Extracorporeal Photopheresis in the Treatment of Mycosis Fungoides and Sézary Syndrome

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KEYWORDS

• Extracorporeal photopheresis • Cutaneous T-cell lymphoma • Sézary syndrome
• Mycosis fungoides • Photochemotherapy

KEY POINTS

- Extracorporeal photopheresis induces an immune response to mycosis fungoides (MF)/Sézary syndrome (SS).
- Extracorporeal photopheresis alone or in combination with other immunostimulatory agents leads to a response rate ranging from 40% to 60% in patients with various stages of MF/SS.
- Extracorporeal photopheresis is a safe procedure with few side effects and no induction of immunosuppression.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a broad term describing cancers of the T cell whereby the skin is the primary organ of involvement. Although the disease was first recognized in 1806 by Alibert,[1] it was not until the 1970s when investigators discovered the T-cell origin of this malignancy.[2] Extracorporeal photopheresis (ECP) or photopheresis is one of many treatment modalities to treat the cutaneous T-cell lymphomas. It is unique among those treatment modalities, however, in that it is the only treatment, aside from allogeneic stem cell transplantation, that specifically induces an immune reaction directed against the malignant T cell.

ECP is an apheresis procedure whereby a leukocyte-enriched fraction of blood spiked with 8-methoxypsoralen (8-MOP) is exposed to a UV-A light source and then returned to patients. ECP is similar to the psoralen followed by UV-A exposure (PUVA) form of phototherapy in that both take advantage of the photoactivated drug 8-MOP and are classified as photochemotherapies. In 1988, the US Food and Drug Administration (FDA) approved the use of a new medical device for the treatment of CTCL. The UVAR instrument (Therakos Inc, Exton, PA) combined, for the first time, leukapheresis with a modified phototherapy chamber.

HISTORICAL ASPECTS

In 1921, J.F. Heymans[3] first published the concept of treating blood by exposing it to physical agents, such as cold, heat, or radiation, as it flows through an extracorporeal shunt. A better understanding of lymphocyte function and life span emerged in the late 1950s leading to the development of procedures to deplete the body of lymphocytes to study

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lymphocyte kinetics and ultimately treat disease.[4] In the early 1960s, Eugene Cronkite, MD, while at the Brookhaven National Laboratory in Upton, New York, developed an extracorporeal system using a venovenous shunt to expose whole blood to gamma rays generated by a ^{60}cobalt irradiator.[5] This modality, called extracorporeal irradiation of the blood (ECIB), was based on the difference between the radiosensitivity of lymphocytes and the radioresistance of erythrocytes.[6] By 1970, at least 150 patients with acute and chronic leukemias were treated with ECIB; but remissions were short lived.[7] Although most authorities thought only gamma radiation could kill activated lymphocytes and leukemic cells, a French team in the late 1960s led by J.L. Binet investigated the effects of using UV radiation (UVR) produced by mercury arc lamps.[8] Their UVR ECIB system was tested on lymphocyte function and ultimately in several patients with chronic lymphocytic leukemia leading to transient clinical remission.[9]

In the mid-1970s, Barbara Gilchrest and colleagues[10,11] at Massachusetts General Hospital discovered that PUVA phototherapy was effective in treating the early skin lesions of mycosis fungoides (MF), the most common subtype of CTCL. At about the same time, Richard L. Edelson,[12] MD, while at the National Cancer Institute, worked with colleagues to treat several patients with Sézary syndrome (SS) using leukapheresis to debulk the circulating tumor load of malignant T cells.[12] The question arose whether the malignant circulating lymphocytes in SS would respond to PUVA phototherapy if the energy could be directed at blood cells. Initial experiments performed in Edelson's laboratory found evidence that an anti-idiotypic response to disease-specific T-cell receptors could be found after exposing autoreactive T cells from rats to 8-MOP and UV-A in an ex vivo system inspired by Cohen and colleagues[13–15] at the Weizmann Institute. With the help of engineers at Therakos, Inc, a subsidiary of Johnson and Johnson, Edelson[16] designed a device that could expose a fraction of leukocyte-enriched blood, removed from patients after they had taken psoralen, to UV-A light in an extracorporeal system before returning the treated blood products back to the patients. After a promising phase I clinical trial, a multicenter clinical trial was performed from 1982 to 1986 testing the efficacy of ECP after ingestion of 8-MOP in the management of refractory erythrodermic patients with MF/SS. In 1987, the landmark report was published that found a significant response in 27 of 37 patients treated with ECP.[17]

