

# Extracorporeal Photophoresis

An Evidence-Based Analysis

March 2006



Medical Advisory Secretariat  
Ministry of Health and Long-Term Care

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# Abbreviations/Acronyms

<b>cGvHD</b>	Chronic graft versus host disease
<b>CI</b>	Confidence interval
<b>CR</b>	Complete response
<b>CTCL</b>	Cutaneous T-cell lymphoma
<b>ECP</b>	Extracorporeal photopheresis
<b>HCT</b>	Hematopoietic cell transplantation
<b>MF</b>	Mycosis fungoides
<b>OR</b>	Odds ratio
<b>PR</b>	Partial response
<b>PUVA</b>	Photoactivation ultraviolet A
<b>RAR</b>	Recurrent acute rejection
<b>RR</b>	Risk ratio
<b>SD</b>	Standard deviation
<b>SS</b>	Sezary syndrome
<b>TSEB</b>	Total skin electron beam

# Glossary

**Allogeneic transplants:** Transplantation procedure that involves patients receiving stem cells from someone other than the patient or an identical twin.

**Autologous transplants:** Transplantation procedure that involves patients receiving their own stem cells.

**Bone marrow transplantation:** A transplantation procedure that restores stem cells that have been destroyed by high doses of chemotherapy and/or radiation therapy.

**Erythroderma:** A nonspecific designation for intense and usually widespread reddening of the skin from dilation of blood vessels, often preceding or associated with exfoliation.

**Indolent:** Causing little pain or annoyance; as, an indolent tumour.

**Insidious disease:** A disease existing without marked symptoms, but ready to become active upon some slight occasion; a disease not appearing to be as bad as it really is.

**Lansky/Karpofsky performance scale:** A play performance scale that records usual play activity as the index of performance in pediatric cancer patients.

**Mycosis fungoides:** A form of nonHodgkin lymphoma that first appears on the skin (cutaneous T-cell lymphoma). This is a tumour of T lymphocytes that accumulate in the dermis and epidermis and cause loss of the epidermis. A frequent secondary feature is fungal infection of lesions in the skin.

**Pheresis:** A procedure in which blood is removed from a donor, separated and a portion retained with the remainder returned to the donor.

**Photoactivation ultraviolet A:** A treatment which consists of psoralens and then exposing the skin to long wave ultraviolet radiation (UVA). It has been available in its present form since 1976. PUVA may be useful for patients with various skin disorders, including psoriasis, dermatitis and MF.

**Psoralens:** Compounds found in plants which make the skin temporarily sensitive to UVA.

**Sezary syndrome:** A form of cutaneous T-cell lymphoma manifested by generalized exfoliative erythroderma, intense itching, peripheral lymphadenopathy and abnormal hyperchromatic mononuclear cells in the skin, lymph nodes and peripheral blood (Sézary cells).

# Executive Summary

## Objective

To assess the effectiveness, safety and cost-effectiveness of extracorporeal photophoresis (ECP) for the treatment of refractory erythrodermic cutaneous T cell lymphoma (CTCL) and refractory chronic graft versus host disease (cGvHD).

## Background

### Cutaneous T Cell Lymphoma

Cutaneous T cell lymphoma (CTCL) is a general name for a group of skin affecting disorders caused by malignant white blood cells (T lymphocytes). Cutaneous T cell lymphoma is relatively uncommon and represents slightly more than 2% of all lymphomas in the United States. The most frequently diagnosed form of CTCL is mycosis fungoides (MF) and its leukemic variant Sezary syndrome (SS). The relative frequency and disease-specific 5-year survival of 1,905 primary cutaneous lymphomas classified according to the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification (Appendix 1). Mycosis fungoides had a frequency of 44% and a disease specific 5-year survival of 88%. Sezary syndrome had a frequency of 3% and a disease specific 5-year survival of 24%.

Cutaneous T cell lymphoma has an annual incidence of approximately 0.4 per 100,000 and it mainly occurs in the 5<sup>th</sup> to 6<sup>th</sup> decade of life, with a male/female ratio of 2:1. Mycosis fungoides is an indolent lymphoma with patients often having several years of eczematous or dermatitic skin lesions before the diagnosis is finally established. Mycosis fungoides commonly presents as chronic eczematous patches or plaques and can remain stable for many years. Early in the disease biopsies are often difficult to interpret and the diagnosis may only become apparent by observing the patient over time.

The clinical course of MF is unpredictable. Most patients will live normal lives and experience skin symptoms without serious complications. Approximately 10% of MF patients will experience progressive disease involving lymph nodes, peripheral blood, bone marrow and visceral organs. A particular syndrome in these patients involves erythroderma (intense and usually widespread reddening of the skin from dilation of blood vessels, often preceding or associated with exfoliation), and circulating tumour cells. This is known as SS. It has been estimated that approximately 5-10% of CTCL patients have SS. Patients with SS have a median survival of approximately 30 months.

### Chronic Graft Versus Host Disease

Allogeneic hematopoietic cell transplantation (HCT) is a treatment used for a variety of malignant and nonmalignant disease of the bone marrow and immune system. The procedure is often associated with serious immunological complications, particularly graft versus host disease (GvHD). A chronic form of GvHD (cGvHD) afflicts many allogeneic HCT recipients, which results in dysfunction of numerous organ systems or even a profound state of immunodeficiency. Chronic GVHD is the most frequent cause of poor long-term outcome and quality of life after allogeneic HCT. The syndrome typically develops several months after transplantation, when the patient may no longer be under the direct care of the



transplant team.

Approximately 50% of patients with cGvHD have limited disease and a good prognosis. Of the patients with extensive disease, approximately 60% will respond to treatment and eventually be able to discontinue immunosuppressive therapy. The remaining patients will develop opportunistic infection, or require prolonged treatment with immunosuppressive agents.

Chronic GvHD occurs in at least 30% to 50% of recipients of transplants from human leukocyte antigen matched siblings and at least 60% to 70% of recipients of transplants from unrelated donors. Risk factors include older age of patient or donor, higher degree of histoincompatibility, unrelated versus related donor, use of hematopoietic cells obtained from the blood rather than the marrow, and previous acute GvHD. Bhushan and Collins estimated that the incidence of severe cGvHD has probably increased in recent years because of the use of more unrelated transplants, donor leukocyte infusions, nonmyeloablative transplants and stem cells obtained from the blood rather than the marrow. The syndrome typically occurs 4 to 7 months after transplantation but may begin as early as 2 months or as late as 2 or more years after transplantation. Chronic GvHD may occur by itself, evolve from acute GvHD, or occur after resolution of acute GvHD.

The onset of the syndrome may be abrupt but is frequently insidious with manifestations evolving gradually for several weeks. The extent of involvement varies significantly from mild involvement limited to a few patches of skin to severe involvement of numerous organ systems and profound immunodeficiency. The most commonly involved tissues are the skin, liver, mouth, and eyes. Patients with limited disease have localized skin involvement, evidence of liver dysfunction, or both, whereas those with more involvement of the skin or involvement of other organs have extensive disease.

## **Treatment**

### **Cutaneous T Cell Lymphoma**

The optimal management of MF is undetermined because of its low prevalence, and its highly variable natural history, with frequent spontaneous remissions and exacerbations and often prolonged survival.

Nonaggressive approaches to therapy are usually warranted with treatment aimed at improving symptoms and physical appearance while limiting toxicity. Given that multiple skin sites are usually involved, the initial treatment choices are usually topical or intralesional corticosteroids or phototherapy using psoralen (a compound found in plants which make the skin temporarily sensitive to ultraviolet A) (PUVA). PUVA is not curative and its influence on disease progression remains uncertain. Repeated courses are usually required which may lead to an increased risk of both melanoma and nonmelanoma skin cancer. For thicker plaques, particularly if localized, radiotherapy with superficial electrons is an option.

“Second line” therapy for early stage disease is often topical chemotherapy, radiotherapy or total skin electron beam radiation (TSEB).

Treatment of advanced stage (IIB-IV) MF usually consists of topical or systemic therapy in refractory or rapidly progressive SS.

