likely to respond to ECP. As will be discussed later and also summarized in

Table 1
The largest series of treatments with ECP of patients with CTCL in North America and Europe

Author [Ref.]	Year	Total patients ^a	Overall response ^b	Partial response ^b	Complete response ^b
Edelson et al. [1]	1987	37	27 (73%)	18	9 (24%)
Heald [39]	1989	32	17 (53%)	12	5 (14%)
Dall' Amico et al. [55]	1991	37	27 (73%)	n.d.	9 (24%)
Koh [44]	1994	34	18 (53%)	13	5 (15%)
Prinz et al. [53]	1995	17	12 (71%)	6	0
Zic et al. [23]	1996	20	10 (50%)	5	5 (25%)
Gottlieb et al. [24]	1996	31	20 (65%)	13	7 (23%)
Duvic et al. [22]	1996	34	17 (50%)	11	6 (18%)
Owsianowski et al. [56]	1996	16	11 (69%)	7	4 (25%)
Konstantinow and Balda [58]	1997	12	8 (67%)	5	1 (8%)
Russell-Jones [30]	1997	19	10 (53%)	7	3 (16%)
Vonderheid [43]	1998	32	10 (31%)	6	4 (13%)
Zouboulis et al. [57]	1998	20	13 (65%)	n.d.	n.d.
Jiang et al. [51]	1999	25	20 (80%)	15	5 (20%)
Crovetti et al. [54]	2000	30	22 (73%)	12	10 (33%)
Bissaccia et al. [50]	2000	37	20 (54%)	15	5 (14%)
Wollina et al. [52]	2001	15	10 (67%)	3	5 (33%)
Total		448	272 (61%)	148 (33%)	83 (19%)

^a Only patients who underwent six or more cycles of photopheresis or have been treated with ECP for at least 6 months are included.

^b Defined heterogeneously by different authors.

Table 2
Characteristics of CTCL patients likely to respond to ECP

1. Duration of disease less than 2 years
2. No bulky adenopathy or major organ involvement
3. Whiteblood count less than 20.000 mm ^{minus3}
4. Presence of a discrete number of Sézary cells (10–20% of mononuclear cells)
5. Natural killer cell activity close to normal
6. Cytotoxic T-lymphocytes close to normal (CD8 ⁺ > 15%)
7. Absence of prior intensive chemotherapy
8. Plaque stage disease should not cover more than 10–15% of total skin surface

Table 2 a normal CD4/CD8 ratio, a normal absolute count of CD8 positive cells in the peripheral blood and short disease duration appear to be best associated with good therapeutic response [2], even though in an of themselves they are not a *conditio sine qua non*. An important and clinically relevant observation which has repeatedly been confirmed by all studies is the very low side-effect profile attributed to ECP [23].

Since a number of Sezary syndrome patients are not good responders to ECP, clinical studies have been initiated evaluating possible synergistic effects with other treatments such as Interferon alfa (IFN α), methotrexate, total skin electron beam therapy, PUVA, retinoids including bexarotene, and others [24–26]. Future multi-center prospective randomized studies should help define the value of this type of combination therapy in overall survival time and response. At this point in time what appears clear is that therapeutic combinations with ECP are not associated with increased side-effects nor negative influence in the efficacy of either treatment. This observation may perhaps indirectly provide clues as to which mechanisms may or may not be involved in ECP besides its proven PUVA-related cyto-reductive effect.

2. Extracorporeal photochemotherapy as monotherapy

ECP was originally introduced as monotherapy in the palliative treatment of therapy resistant CTCL (Sézary Syndrome). Since the original publication by Edelson and co-workers [1] a number of groups in the USA. and Europe have

reported on a total of 448 patients (see Table 1). The overall response rate with the use of ECP as monotherapy is 61% in 448 patients studied.