In 2000, the FDA approved a sterile liquid formulation of 8-MOP to replace the oral formulation. The liquid formulation (UVADEX) is added directly to the collection bag in the extracorporeal circuit, thus avoiding the gastrointestinal intolerance and unreliable blood levels of the oral formulation.[15] The latest fourth-generation photopheresis instrument, the CELLEX System (Therakos, Inc, Raritan, NJ), was approved in 2009 by the FDA and combines state-of-the-art cell collection, photoactivation, and reinfusion technologies in a single, integrated, closed system.[18]

MECHANISM OF ACTION

Despite the safe and effective use of ECP for more than 25 years, the precise mechanism of action continues to be explored. There is good evidence that ECP induces an immune-mediated response to the malignant T-cell clone.[17] This is supported, in part, by the clinical observation that, although less than 10% of the total population of white blood cells is treated during one ECP treatment, there is often a larger reduction of malignant T cells in the peripheral circulation.[19] The proposed mechanism of action involves the following processes: (1) the induction of apoptosis of malignant T cells, (2) the conversion of circulating monocytes to immature dendritic cells (DCs), (3) the presentation of tumor-loaded DCs to cytotoxic T cells, and (4) expansion of a population of cytotoxic T cells against the malignant T-cell clone.

Because they lack nuclei, the radioresistance of erythrocytes and platelets may be expected. However, the differences in the radiosensitivity of peripheral blood mononuclear cells (PBMCs) are more difficult to explain. Why are lymphocytes more radiosensitive than other peripheral blood mononuclear cells?[20,21] Also intriguing are the results of Spary and colleagues[22] demonstrating enhancement of the Th1 T-cell responses as a result of synergy between lower doses of ionizing radiation (0.6–2.4 Gy) and T-cell stimulation. Further studies are needed that focus on the impact of ECP (UV energy) on enhancement of Th1 T-cell responses of normal T cells. ECP and PUVA induce apoptosis in CD4+ and CD8+ lymphocytes but not monocytes, and the apoptosis is likely attributed to dysregulation in the expression of the apoptotic genes Bcl-2 and Bax.[23–26] But what about the surviving malignant T cells exposed to UV-A energy and psoralen? Studies using ionizing radiation demonstrate alteration in the biology of surviving tumor cells from patients with solid organ carcinomas, rendering them more susceptible to T cell–mediated killing possibly via increased cell-surface expression of calreticulin.[27]

It has been established that monocytes differentiate to immature DCs in the presence of

interleukin (IL)-4 and granulocyte-macrophage colony stimulating factor (GM-CSF).[28] In 2001, Berger and colleagues[29] published their observation of the conversion of monocytes to immature DCs during overnight incubation in gas-permeable bags of ECP-treated leukocytes from 5 patients with refractory CTCL. Further observations confirmed that both the initial leukapheresis step and subsequent passage through the narrow plastic photoactivation plate initiated and contributed to the monocyte to immature dendritic cell differentiation. Edelson proposed that the frequent encounters of monocytes with the plastic surface of the photoactivation plate activated the cells to begin differentiation to immature DCs.[30] The adsorption of fibronectin on the photoactivation plate may be a convincing candidate for influencing monocyte biology during ECP and participating in the early events of monocyte-to-DC conversion.[31] Recently, Berger and colleagues[32] demonstrated that ECP-derived DCs are maturationally synchronized and show a reproducible distinctive molecular signature, common to ECP-processed monocytes from normal subjects and those from patients.

There are 2 major subsets of DCs in human peripheral blood: myeloid (mDC) and plasmacytoid (pDC).[33] It is known that mDCs primarily polarize naïve T cells toward a Th1 phenotype, whereas pDCs primarily result in a Th2/Treg phenotype.[34] Recently, Shiue and colleagues[35] found increased mDC populations, increased mDC/pDC ratios, and upregulation of HLA-DR expression on DCs following ECP in two-thirds of patients with MF and B1/B2 blood stage or SS. Their results suggest that ECP treatment is associated with favorable mDC modulation.