Bone marrow transplantation and peripheral blood stem cell transplantation have been used to treat many malignant hematologic disorders (e.g., leukemias) that are refractory to conventional treatment. Reports on the use of these procedures for the treatment of CTCL are limited and mostly consist of case reports or small case series.

### **Chronic Graft Versus Host Disease**

Patients who develop cGvHD require reinstatement of immunosuppressive medication (if already discontinued) or an increase in dosage and possibly addition of other agents. The current literature regarding cGvHD therapy is less than optimal and many recommendations about therapy are based on common practices that await definitive testing. Patients with disease that is extensive by definition but is indolent in clinical appearance may respond to prednisone. However, patients with more aggressive disease are treated with higher doses of corticosteroids and/or cyclosporine.

Numerous salvage therapies have been considered in patients with refractory cGvHD, including ECP. Due to uncertainty around salvage therapies, Bhushan and Collins suggested that ideally, patients with refractory cGvHD should be entered into clinical trials.

Two Ontario expert consultants jointly estimated that there may be approximately 30 new erythrodermic treatment resistant CTCL patients and 30 new treatment resistant cGvHD patients per year who are unresponsive to other forms of therapy and may be candidates for ECP.

Extracorporeal photopheresis is a procedure that was initially developed as a treatment for CTCL, particularly SS.

### **Current Technique**

Extracorporeal photopheresis is an immunomodulatory technique based on pheresis of light sensitive cells. Whole blood is removed from patients followed by pheresis. Lymphocytes are separated by centrifugation to create a concentrated layer of white blood cells. The lymphocyte layer is treated with methoxsalen (a drug that sensitizes the lymphocytes to light) and exposed to UVA, following which the lymphocytes are returned to the patient. Red blood cells and plasma are returned to the patient between each cycle.

Photosensitization is achieved by administering methoxsalen to the patient orally 2 hours before the procedure, or by injecting methoxsalen directly into the leucocyte rich fraction. The latter approach avoids potential side effects such as nausea, and provides a more consistent drug level within the machine.

In general, from the time the intravenous line is inserted until the white blood cells are returned to the patient takes approximately 2.5-3.5 hours.

For CTCL, the treatment schedule is generally 2 consecutive days every 4 weeks for a median of 6 months. For cGvHD, an expert in the field estimated that the treatment schedule would be 3 times a week for the 1<sup>st</sup> month, then 2 consecutive days every 2 weeks after that (i.e., 4 treatments a month) for a median of 6 to 9 months.

### **Regulatory Status**

The UVAR XTS Photopheresis System is licensed by Health Canada as a Class 3 medical device (license # 7703) for the “palliative treatment of skin manifestations of CTCL.” It is not licensed for the treatment

of cGvHD.

UVADEX (sterile solution methoxsalen) is not licensed by Health Canada, but can be used in Canada via the Special Access Program. (Personal communication, Therakos, February 16, 2006)

According to the manufacturer, the UVAR XTS photopheresis system licensed by Health Canada can also be used with oral methoxsalen. (Personal communication, Therakos, February 16, 2006) However, oral methoxsalen is associated with side effects, must be taken by the patient in advance of ECP, and has variable absorption in the gastrointestinal tract.

According to Health Canada, UVADEX is not approved for use in Canada. In addition, a review of the Product Monographs of the methoxsalen products that have been approved in Canada showed that none of them have been approved for oral administration in combination with the UVAR XTS photopheresis system for "the palliative treatment of the skin manifestations of cutaneous T-cell Lymphoma".

In the United States, the UVAR XTS Photopheresis System is approved by the Food and Drug Administration (FDA) for *"use in the ultraviolet-A (UVA) irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other therapy."*

UVADEX is approved by the FDA for use in conjunction with UVR XTS photopheresis system for "use in the ultraviolet-A (UVA) irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other therapy."

The use of the UVAR XTS photopheresis system or UVADEX for cGvHD is an off-label use of a FDA approved device/drug.

## Summary of Findings

The quality of the trials was examined.

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence.

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

## Cutaneous T Cell Lymphoma

- Overall, there is low-quality evidence that ECP improves response rates and survival in patients with refractory erythrodermic CTCL (Table 1).
- Limitations in the literature related to ECP for the treatment of refractory erythrodermic CTCL include the following:
  - Different treatment regimens.
  - Variety of forms of CTCL (and not necessarily treatment resistant) – MF, erythrodermic MF, SS.

- SS with peripheral blood involvement → role of T cell clonality reporting?
  - Case series (1 small crossover RCT with several limitations)
  - Small sample sizes.
  - Retrospective.
  - Response criteria not clearly defined/consistent.
  - Unclear how concomitant therapy contributed to responses.
  - Variation in definitions of concomitant therapy
  - Comparison to historical controls.
  - Some patients were excluded from analysis because of progression of disease, toxicity and other reasons.
  - Unclear/strange statistics
  - Quality of life not reported as an outcome of interest.
- The reported CR range is ~ 16% to 23% and the overall reported CR/PR range is ~ 33% to 80%.
  - The wide range in reported responses to ECP appears to be due to the variability of the patients treated and the way in which the data were presented and analyzed.
  - Many patients, in mostly retrospective case series, were concurrently on other therapies and were not assessed for comparability of diagnosis or disease stage (MF versus SS; erythrodermic versus not erythrodermic). Blood involvement in patients receiving ECP (e.g., T cell clonality) was not consistently reported, especially in earlier studies. The definitions of partial and complete response also are not standardized or consistent between studies.
  - Quality of life was reported in one study; however, the scale was developed by the authors and is not a standard validated scale.
  - Adverse events associated with ECP appear to be uncommon and most involve catheter related infections and hypotension caused by volume depletion.

**Table 1: GRADE Quality of Studies – Extracorporeal Photopheresis for Refractory Erythrodermic Cutaneous T-Cell Lymphoma**

Outcome	Design	Quality	Consistency	Directness	Overall Quality
<b>Response rates</b>	1 small crossover RCT	Unbalanced arms Unclear biometry Not blinded No details regarding interim analysis. Results based on 8 patients	Worsening of skin scores	Uncertainty regarding diagnostic and outcome criteria	Low
	Case series	Treatment heterogeneity Disease stage/acuity variation Concomitant treatment No blinded assessment	Wide range of responses		
<b>Survival</b>	Retrospective case series	Same as above	Wide range of survival results	Same as above	Low

### Chronic Graft-Versus-Host Disease

- Overall, there is low-quality evidence that ECP improves response rates and survival in patients with refractory cGvHD (Table 2).
- Patients in the studies had stem cell transplants due to a variety of hematological disorders (e.g., leukemias, aplastic anemia, thalassemia major, Hodgkin’s lymphoma, non Hodgkin’s lymphoma).

- In 2001, The Blue Cross Blue Shield Technology Evaluation Centre concluded that ECP meets the TEC criteria as treatment of cGvHD that is refractory to established therapy.
- The Catalan health technology assessment (also published in 2001) concluded that ECP is a new but experimental therapeutic alternative for the treatment of the erythrodermal phase of CTCL and cGvHD in allogenic HPTC and that this therapy should be evaluated in the framework of a RCT.
- Quality of life (Lansky/Karnofsky play performance score) was reported in 1 study.
- The patients in the studies were all refractory to steroids and other immunosuppressive agents, and these drugs were frequently continued concomitantly with ECP.
- Criteria for assessment of organ improvement in cGvHD are variable, but PR was typically defined as >50% improvement from baseline parameters and CR as complete resolution of organ involvement.
- Followup was variable and incomplete among the studies.

**Table 2: GRADE Quality of Studies – ECP for Refractory cGvHD**

Outcome	Design	Quality	Consistency	Directness	Overall Quality
<b>Response rates</b>	Case series	Treatment heterogeneity Concomitant treatment No blinded assessment Lack of consistent scoring Different lengths of follow-up Quality of life reported in 1 pediatric case series	Wide range of responses (~50-90%)	Uncertainty regarding diagnostic and outcome criteria	Low
<b>Survival</b>	Case series	Same as above	Wide range of survival results (~39%-98%)	Same as above	Low

## Conclusion

As per the GRADE Working Group, overall recommendations consider 4 main factors.