In 1992 Heald and co-workers reported on the original group of patients described by Edelson et al. in 1987 [2]. Based on this study which unfortunately was not carried out in a prospective fashion, and thus frequently open to criticism [27,28], is the suggestion that when compared to historical controls the median survival of the patients treated is 60 months, 33 months from the date of diagnosis and 47.9 from the date of initiation of ECP. In four of the six patients who went into complete remission this has been maintained. In this report the observation, later confirmed by others, was made that best responders are found among patients with a lower CD4/CD8 ratio in the peripheral blood when ECP was initiated [29]. All reported subsequent studies suggest that survival may be increased but, again, formal well designed studies are absent. Gottlieb et al. [24] reported on a larger group of 41 patients. In this, a 10 year retrospective study, they evaluated their results on the value of ECP used as monotherapy as well as in combination with IFN α (12 patients) and other local or systemic medication. In their group 31 of 41 patients received six or more cycles of ECP, 28 patients had ECP as monotherapy. Seventy-one percent of these patients were described as responders to ECP; seven patients (25%) had a partial remission as defined by more than 50% clearing of skin disease. Of significance in this study was the observation that presence of Sézary cells in the peripheral blood was associated with a favorable response, an observation later confirmed by others as well as in our own experience [29]. From a retrospective point of view Gottlieb et al.

also suggest that ECP may be associated with increased survival. In their study median time to treatment failure was 18 months, median survival from initiation of therapy was 77 months and from time of diagnosis 100 months. This appears to be significantly longer than reported by previous studies of a similar patient cohort where use of other accepted therapies revealed survival rates of 30–40 months [29]. In a similarly retrospective review Duvic et al. [22] reported on 34 patients with an overall response rate of 50%; six patients (18%) achieved a CR and 11 (32%) were able to obtain a PR. Of note was the fact that 28 of these 34 patients had erythrodermic CTCL and that best response was obtained on a treatment schedule of at least two consecutive treatments at monthly intervals. Duvic et al. tried to modify the original schedule reported by Edelson by increasing the number of collection cycles/treatment from six to nine and also using an alternate anticoagulant—acid citrate dextrose-A instead of heparin. Non-responders were treated at intervals of two weeks. No significant advantage could be observed under these changes. Interestingly they report on an increase in IgG values in their responders suggesting that ECP may be associated with improved immune function. This observation has not been reproduced by others. Most observers report that among responders there appears to be a significant decrease in the absolute number of CD4⁺ peripheral blood cells suggesting that this may correlate with a drop in circulating malignant cells with this marker [29]. Gottlieb et al. also observed that in patients where a complete clinical response was documented the circulating Sézary cells could not be detected and molecular biological studies for T-cell receptor gene rearrangements (Southern blot analysis, polymerase chain reaction) suggested disappearance of the malignant clone from circulation.

A major issue of controversy regarding increased survival times has been the report published by Heald and co-workers in 1992 [39] where they retrospectively analyze survival of the original group of patients and conclude increased survival when compared to historical controls. In 1997 a European group under Russell-Jones and co-workers reported on their experiences with ECP as

monotherapy in 19 patients [30] with the Sézary Syndrome. Their results show minor responses (>25% improvement in skin score) in 10 patients (53%). Of the responding group these (16%) had a complete response which was defined as greater than 90% improvement in their skin score. Of value in this study is not so much the fact that their response rates are lower than those reported in the original study but the fact that there appeared to be a presumed major discrepancy in their definition of the Sézary syndrome. This group included only patients where a T-cell clone had been detected in the peripheral blood prior to consideration for treatment with ECP. As pointed out in the original Edelson study only 11 of the 37 patients included had been proven to have clonal disease. At issue is the observation that all studies performed which included series with ECP as monotherapy or in combination are easy targets for criticism: none was qualified as a truly prospective, randomized study using established and standardized elements of classification and diagnosis. These issues still have difficulty in finding major agreement among experts and recent new classification attempts (such that of the European Organization for Research and Treatment of Cancer—EORTC—Cutaneous Lymphoma Project Group) [31] have yet to be met with universal acceptance for planning clinical trials.