Inducing a Th1 phenotype produces a cell-mediated T-cell response capable of launching a cytotoxic T-cell response against a malignant clone. Clinical improvements after ECP in patients with MF/SS are associated with a shift from Th2 to IL-12/Th1 phenotype.[36]

Using an animal model of ECP, investigators identified the induction of a CD8+ T-cell response against expanded clones of pathogenic T cells.[14] Moor and Schmitt[37] demonstrated increased synthesis of class I major histocompatibility complex molecules on the surface of a murine T-cell lymphoma line after exposure to UV-A and 8-MOP. In addition, Berger and colleagues[38] used monoclonal antibodies and magnetic bead technology to demonstrate a tumor-specific cytolytic CD8+ T-cell response to distinctive class I–associated peptides on the surface of CTCL tumor cells in blood samples from 4 ECP patients with advanced CTCL. These data support the assertion that ECP exerts its immunologic effects by stimulating a tumor-specific CD8 T-cell response triggered by a population of tumor-loaded DCs after the ECP procedure.

To summarize: In patients with MF/SS and significant blood involvement, ECP treatment not only induces apoptosis of malignant Th2/Treg cells but also induces more mDCs, creates a proinflammatory environment for DCs to activate, and further stimulates Th1/cytotoxic T cells and immune responses.[35]

PHARMACOKINETICS

8-MOP or methoxsalen is a furocoumarin with photoactivating properties. Methoxsalen, on photoactivation, conjugates and forms covalent bonds with DNA, which lead to the formation of both monofunctional (addition to a single strand of DNA) and bifunctional (crosslinking of psoralen to both strands of DNA) adducts.[39] Reactions with proteins have also been described. The formation of photoadducts results in inhibition of DNA synthesis, cell division, and epidermal turnover.[39] Liquid methoxsalen (UVADEX 20 mcg/mL) is administered in a dose of 0.017 mL per 1 mL of pheresed leukocyte volume.[18] The total dose of methoxsalen delivered in UVADEX is substantially less than (approximately 200 times) that used with oral administration. More than 80% of blood samples collected 30 minutes after reinfusion of the photoactivated cells had methoxsalen levels less than the detection limits of the assay (<10 ng/mL).[40]

Just and colleagues[41] explored the trafficking of the treated leukocytes following ECP using radioactively labeled leucocytes and monitoring with whole-body scintigraphy. Comparison of distribution patterns showed that PBMCs and neutrophils have different kinetic patterns after intravenous reinjection. The most prominent difference was immediate retention of PBMCs but not of neutrophils in the lungs corresponding to a signal 3 times more intense. After 24 hours, more than 80% of both cell populations could be detected in the liver and spleen.

TYPICAL REGIMEN

For patients with MF/SS, the typical ECP regimen is one treatment on 2 consecutive days every 4 weeks. Since FDA approval of ECP in 1988, there has been minor variability in the 2-day cycle every 4 weeks in the treatment of MF/SS. Duvic and colleagues[42] found no increased response rate using an accelerated regimen of one 2-day cycle every 2 weeks to treat a small cohort of patients with MF/SS. More recently, Siakantaris and

colleagues[43] from Greece published their retrospective experience (N = 18) using an accelerated treatment schedule of one cycle of ECP every week for 1 month, followed by 1 cycle of ECP every 2 weeks for 2 months, and then one cycle of ECP every month. The overall response rate of 61% compares quite favorably with previously published response rates of patients with MF/SS treated with ECP combined with other systemic therapies.

The European Dermatology Forum's guidelines on the use of ECP published in January 2014 recommends the following ECP schedule for the treatment of MF/SS: 1 cycle every 2 weeks for the first 3 months then once monthly or every 3 weeks.[44] The investigators note, however, that there is no clear optimal therapy; other published guidelines, including the UK consensus statement on the use of ECP,[45] have recommended 1 cycle every 2 to 4 weeks followed by tapering after maximum response.[44]

Each ECP procedure varies between 2 and 3 hours in length based on several factors, including venous access, blood flow, hemoglobin concentrations, and technical issues. Most centers achieve peripheral access using one 16-gauge or 18-gauge needle inserted into the antecubital vein though central venous catheters, or specialized subcutaneous ports (eg, Vortex AngioDynamics, Latham, NY) that allow for rapid reverse flow during the blood collection phase of the procedure may also be used.[46]

RESPONSE TO THERAPY

The efficacy of ECP has been reported in more than 500 patients worldwide. Most of these reports have been small to medium size case series. There are no randomized controlled clinical trials demonstrating the efficacy of photopheresis as monotherapy in the treatment of MF/SS. Despite this, several national and international organizations have listed photopheresis as first-, second-, or third-line therapy for various stages of MF/SS.

The clinical data support the use of ECP to treat patients with erythrodermic MF ($T_4N_{0-3}M0B_1$) with at least some atypical circulating lymphocytes or SS ($T_4N_{0-3}M0B_2$), which requires significant blood involvement for diagnosis. The clinical data do not support the use of ECP to treat patients with tumor stage MF. There is some clinical data to support the use of photopheresis to treat early stage patients with MF, especially those that have at least some atypical circulating lymphocytes.