- The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates and the relative value placed on the outcome.
- The quality of the evidence (Tables 1 and 2).
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects such as proximity to a hospital or availability of necessary expertise.
- Uncertainty about the baseline risk for the population of interest.

The GRADE Working Group also recommends that incremental costs of healthcare alternatives should be considered explicitly alongside the expected health benefits and harms. Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. The last column in Table 3 is the overall trade-off between benefits and harms and incorporates any risk/uncertainty.

For refractory erythrodermic CTCL, the overall GRADE and strength of the recommendation is “weak” – the quality of the evidence is “low” (uncertainties due to methodological limitations in the study design in terms of study quality and directness), and the corresponding risk/uncertainty is increased due to an annual budget impact of approximately \$1.5M Cdn (based on 30 patients) while the cost-effectiveness of ECP is unknown and difficult to estimate considering that there are no high quality studies of effectiveness. The device is licensed by Health Canada, but the sterile solution of methoxsalen is not licensed.

With an annual budget impact of \$1.5 M Cdn (based on 30 patients), and the current expenditure is \$1.3M Cdn (for out of country for 7 patients), the potential cost savings based on 30 patients with refractory erythrodermic CTCL is about \$3.8 M Cdn (annual).

For refractory cGvHD, the overall GRADE and strength of the recommendation is “weak” – the quality of the evidence is “low” (uncertainties due to methodological limitations in the study design in terms of study quality and directness), and the corresponding risk/uncertainty is increased due to a budget impact of approximately \$1.5M Cdn while the cost-effectiveness of ECP is unknown and difficult to estimate considering that there are no high quality studies of effectiveness. Both the device and sterile solution are not licensed by Health Canada for the treatment of cGvHD.

If all the ECP procedures for patients with refractory erythrodermic CTCL and refractory cGvHD were performed in Ontario, the annual budget impact would be approximately \$3M Cdn.

**Table 3: Overall GRADE and Strength of Recommendation (Including Uncertainty)**

	Licensed by Health Canada?	Quality	Estimated Incidence in Ontario	Cost-Effectiveness	Cost in Ontario	Overall Grade and Strength of Recommendation  (Including Uncertainty)
Treatment resistant Erythrodermic CTCL	Device - Yes  Drug solution - No	Low	~ 30	? Unknown	<u>If all procedures done in Ontario</u> ~ \$1.5M CDN  <u>If all procedures done in the US</u> ~ \$5M CDN	Weak
Treatment resistant cGvHD	Device - No  Drug solution - No	Low	~30	? Unknown	Same as above	Weak

# Objective

To assess the effectiveness, safety and cost-effectiveness of extracorporeal photophoresis (ECP) for the treatment of refractory erythrodermic cutaneous T cell lymphoma (CTCL) and refractory chronic graft versus host disease (cGvHD).

## Background

### Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is a general name for a group of skin disorders caused by malignant white blood cells (T lymphocytes). Cutaneous T-cell lymphoma is relatively uncommon and represents slightly more than 2% of all lymphomas in the United States. (1) The most frequently diagnosed form of CTCL is mycosis fungoides (MF) and its leukemic variant Sezary syndrome (SS). The relative frequency and disease-specific 5 year survival of 1,905 primary cutaneous lymphomas classified according to the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification is shown in Appendix 1. Mycosis fungoides had a frequency of 44% and a disease specific 5-year survival of 88%. (2) Sezary syndrome had a frequency of 3% and a disease specific 5-year survival of 24%. (2)

Cutaneous T-cell lymphoma has an annual incidence of approximately 0.4 per 100,000 and it mainly occurs in the 5<sup>th</sup> to 6<sup>th</sup> decade of life, with a male/female ratio of 2:1. (3) Mycosis fungoides is an indolent lymphoma with patients often having several years of eczematous or dermatitic skin lesions before the diagnosis is finally established. (4) MF commonly presents as chronic eczematous patches or plaques and can remain stable for many years. Early in the disease biopsies are often difficult to interpret and the diagnosis may only become apparent by observing the patient over time. (4)

The course of MF is unpredictable. Some patients will progress slowly, rapidly or not at all. Most patients will live normal lives and experience skin symptoms without serious complications. Approximately 10% of MF patients will experience progressive disease involving lymph nodes, peripheral blood, bone marrow and visceral organs. (4) A particular syndrome in these patients involves erythroderma (intense and usually widespread reddening of the skin from dilation of blood vessels, often preceding or associated with exfoliation), and circulating tumour cells. This is known as Sezary's Syndrome (SS). (4) It has been estimated that approximately 5-10% of CTCL patients have SS. (5) Patients with SS have a median survival of approximately 30 months. (5)

The most common definition of SS is one of pruritic exfoliative or infiltrated erythroderma (with histological features of CTCL) accompanied by circulating Sezary cells. To date, there does not appear to be a consensus about the number of Sezary cells required to define the syndrome, however most commonly, a Sezary cell count of  $>1 \times 10^9$  per litre or  $>5\%$  of peripheral blood leukocytes is used. (6)

The prognosis for patients with CTCL is dependent on stage, as determined by type and extent of skin lesions and the degree of extracutaneous involvement. Cutaneous tumours, erythroderma, peripheral blood involvement, lymph node or visceral invasion generally denote a poor prognosis.

The therapy of MF offers symptomatic improvement of skin lesions, but has not been proven to affect the natural history of the disease. (7)

The optimal management of MF is undetermined because of its low prevalence, and its highly variable natural history, with frequent spontaneous remissions and exacerbations and often prolonged survival. (8)

Very few randomized controlled trials have been performed in early stage IA IIA MF (See Appendix 1 for staging information). (6) There has been only 1 RCT comparing aggressive systemic chemotherapy combined with total skin electron beam (TSEB) to skin directed therapy involving emollients, topical chemotherapy, phototherapy and superficial radiation. (8) This study showed that the early use of combined therapy in patients with all stages of MF produced improvement in complete response rates (38% versus 18% in the conservative therapy group,  $p=0.032$ ), but not in overall or disease-free survival after a median follow-up of 75 months. (8)

Nonaggressive approaches to therapy are usually warranted with treatment aimed at improving symptoms and cosmesis while limiting toxicity.(6) Given that multiple skin sites are usually involved, the initial treatment choices are usually topical or intralesional corticosteroids or phototherapy using psoralen with ultraviolet A (PUVA). (6) Psoralen with ultraviolet A is not curative and its influence on disease progression remains uncertain. Repeated courses are usually required which may lead to an increased risk of both melanoma and nonmelanoma skin cancer. (6) For thicker plaques, particularly if localized, radiotherapy is an option. (6)

“Second line” therapy for early stage disease is often topical chemotherapy, radiotherapy or TSEB. (6)

Treatment of advanced stage (IIB-IV) MF usually consists of topical therapy; systemic therapy (e.g., single or multiple chemotherapy regimens) may be considered in refractory or rapidly progressive disease. (6)

The treatment of SS is similar to that of advanced stage MF.

Bone marrow transplantation and peripheral blood stem cell transplantation have been used to treat many malignant hematologic disorders (e.g., leukemia, lymphoma) that are refractory to conventional treatment. Reports on the use of these procedures for the treatment of CTCL are limited and mostly consist of case reports or small case series.

Extracorporeal photopheresis is a procedure that was initially developed as a treatment for CTCL, particularly SS. (9)

If the incidence of CTCL in the literature is reported to be approximately 0.4 per 100,000; therefore in Ontario (population 12.5 million) the incidence of CTCL is approximately 50 patients per year.

Two Ontario physicians jointly estimated that there may be approximately 30 new erythrodermic CTCL patients per year who may be candidates for ECP.