3. Extracorporeal photochemotherapy in combination with other treatment modalities

ECP appears to obtain surprising long term and frequent responses in patients with the Sézary syndrome in its early stages but there remains a large group where response is not quite as satisfactory. The lack of response in a significant number of patients with tumor stage disease (plaque, patch, tumor) as well as refractory Sézary patients has prompted the search for ideal combination therapies though not in a systematic fashion. Among the earliest to be reported and among the most widely used is IFN α -2b. A number of reports suggest that the addition of a biological response modifier to ECP in refractory patients may be highly beneficial [21,24,25,

32–34,36]; Rook and co-workers reported as early as 1991 that the combination of ECP and low dose IFN α -2b has a possible synergistic effect that can lead to complete remission with disappearance of the malignant T-cell alone from the peripheral blood as documented by Southern blot analysis [21]. As described in subsequent reports and in our own hands normalization of the peripheral blood lymphocyte phenotypic profile and concomitant increase in natural killer cell activity can also take place (Knobler, unpublished observation) [37].

The report by Dippel and co-workers ranks among the larger studies that support possible synergistic effects between ECP and IFN α -2b [35]. In this study 19 patients with advanced disease were treated with ECP and IFN α -2a. Their ECP treatment schedule was standard, namely on two consecutive days every 2–4 weeks for an average of 16 months. This was an open two arm trial comparing ECP alone (10 patients) to the combination (9 patients) whereby the dosage range of IFN α -2b was 3–18 million units three times weekly. Using their own severity index score (CTCL-SI) designed for this study they obtained one complete remission in the ECP arm, one minor response, eight patients with stable disease, the reduction in their CTCL-SI reduction rate being 1.4%. In contrast, the combined therapy showed four complete remissions, two partial responses and two stable disease with a median reduction in the CTCL-SI score of 65.7%. Though impressive, this study has repeatedly been criticized for not including a third arm with Interferon alfa 2b alone [38]. Among the critics, Zackheim points out other studies that document that IFN α -2b maybe be at least as good if not better when used as monotherapy [34]. Clearly as has been the case since the appearance of the first study, prospective, randomized studies are lacking to confirm either observation. In this particular instance a three armed study with an appropriate number of patients may be needed to document the true value of combining ECP with IFN α .

Within the same framework reports of response in refractory patients when a third agent is added such as interleukin 2 or interleukin 12 plus GM-CSF [29,40,41] have to wait for appropriate confirmatory studies. Similarly speculative due to

lack of properly designed studies are the results reported by Gottlieb et al. [24] where from their 10 year review series on 41 patients of which 31 had at least 6 cycles of ECP, they report on 9 patients who presented with an enhanced clinical response when IFN α -2b was added to ECP monotherapy.

Among the alternatives available such as PUVA, Chemotherapy, cytokines, retinoids including the newest generation—bexarotene, the most extensive series which try to document a synergistic effect with increase in long term survival are those where total skin electron beam therapy (TSEB) has been used [42–45]. In their first report Wilson et al. [42] evaluated 163 patients with CTCL who were all treated with a full dose of TSEB therapy (36 Gy at 1 Gy/day for 9 weeks and 6 MeV electrons) with curative intent. All patients achieving a clinical complete response or good partial responses to TSEB therapy were further randomized to be treated with either adjuvant doxorubicin/cyclophosphamide chemotherapy or ECP. In this retrospective analysis they were able to show that at 3 years those patients who had been in a more advanced stage disease namely T3 and T4 had an improved overall survival. For the group treated with combination chemotherapy survival was 75% at 3 years, those with ECP 100% and those with neither 50%. In the analysis of the overall survival curves only the group treated with ECP approached statistical significance ($p < 0.06$), while a significant survival benefit from the addition of chemotherapy could not be noted. The results of these studies should serve as the basis for the planning and development of prospective, randomized trials so that the value of ECP as adjuvant maintenance therapy after TSEB in patients with advanced T3 and T4 stage CTCL can be better established. The same group reported on their experiences using ECP concurrently to TSEB in erythrodermic (T4) mycosis fungoides patients who had been treated with TSEB and concurrent ECP and those receiving TSEB only [45]. In this retrospective non randomized study a total of 44 patients were evaluated. All patients received TSEB obtaining a CR of 73% within 2 months of completion. Their 32 patients with CR had a disease free survival (DFS) of 63%. Within this group DFS was 49% for the 17 patients who