EARLY STAGE MYCOSIS FUNGOIDES

After ECP was FDA approved in 1988, several reports emerged of patients with early stage MF responding to ECP often combined with other treatment modalities.[47–50] Zic and colleagues[48,49] at Vanderbilt reported preliminary and long-term follow-up data on a cohort of 20 refractory patients with MF/SS treated with ECP and adjunctive therapies. This cohort included 14 treatment-refractory patients with early stage disease (T2). Nine of 14 (64%) achieved an objective response (OR) in the skin (greater than 50% clearing of skin lesions) with 4 complete responses (CRs). For the 7 patients who at some point in their treatment achieved a CR, the median time to clearing was 11 months. For the 7 patients weaned from ECP, the mean relapse-free interval was approximately 45 months (range, 20–64 months, 2 relapses). Another important observation was that patients who responded within 6 to 8 months after starting ECP maintained their response over time.[49]

In 2004, Child and colleagues[51] published the results of a randomized crossover study comparing PUVA and ECP in the treatment of 20 patients with plaque stage (T2) MF who had a detectable peripheral blood T-cell clone. Eight patients completed the study. Although PUVA was more effective than ECP in improving skin scores, neither treatment modality cleared malignant T cells from the peripheral blood.

In a retrospective analysis of patients treated with ECP combined with adjuvant therapies, Siakantaris and colleagues[43] from Greece reported a response rate of 40% (2 of 5) in patients with early stage MF as compared with a response rate of 62% (9 of 13) in patients with advanced MF/SS.

Recently, a prospective, open-label, single-arm, multicenter, investigator-initiated pilot study was completed to assess the response to ECP in patients with early stage MF (stages IA–IIA).[52] The UVAR XTS Photopheresis System (Therakos, Inc Raritan, NJ) was used to administer ECP for 2 consecutive days once monthly for 12 months. Patients who did not respond after 6 months of ECP were treated adjunctively with oral bexarotene (150 mg/m^2) alone or combined with interferon (IFN) alfa (1–3 million units 3 times per week). Patients with stage IA disease were only enrolled if they showed evidence of minor blood abnormality by flow cytometry assessment (B1). The primary end point was a skin involvement response assessed monthly by using the modified severity weighted assessment tool (mSWAT) assessment tool (partial response [PR] >50% improvement in mSWAT). A total of 19 patients with early stage MF (IA = 3, IB = 14, IIA = 2) were enrolled. Eight of the 12 patients who were treated with ECP monotherapy responded (67%, 2 CR), and 4 of the 7 patients who received combination therapy

responded (57%, 0 CR). The overall response rate for the entire cohort (12 of 19) was 63.1%. However, if the 7 patients requiring combination therapy are considered ECP treatment failures, then the overall response rate for ECP alone was 42% (8 of 19). The median time to response was 4 months (3–8 months), and the median duration of response was 6.5 months (1–48 months). Also, quality-of-life measurements indicated an improvement in emotional scores over time.[52]

Current National Comprehensive Cancer Network (NCCN) guidelines for non-Hodgkin lymphoma (NHL) (Version 5.2014) do not recommend ECP as primary treatment in early stage MF (IA, IB, IIA). However, in patients with stage IA, IB, and IIA disease and B1 blood involvement or those with treatment refractory disease, ECP is listed as a systemic treatment option along with retinoids, IFNs, histone deacetylase inhibitors, and methotrexate.[53] The European Dermatology Forum published guidelines on the use of ECP in January 2014. The consensus decision was that ECP should only be considered in patients with early stage MF for clinical trial purposes as a variety of other safe, effective, and easily accessible treatment options are available for use at these stages.[44]

TUMOR STAGE MYCOSIS FUNGOIDES

ECP should not be considered a primary treatment option in patients with tumor stage MF (stage IIB). In 15 patients extracted from the literature with skin stage T3 (tumor stage), no patient responded to photopheresis.[49,50,54,55] One retrospective study examined the use of ECP or chemotherapy as a maintenance adjuvant treatment regimen in patients with tumor stage MF (N = 41) or erythrodermic MF/SS (N = 21) who had achieved a CR from total skin electron beam radiotherapy (TSEB).[56] The difference between overall survival for those who received ECP (100% at 3 years) versus those who received no adjuvant therapy (50% at 3 years) approached statistical significance ($P<.06$), whereas significant survival benefit from the addition of chemotherapy (75% at 3 years) for TSEB CRs was not observed. Neither adjuvant therapy provided benefit with respect to relapse-free survival after TSEB.[56]