### **Chronic Graft Versus Host Disease**

Allogeneic hematopoietic cell transplantation (HCT) is a treatment used for a variety of malignant and nonmalignant disease of the bone marrow and immune system. (10) The procedure is often associated with serious immunological complications, particularly GvHD. (10) A chronic form of GvHD (cGvHD) afflicts many allogeneic HCT recipients which results in dysfunction of numerous organ systems or even a



profound state of immunodeficiency. (10) Histopathologic changes include sclerodermatous skin changes from collagen deposition, pulmonary fibrosis, esophageal dysfunction, dry mouth or mucocutaneous ulcerations, cholestasis and fasciitis. (11) Chronic GVHD is the most frequent cause of poor long-term outcome and quality of life after allogeneic HCT. (10) The syndrome typically develops several months after transplantation, when the patient may no longer be under the direct care of the transplant team. (10)

Approximately 50% of patients with cGvHD have limited disease and a good prognosis. (10) Of the patients with extensive disease, approximately 60% will respond to treatment and eventually be able to discontinue immunosuppressive therapy. (10) The remaining patients will develop opportunistic infection, or require prolonged treatment with immunosuppressive agents. (10)

Chronic GvHD occurs in at least 30% to 50% of recipients of transplants from human leukocyte antigen matched siblings and at least 60% to 70% of recipients of transplants from unrelated donors. Risk factors include older age of patient or donor, higher degree of histoincompatibility, unrelated versus related donor, use of hematopoietic cells obtained from the blood rather than the marrow, and previous acute GvHD. (10) Bhushan and Collins estimated that the incidence of severe cGvHD has probably increased in recent years because of the use of more unrelated transplants, donor leukocyte infusions, nonmyeloablative transplants and stem cells obtained from the blood rather than the marrow. (10) The syndrome typically occurs 4 to 7 months after transplantation but may begin as early as 2 months or as late as 2 or more years after transplantation. Chronic GvHD may occur by itself, evolve from acute GvHD, or occur after resolution of acute GvHD. (10)

The onset of the syndrome may be abrupt but is frequently insidious with manifestations evolving gradually for several weeks. The extent of involvement varies significantly from mild involvement limited to a few patches of skin to severe involvement of numerous organ systems and profound immunodeficiency. The most commonly involved tissues are the skin, liver, mouth, and eyes. Patients with limited disease have localized skin involvement, evidence of liver dysfunction, or both, whereas those with more involvement of the skin or involvement of other organs have extensive disease.

Patients who develop cGvHD require reinstatement of immunosuppressive medication (if already discontinued) or an increase in dosage and possibly addition of other agents. (10) According to Bhushan and Collins (10), the current literature regarding cGvHD therapy is less than optimal and many recommendations about therapy are based on common practices that await definitive testing. Patients with disease that is extensive by definition but is indolent in clinical appearance may respond to prednisone. However, patients with more aggressive disease are treated with higher doses of corticosteroids and/or cyclosporine. (10)

Numerous salvage therapies have been considered in patients with refractory cGvHD, including ECP. (10) Due to uncertainty around salvage therapies, Bhushan and Collins (10) suggested that ideally, patients with refractory cGvHD should be entered into clinical trials.

An Ontario physician estimated that there may be approximately 30 new patients in Ontario each year with refractory cGvHD who may be candidates for ECP.

### **Extracorporeal Photopheresis - Treatment Procedure**

In the early 1980s, PUVA was modified for the treatment of CTCL patients with more advanced disease. After ingestion of oral methoxsalen (a photosensitizing drug), whole blood was collected and enriched for white blood cells. The leukocyte enriched population was then irradiated with UVA and returned to the patient intravenously. This technique was referred to as extracorporeal photopheresis.

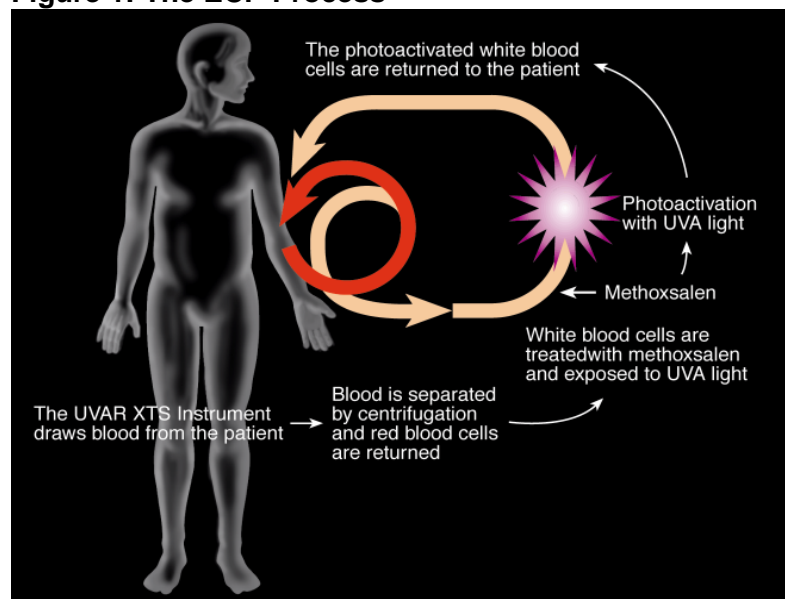
After an intravenous line is inserted in a patient's arm or leg, blood is withdrawn and collected (with an anticoagulant) in the ECP device (Figure 1). The lymphocytes are separated by centrifugation to create a concentrated layer of white blood cells over a number of cycles. In the white blood cell collection bag, the lymphocyte layer is treated with a sterile solution of methoxsalen and exposed to UVA, following which the lymphocytes are returned to the patient. Red blood cells and plasma are returned to the patient between each cycle.

When ECP was initially used to treat CTCL patients, photosensitization was achieved by giving oral methoxsalen to the patient 2 hours before the procedure. However, in the late 1990s a sterile solution of methoxsalen was approved by the US FDA which can be injected directly into the leucocyte rich fraction. (12) This latter approach avoids potential side effects such as nausea, and provides a more consistent drug level within the ECP device. (13) After oral dosing, methoxsalen plasma levels have shown interindividual and intraindividual variations due to variable absorption from the gastrointestinal tract and a variable first pass hepatic elimination. (13)

Methoxsalen is a compound that binds to DNA and to some cell surface molecules and cytoplasmic components on activation by UVA. The affected cells are unable to replicate and subsequently undergo accelerated removal from the circulation over a 1-2 week period. Because only 10%-15% of the circulating mononuclear cells are affected by a single ECP session, the mechanism of action is not primarily through lymphocyte depletion.

A theory to explain the therapeutic benefit of photopheresis in CTCL is that the malignant T cells undergo apoptosis and are phagocytosed by stimulated monocytes ("vaccination theory"). (14) The reinfused methoxypsoralen-affected cells stimulate a suppresser response that targets T cells of similar clones not reached by the photopheresis process. On this basis the return of phototreated cells to the patient is central to the ECP mode of action. (14)

**Figure 1: The ECP Process**



Used with permission from Therakos Inc.; [www.therakos.com](http://www.therakos.com)

ECP is a systemic treatment, and therefore treats only malignant T cells in the peripheral blood as opposed to PUVA which irradiates only skin homing lymphocytes.

It has been speculated, that the mechanism of action of ECP in GvHD may be associated with selective effects of ECP on autoreactive T cell clones. (11)

In general, from the time the intravenous line is inserted until the white blood cells are returned to the patient takes approximately 2.5-3.5 hours.

For CTCL, the treatment schedule is generally 2 consecutive days every 4 weeks for a median of 6 months. For cGvHD, an expert in the field estimated that the treatment schedule would be 3 times a week for the 1<sup>st</sup> month, then 2 consecutive days every 2 weeks after that (i.e., 4 treatments a month) for a median of 6 to 9 months.

## Regulatory Status

The UVAR XTS Photopheresis System is licensed by Health Canada as a Class 3 medical device (license # 7703) for the “palliative treatment of skin manifestations of CTCL.” The device is not licensed for the treatment of cGvHD.

UVADEX (sterile solution methoxsalen) is not licensed by Health Canada, but can be used in Canada via the Special Access Program. (Personal communication, Therakos, February 16, 2006)

According to the manufacturer, the UVAR XTS photopheresis system licensed by Health Canada can also be used with oral methoxsalen. (Personal communication, Therakos, February 16, 2006) However, oral methoxsalen is associated with side effects, must be taken by the patient in advance of ECP, and has variable absorption in the gastrointestinal tract.

According to Health Canada, UVADEX is not approved for use in Canada. In addition, a review of the Product Monographs of the methoxsalen products that have been approved in Canada showed that none of them have been approved for oral administration in combination with the UVAR XTS photopheresis system for "the palliative treatment of the skin manifestations of cutaneous T-cell Lymphoma".