had not received concomitant ECP whereas those 15 patients who had received TSEB + CP had a DFS of 81%. From this data the authors concluded that the concurrent use of ECP with TSEB warrants future studies.

Other trials supporting the increased rate of ECP in maintaining CR have also not been performed within the framework of properly designed trials. From the information available and based on our own experience ECP is the treatment of choice in Erythrodermic CTCL patients—Sézary Syndrome variant. Lack of trials has attracted justified criticism and hopefully future trials will be designed to answer all open questions and help put the value of ECP in proper perspective. Since ECP is from the outset an immuno-modulating therapy requiring still a working immune system capable of an immune response it is recommended that in general ECP should be administered in earlier rather than later stages of CTCL. Due to the very low side-effect profile and lack of significant side-effects ECP is often utilized in our center as first line therapy. Use of biological response modifiers as adjunctive therapy such as Interferon alfa are recommended with the constraints previously described [29]. Recommendations for optimal choice of patients have been made as a result of the many studies performed but none appears to be truly conclusive since they are not the result of properly performed trials. Still and even though exceptions are many, even in our own hands, the recommendations as shown in Table 2 can be helpful in the choice of patients.

4. Characteristics of CTCL patients likely to respond to ECP

The characteristics that seem to help identify the best responders to ECP, particularly as monotherapy, and which are agreed upon by a number of major investigators [29,43,44] are delineated in Table 2. They include the following: (1) Short duration of disease, preferably less than 2 years. (2) Absence of bulky lymphadenopathy or major internal organ involvement. (3) No high blood count leucocytosis/leukemia with more than 20,000 per mm³. (4) Presence of a discrete number

of Sézary cells (10–20% of mononuclear cells). (5) Normal or close to normal natural killer cell activity. (6) Close to normal numbers of cytotoxic T lymphocytes whereby suppressor CD8⁺ T-cells should be above 15%. (7) Lack of prior intensive chemotherapy. (8) Plaque stage disease should not cover more than 10–15% of the skin surface area. The above criteria are helpful in identifying best responders they are not absolute as we and others have had impressive responders who did not meet these criteria. These criteria do reflect however the necessity that the individual must have an immune system capable of responding to the malignant cells treated in the photo-activating device. Recent experimental findings certainly suggest strongly that this may be the case [46–49]. The concept that ECP may serve as the basis so that in the long run it may be possible to establish a patient specific tumor vaccine without prior requirement of identifying the tumor distinctive antigen is very exciting [59]; future research should certainly intensify a search for avenues to make these and similar concepts a practical reality.