ERYTHRODERMIC MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

Erythrodermic CTCL may be divided into erythrodermic MF (stage III, $T_4N_{0\text{-}2}M_0B_{0\text{-}1}$) and SS (stage $IVA_{1\ or\ 2}$, $T_4N_{0\text{-}3}M_0B_2$). Although there is considerable variability in the presentation and prognosis of patients with erythrodermic MF/SS, photopheresis is considered the first-line treatment by most experts. The publication of the landmark article in 1987 by Edelson and colleagues[17] established the safety and efficacy of ECP in 22 of 29 erythrodermic patients with MF/SS. Since then, the responses of more than 518 ECP-treated patients with erythrodermic MF/SS have been published and summarized with a wide range of response rates from 33% to 74%.[44,57] Many of these patients were treated with photopheresis in combination with other therapies. In addition, none of the patients were part of prospective randomized controlled clinical trials.

The United States Cutaneous Lymphoma Consortium (USCLC) recently published guidelines for the treatment of SS.[58] In this review 118 patients with SS treated with ECP as monotherapy were extracted from the literature based on clearly defined criteria and an overall response rate defined as at least 50% clearing. Of these 118 patients, 28 (24%) responded to ECP monotherapy and 11 patients achieved a CR (9%). Higher response rates were seen in patients who received ECP in combination with other therapies (**Fig. 1**). ECP was recommended by the USCLC as one of the primary (category A) systemic monotherapies for the treatment of SS (II-2 evidence: $\geq$1 prospective, well-designed cohort or case-controlled study, preferably >1 center or research group). Others in this category included IFN alfa, bexarotene, low-dose methotrexate, and denileukin diftitox plus corticosteroids.[58]

Based on ECP data from 1987 to 2001, the British Photodermatology Group and United Kingdom Skin Lymphoma Group published their report in 2006 on evidence-based practice of ECP.[59] The investigators concluded that there was fair evidence of clinical benefit in erythrodermic MF/SS from ECP (B level recommendation [A to E], II-i evidence [nonrandomized controlled trials]).

Based on category 2A evidence (lower-level evidence and uniform NCCN consensus that the intervention is appropriate), current NCCN guidelines for NHL (version 5.2014) do recommend ECP as one of the primary treatments for SS and erythrodermic MF with B1 blood stage but not for patients with erythrodermic MF with no evidence of blood involvement (B0).[53] In contrast, the European Dermatology Forum's guidelines recommend ECP as first-line therapy for all patients with T4 skin stage regardless of blood and lymph node involvement and patients with T1/T2 skin stage with B2 blood involvement according to the revised International Society for Cutaneous Lymphomas (ISCL)/European Organization of Research and Treatment of Cancer (EORTC)