In the United States, the UVAR XTS Photopheresis System is approved by the Food and Drug Administration (FDA) for use in the ultraviolet-A irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in patients who have not been responsive to other therapy.

UVADEX is approved by the FDA for use in conjunction with UVR XTS photopheresis system for use in the ultraviolet-A irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in patients who have not been responsive to other therapy.

The use of the UVAR XTS photopheresis system or UVADEX for cGvHD is an off-label use of a FDA approved device/drug.

# Updated Literature Review on Effectiveness

## Objective

To assess the effectiveness, safety and cost effectiveness of ECP for the treatment of refractory erythrodermic CTCL.

To assess the effectiveness, safety and cost effectiveness of ECP for the treatment of refractory cGvHD.

## Methodology

### Inclusion criteria:

English language articles (2000 – 2005).

Journal articles that report primary data on the effectiveness or cost effectiveness of ECP treatment obtained in a clinical setting, or analysis of primary data maintained in registries or databases.

Study design and methods must be clearly described.

Systematic reviews, randomized controlled trials (RCTs), non-randomized controlled trials and/or cohort studies that have  $\geq 20$  patients, cost effectiveness studies.

### Exclusion criteria

Studies that are duplicate publications (superseded by another publication by the same investigator group, with the same objective and data).

Studies with less than 10 patients.

Non-English articles.

Non-systematic reviews, letters and editorials.

Animal and in-vitro studies.

Case reports.

Studies that do not examine the outcomes of interest.

### Literature Search

Cochrane database of systematic reviews

ACP Journal Club

DARE

INAHTA

Embase

Medline

Reference section from reviews and extracted articles

### Outcomes of Interest

Mortality  
 Response rates (e.g., decrease in skin lesions)  
 Survival  
 Quality of life  
 Economics analysis data

Strength of Recommendation

The GRADE approach was used to systematically and explicitly make judgments about the quality of evidence and strength of recommendations. (15) GRADE provides a framework for structured reflection and can help to ensure that appropriate judgments are made. GRADE takes into account study design, study quality, consistence and directness in judging the quality of evidence for each outcome. (15) The balance between benefits and harms, quality of evidence, applicability and the certainty of the baseline risks are all considered in judgments about the strength of recommendations. (15)

**Results of Literature Search**

The Cochrane Library and the Centre for Reviews and Dissemination Health Technology Assessment databases yielded 3 health technology assessments on ECP. A search of Medline and Embase was conducted and this search produced 147 citations, of which 25 met the inclusion criteria. The quality of the included articles is presented below (Table 1).

**Table 1. Quality of Evidence**

Study Design	Level of Evidence	Number of Eligible Studies
Large randomized controlled trial, systematic reviews of RCTs	1	
Large randomized controlled trial unpublished but reported to an international scientific meeting	1(g)	
Small randomized controlled trial	2	1
Small randomized controlled trial unpublished but reported to an international scientific meeting	2(g)	
Nonrandomized study with contemporaneous controls	3a	
Nonrandomized study with historical controls	3b	
Nonrandomized study presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multi-site)	4b	7
Case series (single site)	4c	17
Retrospective review, modeling	4d	
Case series presented at international conference	4(g)	

g=grey literature

## **Summary of Cutaneous T-Cell Lymphoma Findings: International Health Technology Assessments**

### **Catalan Agency for Health Technology Assessment and Research, July 2001**

The following is a summary of the Catalan report. (16)

Similar to the FDA in the United States, ECP is approved by the Spanish Ministry of Health and Consumption for the treatment of SS, but not for GvHD. (16)

#### **Cutaneous T-Cell Lymphoma**

- Since the publication of the first work in 1987, 14 studies have appeared in the literature (all case series) that assessed clinical response (complete, partial, minor or nonremission) and survival. (16)
- No RCT has been identified confirming the efficacy/effectiveness of ECP versus other types of treatment or placebo. (16)
- The studies had small sample sizes and included different types of patients affected by CTCL; however most patients had erythroderma. (16)
- Overall, studies showed some response in 50-100% of the patients with erythrodermal CTCL. (16)

Table 2 summarizes the Catalan report.

**Table 2: Studies That Assessed Extracorporeal Photophoresis in Patients With Cutaneous T-Cell Lymphoma – Clinical Response Rate**

Study (year)	Total Patients (N)	Complete or Partial Response n (%)	Complete Response n (%)	Patients with Erythroderma (N)	Complete or Partial Response n (%)	Complete Response n (%)
Edelson, 1987	41	22 (54)	6(15)	33	24 (73)	6 (21)
Heald 1989, 1991	32	-	-	22	10 (53)	5 (23)
Armus 1990	8	6 (75)	2 (25)	5	4 (80)	Unknown
Zic 1992	20	11 (55)	5 (25)	6	Unknown	Unknown
Gottlieb 1996	28	20 (71)	7 (25)	-	-	-
Duvic 1996	34	17 (50)	6 (18)	28	-	-
Zic 1996	20	10 (50)	5 (25)	3	-	-
Vonderheid 1998	36	12 (33)	5 (14)	29	-	-
Bisaccia 2000	37	20 (54)	5 (14)	-	-	-

From: Almazan C, Espallargues M, Catalan Agency for Health Technology Assessment and Research. Extracorporeal phototherapy (photopheresis) for the treatment of Sezary syndrome and graft versus host disease. Available from: [www.aatm.es](http://www.aatm.es) (16)

The Catalan report stated that the differences observed in the results of the studies may be attributed to differences in patient inclusion criteria or differences in the presentation of results. Limitations to the studies included lack of clearly defined response criteria, different treatment protocols (duration of treatment, time interval between diagnosis and the start of treatment with ECP) as well as previous or concomitant administration of other drugs with ECP. These limitations make it difficult to assess the effectiveness of ECP.

The Catalan report concluded:

*“...ECP is a new but experimental therapeutic alternative for the treatment of the erythrodermal phase of CTCL.... This therapy should be evaluated in the framework of a RCT to isolate the clinical benefit associated with ECP for this indication.*

*In the case of SS, in view of its low incidence and the fact that it is an officially approved treatment, its use as a compassion therapy could be considered, but in the framework of a research protocol.” (16)*

### **Systemic Therapy of Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sezary Syndrome), 1994**

Bunn et al. (17) conducted a review of therapeutic studies for MF and SS. Extracorporeal photophoresis was one of the treatments reviewed. A MEDLINE search was conducted from 1988 to 1994 for case series and RCTs. The patient outcome assessed in the review was the response to treatment (complete response or partial response).

Bunn et al. (9;18) stated that at the time the review was conducted, the ECP studies were difficult to

interpret for a number of reasons. These include:

- The response criteria were not well defined and were not those generally applied in standard oncology studies.
- It is unclear what percentage of the patients with erythroderma had SS with peripheral blood involvement (Table 3).
- It is unclear whether the improvement in erythroderma was due to an antitumour effect or to some change in cytokines that decreased the erythroderma without affecting the tumour burden.
- Many reviews and non-peer reviewed summaries of these data have appeared in the literature. Some of these implied that the therapy prolonged the survival of the subset of patients with erythroderma. This conclusion was reached by comparing the survival of the patients with erythroderma with historical controls from the literature. This comparison is invalid because established prognostic factors in the treated patients with erythroderma were not provided. (17)
- Some studies (19;20) showed that patients with erythroderma and good prognoses (such as those with normal leukocyte counts and no node or visceral involvement) survive longer than do the treated patients in earlier studies by the initial investigators of ECP for CTCL e.g., Edelson et al. (9) and Heald et al. (18)
- Many patients were concurrently on other therapies. Heald et al. (18) reported that all of the responding patients who did not have a complete response were treated with additional forms of therapy. Some patients were excluded from analysis because of toxicity and other reasons. These patients should be included in the response analysis as nonresponders.
- Confirmatory data on the effectiveness of ECP are difficult to find. Three small reports of 1 to 20 patients reported responses in 55% to 100% of patients and complete responses in about 25% of patients (see Catalan assessment). These reports were primarily limited to patients with erythroderma.
- No RCTs compared this form of therapy with any other type of treatment.