References

- [1] Edelson RL, Berger CL, Gasparro FP, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. *N Engl J Med* 1987;316:297–303.
- [2] Knobler RM, Girardi M. Extracorporeal photochemoimmunotherapy in cutaneous T cell lymphomas. *Ann NY Acad Sci* 2001;941:123–38.
- [3] Knobler RM, Trautinger F, Graninger W, et al. Parenteral administration of 8-methoxypsoralen in photopheresis. *J Am Acad Dermatol* 1993;28:580–4.
- [4] Knobler RM, Edelson RL. Cutaneous T-cell lymphoma. *Med Clin North Am* 1986;70:109–38.
- [5] Knobler RM. Photopheresis—extracorporeal irradiation of 8-MOP containing blood—a new therapeutic modality. *Blut* 1987;54:247–50.
- [6] Berger CL, Perez M, Laroche L, Edelson RL. Inhibition of autoimmune disease in a murine model of systemic lupus erythematosus induced by exposure to syngeneic photo-inactivated lymphocytes. *J Invest Dermatol* 1990;94:52–7.
- [7] Berger CL, Wang N, Christensen I, et al. The immune response to class I-associated tumor-specific cutaneous T-cell lymphoma antigens. *J Invest Dermatol* 1996;107:392–7.
- [8] Edelson R. Light activated drugs. *Sci Am* 1988;259:68–75.
- [9] Gasparro FP, Song J, Knobler RM, Edelson RL. Quantitation of psoralen photoadducts in DNA isolated from lymphocytes treated with 8-methoxypsoralen and

- ultraviolet a radiation extracorporeal photopheresis. *Curr Probl Dermatol* 1986;15:67–84.
- [10] Gasparro FP, Dall'Amico R, O'Molloy M, Heald PW, Edelson RL. Cell membrane DNA: a new target for psoralen photoadduct formation. *Photochem Photobiol* 1990;52:315–21.
- [11] Perez M, Edelson RL, Laroche L, Berger C. Inhibition of antiskin allograft immunity by infusions with syngeneic photoinactivated effector lymphocytes. *J Invest Dermatol* 1989;92:669–76.
- [12] Vowels BR, Cassin M, Boufal MH, Webster LJ, Rook AR. Extracorporeal photo-chemotherapy induces the production of tumor necrosis factor- α by monocytes: implications for the treatment of cutaneous T-cell lymphoma and systemic sclerosis. *J Invest Dermatol* 1992;96:686–92.
- [13] Gasparro FP, Berger CL, Edelson RL. Effect of monochromatic UVA light and 8-methoxypsoralen on human lymphocyte response to mitogen. *Photodermatol* 1984;1:10–7.
- [14] Santella RM, Dharmaraja N, Gasparro FP, Edelson RL. Monoclonal antibodies to DNA modified by 8-methoxypsoralen and ultraviolet a light. *Nucleic Acids Res* 1985;13:2533–44.
- [15] 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;46:45–9.
- [16] Reinisch W, Nahavandi H, Santella R, et al. Extracorporeal photochemotherapy in patients with steroid-dependent Crohn's disease: a prospective pilot study. *Aliment Pharmacol Ther* 2001;15:1313–22.
- [17] Sumpio BE, Phan SM, Gasparro FP, Deckelbaum LI. Control of smooth muscle cell proliferation by psoralen photochemotherapy. *J Vasc Surg* 1993;17:1010–6.
- [18] Trautinger F, Knobler RM, Macheiner W, Grunwald C, Micksche M. Release of oxygen-free radicals by neutrophils is reduced by photopheresis. *Ann NY Acad Sci* 1991;636:383–5.
- [19] van Iperen HP, Beijersbergen van Henegouwen GM. Animal model for extracorporeal photochemotherapy based on contact hypersensitivity. *J Photochem Photobiol Biol* 1992;15:361–6.