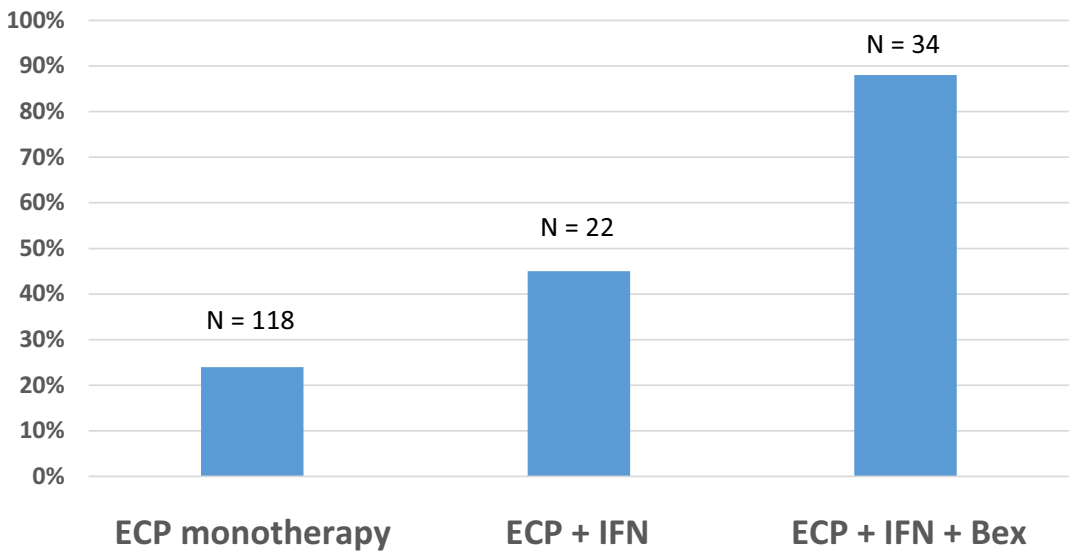

Fig. 1. Estimated pooled response rates for patients with SS to ECP monotherapy, ECP + IFN alfa or gamma, and ECP + IFN + bexarotene capsules (Bex). N = number of patients extracted from the literature with a clear definition of SS and an overall response rate defined as 50% or greater clearing of skin. (*Data from* Olsen EA, Rook AH, Zic J, et al. Sezary syndrome: immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma Consortium (USCLC). J Am Acad Dermatol 2011;64(2):352–404.)

staging.[60] The American Society for Apheresis also categorized ECP as an accepted first-line therapy for erythrodermic MF/SS as a primary stand-alone treatment or in conjunction with other modes of treatment.[61]

EXTRACORPOREAL PHOTOPHERESIS AND ADJUNCTIVE THERAPIES

Most patients with MF/SS treated with ECP receive adjunctive therapies, especially IFN alfa and bexarotene capsules. There is evidence to support higher response rates when ECP is combined with adjunctive therapies. In one report, ECP monotherapy showed a 40% response rate in patients with stage III/IV MF/SS in contrast to a 57% response rate in those treated with a combination of ECP plus IFN alfa, bexarotene, or GM-CSF.[62] In a retrospective review of 98 patients with SS treated with ECP (>3 months) and 1 or more systemic immunostimulatory agents (IFN gamma, IFN alfa, GM-CSF, systemic retinoids), Raphael and colleagues[63] at the University of Pennsylvania reported a significant improvement in 73 patients (75%) with 29 CRs (30%).

There are retrospective and small cohort data to support the combination of photopheresis and IFN in the treatment of erythrodermic CTCL. In the USCLC review of SS in which all patients so reported had to meet the criteria of T4B2 staging and an overall response rate defined as at least 50% clearing of disease, 10 of 22 patients treated with ECP and IFN alfa (45.4%) responded, including 4 patients who achieved a CR (18.2%) (see **Fig. 1**).[58] In the only published prospective randomized trial of IFN versus IFN and ECP, 20 patients with MF/SS stages IA to IVB were treated with IFN 3 to 18 million units (MU) daily intramuscularly versus same-dosing IFN plus ECP 2 days per month. Two of the 9 patients (22%) assigned to the combination arm had an OR versus 4 of the 11 patients (36%) assigned to the IFN alone arm, including one CR.[64] Thus there was no advantage to adding ECP to IFN alone in this small study.

The combination of ECP, IFN alfa/gamma, and bexarotene capsules may lead to the highest response rates in patients with SS. In the USCLC review of the 34 patients with SS treated with ECP, IFN, and bexarotene, 30 of 34 (88.2%) responded to the combined therapy, including 11 patients with a CR (32.4%) (see **Fig. 1**).[58] Bexarotene dosages ranged from 75 mg to 450 mg by mouth per day. IFN alfa dosages ranged from 1.5 MU to 6 MU subcutaneous injections 3 to 5 times weekly. IFN gamma dosages ranged from 40 mcg to 100 mcg subcutaneous injections 3 to 5 times weekly.[58]

In contrast to these pooled results, Polansky and colleagues[65] at the M.D. Anderson Cancer

Center recently reported the results of 18 of 217 patients with SS who had achieved long-term CR of greater than 1 year: 3 CRs were achieved with combined immunomodulatory therapy (ECP, IFN alfa, and/or retinoids), 13 CRs were achieved after allogeneic stem cell transplantation, one CR with alemtuzumab, and one CR with mogamulizumab.

PREDICTORS OF RESPONSE

In a small cohort of 21 patients with MF/SS treated with ECP as monotherapy for at least 6 months, the following baseline blood parameters were associated with a favorable clinical response: lower percentage of Sézary cells (32% vs 54% lymphocytes) and a higher absolute eosinophil count (388/mm^3 vs 87/mm^3). Comparison of cytokines, gene transcripts, and other laboratory measures of disease did not correlate with the subsequent clinical response.[66] In a more recent analysis of microRNA (miR) levels on a subset of this cohort (n = 13), McGirt and colleagues[67] discovered that an early increase of PBMC miR-191, miR-223, and miR-342 at 3 months into ECP monotherapy predicted a clinical response to ECP at 6 and 12 months.