**Table 3. Studies of Photopheresis in Mycosis Fungoides and the Sezary Syndrome**

Study (Reference)	Patients with Mycosis Fungoides	Complete or Partial Responses	Complete Responses*	Median Duration of Response	Patients with the Sezary Syndrome	Complete or Partial Responses	Complete Responses	Median Duration of Response
	<i>n</i>	<i>n</i> (%)	<i>n</i> (%)		<i>n</i>	<i>n</i> (%)	<i>n</i> (%)	<i>mo</i>
Edelson et al. (76)	41 (37)†	22 (54)	6 (15)	Not reported	33 (29)†	24 (73)	6 (21)	48‡
Heald et al. (77)					22	Undefined§	5 (23)	Not reported
Zic et al. (80)	20‡	11 (55)	5 (25)	Not reported	6	Not reported	Not reported	Not reported
Armus et al. (81)	8	6 (75)	2 (25)	Not reported	5	4 (80)	Not reported	Not reported
Rook et al. (82)					1	1 (100)	0	Not reported
Total	92	40 of 70 (57)	18 (20)	Not reported	55	24 of 41 (59)	11 (20)	

\* Pathologic documentation not required.

† Number in parentheses is often cited by authors, but actual patient numbers are first.

‡ Many patients received other therapies.

§ Undefined because all patients who had a partial response also received other therapy.

|| Interferon also given.

*Reproduced with permission from the American College of Physicians; From: Bunn PA, Jr., Hoffman SJ, Norris D, Golitz LE, Aeling JL. Systemic therapy of cutaneous T-cell lymphomas (mycosis fungoides and the Sezary syndrome). Annals of Internal Medicine 1994; 121(8): 592-602 (17)*

Bunn et al. concluded that ECP should be regarded as experimental until convincing data demonstrating



efficacy is published. (17)

Methodological limitations with the review by Bunn et al. included:

- The authors do not report a method for assigning validity (or quality) to the studies assessed.
- The authors do not state how the papers were selected for the review
- The data were extracted without making any judgments on the response criteria used in a study, or the patient numbers.

The Centre for Reviews and Dissemination (University of York, UK) provided the following comments regarding the review by Bunn et al. (17)

- The data in the review were primarily case series and have not been assessed for comparability of diagnosis, disease stage and other prognostic factors.
- The definitions of partial and complete response are not standardized.
- More RCTs are required to assess effectiveness.

### **Comment About Results of the Catalan Health Technology Assessment: How are Erythroderma and Sezary Syndrome Defined?**

The International Society for Cutaneous Lymphomas provided the following hematological staging of CTCL. (21) Generally, there is a lack of consensus about defining SS. (21)

- B0 Erythrodermic MF
- B1 >5% atypical cells + clone (PCR or Southern Blot Analysis)  
*OR*  
>20% atypical cells without clone
- B2 Sezary cells  $>1 \times 10^9 \text{ L}^{-1}$   
*OR* cytogenetic clone  
*OR* absolute lymphocytosis + clone  
*OR* CD4/CD8 ratio >10 (due to increased population of CD4+ cells)  
*OR* circulating cells with aberrant phenotype

An inconsistency noted in the literature is how erythroderma is defined. (5) The term erythrodermic CTCL includes patients with typical MF who then become erythrodermic (erythrodermic MF) and patients who present with erythroderma and are found to have atypical cells in the peripheral blood (SS). (5)

Russell-Jones noted that since the term erythrodermic CTCL was coined, there has been a tendency to regard SS as an advanced form of MF without regard to its clinical and biological characteristics. (5) Patients with erythrodermic MF may or may not develop hematological involvement while some patients who fulfill the clinical criteria for a diagnosis of SS may only have a reactive erythroderma with activated T cells in the peripheral blood resembling small SS cells morphologically. Atypical circulating Sezary cells are not unique to SS but may be found in normal individuals and in patients with a variety of benign inflammatory dermatoses. Thus patients may fulfill the criteria for SS but have a reactive lymphocyte population rather than neoplastic Sezary cells. (22)

Sezary cells may resemble activated lymphocytes. Both large and small variants have been described. (22) The presence of large Sezary cells (>14  $\mu\text{m}$ ) is seen only with malignant disease, so a diagnosis of erythrodermic CTCL can be made with certainty. (22) However, the small and medium sized variants can

be difficult to distinguish from normal lymphocytes. Morphologic interpretation may be subjective and susceptible to interobserver variability.

Diagnosis may be best confirmed by demonstrating a clonal population of T cells in the peripheral blood (e.g., using T cell receptor [TCR] gene analysis). (5;22) For example, patients who are negative may have a reactive erythroderma rather than a T cell lymphoma/leukemia. Such patients can be designated as having nonclonal SS and require follow-up to establish their true status.(5;22) Therefore TCR analysis of peripheral blood could be important in evaluating patients with erythrodermic CTCL since it can clarify whether patients with erythrodermic MF have hematological involvement and will identify patients with nonclonal SS. (5)

If the therapeutic benefit of ECP depends upon the presence of a neoplastic population of T cells in the peripheral blood, then patients with erythrodermic MF who do not have hematological involvement may be unresponsive to ECP. Similarly, patients with nonclonal SS may confound studies reporting response rates and survival data with ECP. (5)

### **How is Erythroderma Defined? - Response Rates**

Russell-Jones reviewed 7 of the largest published studies reporting response rates with ECP. Most patients in all studies had erythrodermic CTCL. However, 2 of the 7 studies reported response rates separately for erythrodermic patients.

In all studies, a partial response was defined as >50% improvement in skin scores. The definition of a complete response varied from >75% improvement to complete clearance. Russell-Jones noted that complete clearance of SS is difficult to achieve.

Complete response rates for ECP in erythrodermic CTCL were relatively consistent with a range of 14-26%. However, there were larger differences in PR rates. Heald et al. (23) reported a partial/minor response of 53% with an overall response rate of 79% in 19 patients with erythrodermic CTCL. Edelson et al. (9) reported that 83% of erythrodermic patients achieved a minor response or better. However, Russell-Jones et al. (24) reported 53% of patients achieving a minor response or better. Vonderheid et al.(25) reported a complete/partial response rate of 33%.

Such differences could be attributed to biological variability as well as:

- Duration of treatment in studies. Duvic et al. (26) reported a mean response time of 10 months.
- Interval between diagnosis and initiation of treatment with ECP. These details are not provided in all the studies.
  - The longest interval between diagnosis and treatment (30 months) was reported by Gottlieb et al. (27) in association with one of the highest response rates (complete/partial response rate of 71%). Since the median survival of patients with SS is 30 months, this may suggest a bias in patient selection such that only those patients with a favourable prognosis survive long enough to receive ECP treatment.

### **How is Erythroderma Defined? - Survival Data**

The 29 erythrodermic patients studied by Heald et al. (28) represented a follow-up of the original cohort of Edelson et al. (9) The authors reported a median survival of 60 months compared with historical data indicating a median survival of 30 month in patients not treated with ECP. However, only 11 of the 37 original patients were known to have a peripheral blood T cell clone. It is not reported if these 11 patients were all erythrodermic, nor the status of the other 26 patients. In 1996, Gottlieb et al.(27) reported a median survival of over 100 months in 28 patients with CTCL. However, at least 4 of these patients had

patch or plaque stage disease which makes comparison with other series more difficult. The data on clonality are incomplete: 13 patients were not tested and 9 of the remaining 15 had peripheral blood T cell clones.

Zic et al. (29) reported a median survival of 96 months; 15% of patients (3 of 20) were erythrodermic. No controls were included in this study so it is difficult to determine the expected survival and whether it had been prolonged by ECP. Vonderheid et al. (25) reported a median survival of 36 months in 36 patients treated with ECP, but this was from the start of ECP therapy and 31 of the 36 patients had >10% circulating Sezary cells. Fraser-Andrews et al. (30) reported a median survival of 39 months (range 3-138) in 29 patients with SS. This was not significantly different from a median survival of 22 months in the nonECP treated group (n=8) or of 27.5 months (range 12-67) in the historical controls treated before ECP was available (n=7). Comparison of both control groups to the ECP group did not produce a statistically significant result.