- [20] Yamane Y, Lobo FM, John LA, Edelson RL, Perez MI. Suppression of anti-skin-allograft response by photodamaged effector cells—the modulating effects of prednisone and cyclophosphamide. *Transplantation* 1992;54:119–24.
- [21] Rook A, Prystowsky MB, Cassin M, Boufal M, Lessin RS. Combined therapy for Sezary syndrome with extracorporeal photochemotherapy and low-dose interferon alfa therapy. *Arch Dermatol* 1991;127:1535–40.
- [22] Duvic M, Hester JP, Lemak NA. Photopheresis therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996;35:573–9.
- [23] Zic J, Stricklin GP, Greer JP, et al. Long term follow-up with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1996;35:935–45.
- [24] Gottlieb S, Wolfe J, Fox FE, 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;35:946–57.
- [25] Cohen J, Lessin SR, Vowels BR, et al. The sign of Leser-Trelat in association with Sezary syndrome: simultaneous disappearance of seborrheic keratoses and malignant T-cell clone during combined therapy with photopheresis and interferon alfa. *Arch Dermatol* 1993;129:1213–5.
- [26] Frieden T, Bia FJ, Heald PW, et al. Cutaneous cryptococcosis in a patient with cutaneous T-cell lymphoma receiving therapy with photopheresis and methotrexate. *Clin Infect Dis* 1993;17:776–8.
- [27] Fraser-Andrew E, Seed P, Whittaker S, Russel-Jones R, et al. Extracorporeal photopheresis in Sézary syndrome. *Arch Dermatol* 1998;134:1001–5.
- [28] Russel-Jones R. Extracorporeal photopheresis in cutaneous T-cell lymphoma inconsistent data underline the need for randomized studies. *Brit J Dermatol* 2000;142:16–21.
- [29] Rook AR, Suchin KR, Kao DM, et al. Photopheresis: clinical applications and mechanism of action. *J Invest Dermatol Symp Proc* 1999;4:85–90.
- [30] Russel-Jones AR. Extracorporeal photopheresis in Sézary syndrome. *Lancet* 1997;350:886.
- [31] Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the cutaneous lymphoma study group of the European Organization for Research and Treatment of Cancer. *Blood* 1997;90:354–71.
- [32] Fimiani M, Rubegni P, De Aloe G, Andreassi L. Role of extracorporeal photochemotherapy alone and in combination with interferon alfa in the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1999;41:502–3.
- [33] Vonderheid EC, Bigler RD, Greenberg AS, Neubaum SJ, Micaily B. Extracorporeal photopheresis and recombination interferon alfa b in Sezary syndrome: use of dual marker labeling to monitor therapeutic response. *Am J Clin Oncol* 1994;17:255–63.
- [34] Olsen EA, Bunn PA. Interferon in the treatment of cutaneous T-cell lymphoma. *Hematol Oncol North Am* 1995;9:1089–107.
- [35] Dippel E, Goerdt S, Assaf C, Stein H, Orfanos CE. Extracorporeal photopheresis and interferon- α in advanced cutaneous T-cell lymphoma. *Lancet* 1997;350:32–3.
- [36] Jumbou O, N'Guyen JM, Tessier MH, Legoux B, Dreno B. Long-term follow-up in 51 patients with mycosis fungoides and Sézary syndrome treated by Interferon-alfa. *Br J Dermatol* 1999;140:427–31.
- [37] Haley HR, Davis DA, Sams WM. Durable loss of malignant T-cell clone in a stage IV cutaneous T-cell lymphomas patient treated with high-doses interferon and photopheresis. *J Am Acad Dermatol* 1999;41:880–3.
- [38] Zackheim HS. Evidence is lacking for a synergistic or additive effect of combination extracorporeal photopheresis.