In a large cohort of patients (n = 98) with SS treated with ECP and immunostimulatory agents, Raphael and colleagues[63] found the following baseline differences in the CR group as compared with the nonresponse group: lower CD4/CD8 ratio (13.2 vs 44.2), lower median percentage of CD4+/CD26− cells (27.4% vs 57.2%), lower median percentage of CD4+/CD7− cells (20.0% vs 41.3%), and higher median monocyte percentage (9.5% vs 7.3%). There were no differences between the group with PR when compared with the nonresponse group.

Other factors that have been reported to predict response to ECP have been recently summarized.[57,68] They include relatively low tumor load of malignant T cells in the blood, lymph nodes, and skin; peripheral blood involvement; relatively intact immune system; erythroderma; and plaques covering less than 10% to 15% of the total skin surface[68] (**Table 1**).

SURVIVAL

The impact of ECP alone or ECP in combination with other therapies on the survival of patients with erythrodermic MF/SS remains to be confirmed with a prospective study. A follow-up analysis of the original cohort of Edelson and colleagues[69] was published in 1992 showing that the median survival for patients who received ECP was 60 months. Gottlieb and colleagues[47] and Zic and colleagues[49] reported similar median survivals in their respective cohorts of ECP-treated patients with MF/SS. In 2012, Knobler and colleagues[70] used ISCL/EORTC criteria to reevaluate the original cohort of 39 patients in the 1987 pivotal trial by Edelson and colleagues[17] with a median follow-up of 71.6 months in this cohort; the median overall survival for a subgroup of 26 patients with erythroderma was 76.9 months from diagnosis.

Fraser-Andrews and colleagues[71] published a retrospective historical control study comparing the survival of a cohort of 44 patients with SS separated into 3 groups: ECP treated 1991 to 1996 (n = 29, median survival 39 months), no ECP treatment 1991 to 1996 (n = 8, median survival 22 months), and no ECP treatment before 1991 (n = 7, median survival 26.5 months). In contrast to the previously published survival data at that time, this study showed no statistically significant difference between the groups and did not support the contention that ECP prolongs survival in patients with SS. In a letter to the editor, Stevens and colleagues[72] argued that this study had low statistical power and an inadequate treatment regimen for proper comparison.

ADVERSE EFFECTS

ECP is well tolerated with rare grade III-IV systemic toxicities reported in the literature and no reports of immunosuppression. In a recent series of 51 patients with erythrodermic MF/SS treated with ECP, the following adverse effects were reported using the National Cancer Institute Common Toxicity Criteria system: transient grade I hypotension (12%), grade I-II anemia (6%), hypokalemia (4%), and 1 urticarial eruption interpreted as a drug reaction to either 8-MOP or heparin.[57] Discomfort and mild hematomas at venipuncture sites are not uncommon and can be relieved with pressure bandages and ice compresses.[17] To avoid catheter-related infections, intermittent peripheral venous access is preferred over indwelling catheters because of the high rate of *Staphylococcus aureus* colonization on the skin in patients with erythrodermic MF/SS. Transient low-grade fever and increased erythroderma have been observed in some patients within 6 to 8 hours of reinfusion of the photoactivated leukocyte-enriched blood.[18] Nausea was a common side effect to the oral formulation of 8-MOP but has now been eliminated with the introduction of the liquid formulation directly injected into the collection bag.[15] A single case of grade III anemia was reported in a patient with SS undergoing treatment with bexarotene and ECP caused by undiagnosed cold agglutinin disease, which was suspected when agglutinated blood was noted in the centrifuge bowl of the photopheresis device.[73]