Vonderheid et al. (25) treated patients with immunomodulatory agents plus ECP. It is difficult to know how much of the clinical benefit related to the immunomodulatory agent and how much to ECP plus the agent. For example, Dippel et al. (31) reported 19 patients with advanced CTCL all of whom had clinical and histological evidence of lymph node involvement. This was cleared in 6 of 9 patients who received ECP plus interferon alpha, compared with 1 of 10 treated with ECP alone. (31) It is unknown if improvement was confirmed histologically. Only 3 of the 19 patients were erythrodermic whereas 6 had skin tumours; Russell-Jones suggested that this is not a clinical situation where one would expect ECP to have a significant benefit. It could be argued that most of the therapeutic effect came from the interferon alpha. (5)

Overall, Russell-Jones states that these issues can only be resolved with RCTs with particular attention to patient selection and entry criteria for CTCL, similar to other disease areas. (5) Russell-Jones suggests that erythrodermic CTCL should be studied separately from other stages of the disease and patients should be stratified on the basis of previous chemotherapy. (5) Furthermore, patients with SS should be defined by the presence of a T cell clone in the peripheral blood. (5)

An Ontario expert in the field stated that in Ontario, the definition of SS includes assessment for a clonal population of T cells in the peripheral blood.

### **Discriminating Between Erythrodermic Cutaneous T-Cell Lymphoma and Reactive Erythroderma**

Russell-Jones (21) suggested an algorithm designed for discriminating between reactive erythroderma and patients with CTCL who present with erythrodermic disease. They suggest that if a clinician is faced with a patient whose chronic erythroderma is of unknown etiology, then there are 3 key procedures which will determine the correct diagnosis: biopsy of lesional skin, analysis of peripheral blood, and lymph node biopsy.

For example, if a skin biopsy demonstrates the typical histological features of CTCL with atypical lymphocytes and/or epidermotropism, then the diagnosis of erythrodermic CTCL is established. (21) However, it has been suggested that one-third of biopsies even from patients with established erythrodermic CTCL are nondiagnostic. (32) TCR gene analysis is important if the histology is nondiagnostic and T cell immunostaining is uninformative. The vast majority of patients with erythrodermic CTCL will show a clonal population of T cells, but due to the marked inflammatory component, the analysis may be nonclonal. Either way, it is important to correlate the skin findings with the result of TCR gene analysis of peripheral blood. If the same T cell clone is present in skin and blood, then that provides strong evidence for a diagnosis of erythrodermic CTCL. (21)

## **Updated Summary of Findings – Cutaneous T-Cell Lymphoma**

A tabulated summary of the studies published since the Catalan health technology assessment is presented in Appendix 2. The Catalan assessment did not attempt to stratify patients according to type of CTCL, treatment resistance, peripheral T cell clone requirement upon study entry, or type of concomitant therapy. As a result, the Medical Advisory Secretariat also reexamined the studies that were included in the Catalan assessment in an attempt to stratify studies according to these criteria.

### **Studies Including Patients Having Refractory Cutaneous T-Cell Lymphoma, Peripheral T Cell Clonality and No Concomitant Therapy**

No studies were identified that fulfilled **all** these inclusion criteria.

### **Studies Including Patients Having Peripheral T Cell Clonality and No Concomitant Therapy**

In order to meaningfully assess studies with some commonality in their inclusion criteria, it was decided to stratify the inclusion criteria by removing the requirement for patients to have refractory CTCL. Therefore, the following set of inclusion criteria were used.

- **All** patients must have: 1) peripheral T cell clone; 2) no concomitant therapy administered with ECP (e.g., TSEB).

Two studies were identified, Child et al. (33) and Evans et al. (34) The following is a summary and critique of these studies.

Child et al. (33) conducted a prospective randomized crossover trial (N=16) to examine the efficacy of PUVA and ECP in the treatment of patients with T2 plaque stage (Stage 1B) MF who had a detectable peripheral blood T cell clone, but no lymph node involvement. (33) No patient had received active treatment (other than topical steroids and emollients) within 3 months of commencing the study.

Between 1998-2000, 16 patients (median age 68 years, range 37-80 years) were randomized to receive either PUVA twice weekly for 3 months followed by ECP once monthly for 6 months at relapse or vice versa. Response was assessed by monthly skin scores and peripheral blood T cell clonality. Ten patients had previously received PUVA as part of their disease management but none had been treated with ECP.

Initially a sample size of 20 was thought to produce adequate information for statistical analysis. Interim analysis after recruitment of 16 patients showed statistical significance and therefore the study was stopped (no further details of the interim analysis were reported). In total, 10 patients were randomized to Group 1 (PUVA twice a week for 3 months; after a washout period of 3 months or at disease relapse they were treated with ECP once a month for 6 months) and 6 patients to Group 2 (ECP once a month for 6 months, followed by PUVA twice a week for 3 months after washout). The authors do not provide details as to why there were an uneven number of patients in each of the study arms or why PUVA was not administered for 6 months, similar to ECP).

Skin scores were carried out a monthly (PUVA) or 2 monthly (ECP) intervals throughout treatment. The same assessor examined all patients at each visit to ensure not interobserver variation. The sum of all the lesions was calculated to give the total skin score.

Eight of the original 16 patients completed the study. Four patients dropped out (2 prior to starting treatment, 1 became mildly hypotensive during ECP and felt unable to tolerate it, 1 due to disease progression). The other 4 patients completed the first arm of the study but were subsequently withdrawn as the study was halted following interim analysis.

There was a reduction in skin scores in all patients during PUVA but with ECP skin scores remained stable or increased. In 8 patients who completed the study, 3 months PUVA was significantly more effective at clearing skin disease than 6 months of ECP (difference in skin score 113; confidence interval [CI] 42-184,  $p=0.002$ ). T cell clones were detected in the peripheral blood both before and after PUVA and before and after ECP. None of the patients had circulating SS cells at any time during the study.

Child et al. stated that since none of the patients who had completed the study gained any benefit from ECP (confirmed by interim statistical analysis), the study was terminated prior to the final 4 patients completing both arms.

#### Followup to August 2000

Of the 8 patients who completed the study, one remained in clinical remission 14 months after completion of PUVA, 4 had active plaque stage disease that remained responsive to PUVA, 1 developed metastatic adenocarcinoma (primary site unidentified), 1 developed SS and 1 was lost to follow-up.

Of the 8 patients who did not complete the study, 2 remained in complete clinical remission following UVA, 1 patient with progressive disease responded to treatment with TSEB, 3 had active plaque stage disease, and 2 died of their disease.

The authors reported that PUVA was well tolerated other than nausea secondary to ingestion of oral psoralen. One patient withdrew from the study because he was unable to tolerate ECP due to hypotension during the procedure and a second patient had one cycle terminated due to poor venous access.

Limitations to the study by Child et al. (33) include:

- Unclear reporting of biometrics and results.
- No patient received active treatment (other than topical steroids) within 3 months of commencing the study. What was the definition of active treatment? Were topical steroids allowed during the trial, and who used them? This may have affected the skin scores.
- Small sample size (8 of the original 16 completed the study).
- 10 patients in the study were known to have previously received/responded to PUVA.
- What corrections were made for pretreatment skin scores?
- Relevance of improvement of skin scores, yet presence of T cell clonality after treatment for both groups is unclear.
- Was the skin score assessment blinded?
- 1 skin score assessor was used.
- Intent to treat (ITT) analysis was not discussed.
- Details about the interim analysis?
- ECP was administered once month. Conventional treatment is usually 2 consecutive days a month.
- Why were skin scores measured monthly for PUVA and at 2 monthly intervals for ECP?

■ Evans et al. (34) retrospectively analyzed 23 patients (mean age 69.3 years, range 43-83) with SS (defined by erythroderma, more than 10% circulating atypical mononuclear cells and peripheral blood T cell clone) undergoing monthly ECP as the sole therapy for up to 1 year.

Five patients had previously undergone intravenous chemotherapy and 5 others had received oral chemotherapy. All systemic treatment had been discontinued at least 6 weeks before ECP was started. The same treatment protocol was used in all patients. Patients had been given ECP as the sole systemic therapy on 2 consecutive days each month for at least 6 months.