- sis with interferon alfa for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2000;42:1087–8.
- [39] Heald PW, Perez MI, Christensen I, Dobbs N, McKiernan G, Edelson R. Photopheresis therapy in cutaneous T-cell lymphoma: The Yale New Haven Hospital Experience. *Yale J Biol Med* 1989;61:629–38.
- [40] Rook AH, Gottlieb SL, Wolfe JT, et al. Pathogenesis of cutaneous T-cell lymphoma: implication for the use of recombinant cytokines and photopheresis. *Clin Exp Immunol* 1997;107:16–20.
- [41] Rook AH, Wood GS, Yoo EK, et al. Interleukin 12 induces lesion regression and cytotoxic T-cell responses in cutaneous T-cell lymphomas. *Blood* 1999;94:902–8.
- [42] Wilson LD, Licola AL, Braverman IM. Systemic chemotherapy and extracorporeal photochemotherapy for T3 and T4 cutaneous T-cell lymphoma patients who have achieved a complete response to total skin electron beam therapy. *Int J Rad Oncol Biol Phys* 1995;32:987–95.
- [43] Vonderheid EC. Use of serum soluble interleukin-2 receptor levels to monitor the progression of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1988;38:207–20.
- [44] Koh HK. Extracorporeal photopheresis for the treatment of 34 patients with cutaneous T-cell lymphoma (CTCL). *J Invest Dermatol* 1994;2:260.
- [45] Wilson LD, Jones WD, Kim D, et al. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. *J Am Acad Dermatol* 2000;43:54–60.
- [46] Berger CL, Wang N, Christensen I, et al. The immune response to class I-associated tumor-specific cutaneous T-cell lymphoma antigens. *J Invest Dermatol* 1996;107:392–7.
- [47] Hanlon DJ, Berger CL, Edelson RL. Photoactivated 8-methoxypsoralen treatment causes a peptide-dependent increase in antigen display by transformed lymphocytes. *Int J Cancer* 1998;76:70–5.
- [48] Berger CL, Longley BJ, Imaeda S, et al. Tumor-specific peptides in cutaneous T-cell lymphoma: association with class I major histocompatibility complex and possible derivation from the clonotypic T-cell receptor. *Int J Cancer* 1998;76:304–11.
- [49] Berger CL, Xu AL, Hanlon D. Induction of human tumor-loaded dendritic cells. *Int J Cancer* 2001;91:438–47.
- [50] Bisaccia E, Gonzalez J, Palangio M, Schwartz J, Klainer AS. Extracorporeal photochemotherapy alone or with adjuvant therapy in the treatment of cutaneous T-cell lymphoma: A 9-year retrospective study at a single institution. *J Am Acad Dermatol* 2000;43:263–71.
- [51] Jiang SB, Dietz SB, Kim M, Lim HW. Extracorporeal photochemotherapy for cutaneous T-cell lymphoma: a 9.7-year experience. *Photodermatol Photoimmunol Photomed* 1999;15:161–5.
- [52] Wollina U, Looks A, Meyer J, et al. Treatment of stage II cutaneous T-cell lymphoma with interferon alfa-2a and extracorporeal photochemotherapy: a prospective controlled trial. *J Am Acad Dermatol* 2001;44:253–60.
- [53] Prinz B, Behrens W, Holzle E, Plewig G. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma: the Düsseldorf and Munich experience. *Arch Dermatol Res* 1995;287:1–6.
- [54] Crovetti G, Carabelli A, Berti F, et al. Photopheresis in cutaneous T-cell lymphoma: five-year experience. *Int J Artif Organs* 2000;23:55–62.
- [55] Dall'Amico R, Zacchello G, Heald P. Applicazione della fotoforesi nella terapia di malattie oncologiche ed autoimmuni. (The application of photopheresis in the therapy of cancerous and autoimmune disease). *Recenti Prog Med* 1991;82:294–9.
- [56] Owsianowski M, Garbe C, Ramaker J, Orfanos CE, Gollnick H. Therapeutische Erfahrungen mit der Extracorporealen Photopherese. *Hautarzt* 1996;47:114–23.
- [57] Zouboulis CC, Schmuth M, Doepfner S, Dippel E, Orfanos CE. Extracorporeal photopheresis of cutaneous T-cell lymphoma is associated with reduction of peripheral CD4+T lymphocytes. *Dermatology* 1998;196:305–8.
- [58] Konstantinow A, Balda BR. Treatment of cutaneous T-cell lymphoma with extracorporeal photochemotherapy. *J Eur Acad Dermatol Venerol* 1996;9:111–7.
- [59] Girardi M, Schechner J, Glusac E, Berger C, Edelson R. Transimmunization and the evolution of extracorporeal photochemotherapy. *Tranfus Apheresis Sci* 2002;26:181–90.