Table 1
Baseline predictors of response to photopheresis

Low Tumor Load of Malignant T Cells		
Skin	Erythroderma[a]	Quaglino et al,[57] 2013; Knobler et al,[44] 2014
	Plaques <10%–15% total skin surface	Atta et al,[68] 2012; Knobler et al,[44] 2014
Blood	Lower percentage of elevated circulating Sézary cells	Heald et al,[69] 1992; Raphael et al,[63] 2011; McGirt et al,[66] 2010
	Lower CD4/CD8 ratio <10–15	Heald et al,[69] 1992; Knobler et al,[74] 2002; Raphael et al,[63] 2011; Quaglino et al,[57] 2013
	Lower % CD4+CD7− <30%	Stevens et al,[75] 2002; Raphael et al,[63] 2011
	Lower % CD4+CD26− <30%	Raphael et al,[63] 2011
	Normal LDH levels	Knobler et al,[74] 2002; Quaglino et al,[57] 2013
	B0 or B1 blood stage	Quaglino et al,[57] 2013
	Lymphocyte count <20,000/μl	Atta et al,[68] 2012
Lymph nodes	Lack of bulky adenopathy	Atta et al,[68] 2012
Visceral organs	Lack of visceral organ involvement	Atta et al,[68] 2012
Peripheral Blood Involvement	B1 blood stage >B2 blood stage[60]	Quaglino et al,[57] 2013; Evans et al,[76] 2001; Atta et al,[68] 2012
	Presence of a discrete number of Sézary cells (10%–20% mononuclear cells)	Knobler et al,[44] 2014
Relatively Intact Immune System	Higher % monocytes >9%	Raphael et al,[63] 2011
	Increased eosinophil count >300/mm^3	McGirt et al,[66] 2010
	No previous intense chemotherapy	Zic,[18] 2012; Atta et al,[68] 2012
	Short disease duration before ECP (<2 y from diagnosis)	Atta et al,[68] 2012; Quaglino et al,[57] 2013
	↑ NK cell count at 6 mo into ECP therapy	Prinz et al,[77] 1995; Quaglino et al,[57] 2013
	Near-normal NK cell activity	Knobler et al,[44] 2014
	Normal CD3+CD8+ cell count >200/mm^3	Quaglino et al,[57] 2013
Other Monitored Factors		
PBMC miR levels	↑ miR-191, ↑ miR-223, ↑ miR-342 at 3 mo into ECP monotherapy	McGirt et al,[67] 2014
Soluble interleukin-2 receptor	↓sIL-2R at 6 mo into ECP	Rao et al,[78] 2006
Neopterin	↓ Neopterin at 6 mo into ECP	Rao et al,[78] 2006
Beta^2-microglobulin	↓ Beta^2-microglobulin at 6 mo into ECP	Rao et al,[78] 2006
Response at 5–6 mo of ECP	Predicts durable response and long-term survival	Stevens et al,[75] 2002; Zic et al,[49] 1996

Abbreviations: LDH, lactate dehydrogenase; NK, natural killer; sIL-2R, soluble interleukin-2 receptor.
[a] Patients with erythrodermic MF/SS often show fewer malignant T cells in skin biopsies than T3 and T2 skin stages.

PEARLS TO HELP THE MANAGEMENT OF PATIENTS WITH MYCOSIS FUNGOIDES/ SÉZARY SYNDROME BEING TREATED WITH EXTRACORPOREAL PHOTOPHERESIS

As with any therapy, patient selection is important. It is important to set patient expectations at the beginning of ECP treatment. Patients rarely obtain a rapid response to ECP; they should, therefore, be told that it may take at least 6 to 8 months of treatment to see a significant response. Patients who tend to respond best to ECP are those with erythrodermic variants (T4 MF or SS), including patients that one suspects are evolving into SS.

Patients who have many predictive factors for response can initiate ECP as monotherapy. If patients do not show a significant response by 6 to 8 months of ECP (stable disease), then the author recommends adding adjunctive therapies (IFN, bexarotene) or switching to an alternative therapy. If patients show progressive disease, then the author would add or switch therapies sooner. In contrast, patients with fewer predictive factors for response, especially those with SS and lymphadenopathy, should be treated up front with combination immunotherapy (ECP, IFN alfa or gamma, bexarotene). If patients do not show a significant response by 6 to 8 months of ECP, the author recommends stopping ECP and switching to an alternative systemic therapy.

Venous access can be a challenge for heavily pretreated patients and older patients. To increase the caliber of the antecubital veins, the author recommends instructing patients to squeeze rubber balls with both hands as a daily exercise.

SUMMARY

In the setting of MF/SS, photopheresis leads to an expansion of peripheral blood DC populations and an enhanced TH1 immune response. ECP is a first-line therapy for erythrodermic MF/SS based on the excellent side effect profile and moderate efficacy in the treatment of patients with T4 (erythroderma) skin stage. Patients with erythrodermic MF/SS are most likely to respond to ECP when they have a measurable but low blood tumor burden. The addition of adjunctive immunostimulatory agents seems to increase the response to ECP. There may be a role for the treatment of refractory early stage MF with ECP, though data are limited. Further studies are needed not only to clarify the mechanism of action of ECP to better optimize therapy but also to maximize the response for patients with advanced MF/SS.

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