Patients were assessed before therapy and at 3, 6, 9 and 12 months after initiation. Skin score was recorded at each time point. Responders were defined as those who achieved at least a 25% reduction in skin score from baseline and nonresponders were defined as those who did not. Peripheral blood samples were also taken and analyzed for total white cell count, lymphocyte count, CD4 count CD8count and Sezary count.

Twenty-three patients completed 6 months of ECP, and 8 (35%) were classified as responders at this stage. Twelve patients completed 12 months of ECP without adjuvant therapy and 8 of these were responders at this stage. Details of the patients who did not complete 12 months were not reported. Overall, 13 of the 23 patients who entered the trial were responders at 3, 6, 9, or 12 months.

The cohort showed a significant reduction in skin score ( $p=0.001$ ) during treatment with ECP. Reduction in skin score was positively and significantly associated with a reduction in the Sezary count as a percentage of total white blood count ( $p=0.03$ ). Positive but not statistically significant correlations were found between reduction in skin score and reduction in absolute CD4 count ( $p=0.024$ ), CD8 count ( $p=0.085$ ) and absolute Sezary cell count ( $p=0.082$ ).

Neither the absolute change in total white cell count, lymphocyte count, CD4 count, CD8 count or absolute Sezary count was significantly different between responders and nonresponders at 6 months.

Previous administration of chemotherapy was not associated with responder status. Ten patients had

undergone prior chemotherapy and 6 were classified as responders. Other clinical parameters such as lymphadenopathy and presence of coexistent tumours were not related to responder status.

The only baseline variable that significantly predicted responder status at 6 months was the baseline Sezary count as a percentage of total white cell count. A 1% increase in the Sezary count as a percentage of total white cell count as baseline was associated with an odds ratio of 1.07 of becoming a responder ( $p=0.02$ ) at 6 months. None of the parameters was significantly associated with responder status at 12 months, though again the numbers were small.

Limitations to the study by Evans et al. included:

- Retrospective case series.
- Small sample size.
- Consecutive patients?
- No details regarding patient dropouts – only 12 patients completed 12 months of treatment. Where did the others go?
- Blinded skin assessment?
- The cohort showed a significant reduction in skin score ( $p=0.001$ ) during treatment with ECP (at how many months?).
- Unknown if active topical treatment was discontinued or comparable among patients. This is important considering skin scores were the outcome measured.

## Studies Including Patients Having Peripheral T Cell Clonality and Concomitant Therapy

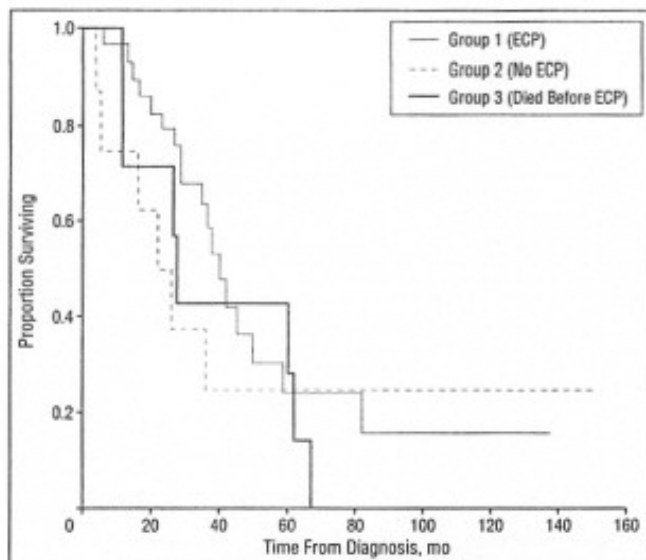
In a retrospective study of 44 patients with SS, Fraser et al. (30) compared survival in patients treated with ECP with that of patients treated conventionally at the same institute. All patients had evidence of a peripheral blood T cell clone. The methoxsalen was given orally to most patients (n=35) and 9 patients had methoxsalen added directly to the leukocyte bag.

Twenty-nine patients received ECP (group 1); 15 patients did not receive ECP, 8 patients when ECP was available at the authors' institution (group 2) and 7 before ECP was available (group 3 – historical control). Forty-three of the 44 patients received other conventional treatments. The median survival from diagnosis of SS was 39 months in group 1, 22 months in group 2 and 27.5 months in group 3.

The median (range) survival of group 1, 2 and 3 was 39 (3-138), 22 (41-51) and 27.5 (12-67) months respectively. Figure 2 shows the survival in Groups 1 (ECP), Group 2 (no ECP) and Group 3 (died before ECP). Cox regression analysis comparing the 3 groups did not show any significant difference in survival in the patients treated with ECP after correcting for age, sex, and initial Sezary cell count.

Groups 2 and 3 were combined to increase numbers in the non-ECP treated patients and the median survival was 26.5 months. Cox regression analysis showed no significant difference between the groups after correcting for age, sex, and initial SS cell count (hazard ratio 0.56, 95% CI 0.26 to 1.17, p=0.12). Figure 3 shows the survival in Groups 1 (ECP) and Groups 2 and 3 combined (no ECP).

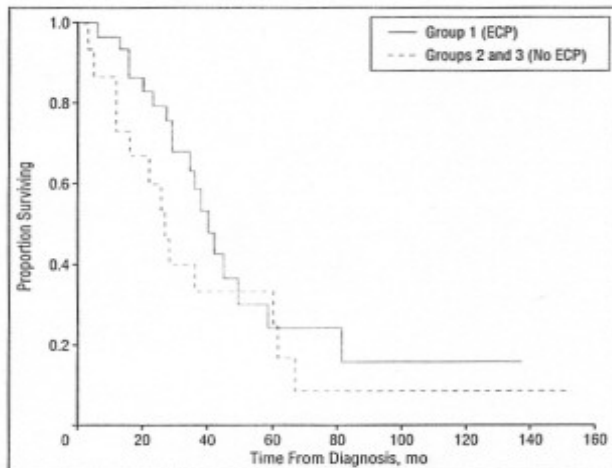
**Figure 2: Survival in Groups 1, 2, and 3 (Kaplan Meier Analysis).**



*Used with permission. Fraser-Andrews EA, Seed PT, Whittaker SJ, Russell-Jones R. Extracorporeal photopheresis in Sezary syndrome: no significant effect in the survival of 44 patients with a peripheral blood T cell clone. Archives of Dermatology 1998; 134: 1001-1005. Copyright © 1998 American Medical Association. All rights reserved.*



**Figure 3: Survival in Group 1 Compared With Groups 2 and 3 Combined (Kaplan Meier Analysis).**



*Used with permission. Fraser-Andrews EA, Seed PT, Whittaker SJ, Russell-Jones R. Extracorporeal photopheresis in Sezary syndrome: no significant effect in the survival of 44 patients with a peripheral blood T cell clone. Archives of Dermatology 1998; 134: 1001-1005. Copyright © 1998 American Medical Association. All rights reserved.*

Limitations to the study by Fraser-Andrews et al. included:

- Retrospective case series design.
- Consecutive patients?
- Historical controls.
- Concomitant therapy.
- Small sample size.
- Unbalanced controls.
- Death from any cause.

## **Studies Including Some Patients Having Peripheral T Cell Clonality and Concomitant Therapy**

Vonderheid et al. (25) examined 36 patients who were all treated with ECP for at least 12 weeks. The median duration of disease was 7 years. The clinical manifestations were heterogeneous: 28 patients had generalized or nearly generalized skin involvement manifested as diffuse erythema or dermatitis.

Blood samples were used to screen patients for evidence of blood involvement by counting Sezary cells and flow immunophenotyping. Although the presence of more than 15 Sezary cells per 100 lymphocytes on smears was used to detect circulating malignant cells, blood involvement was not considered to be documented unless:

1. Flow immunophenotyping of blood lymphocytes showed evidence of a CD4+ T cell population with aberrant loss of markers normally expressed on mature T cells; or
2. Molecular genetic studies showed evidence of a clonal rearrangement of the T cell receptor gene; or
3. A chromosomally abnormal T cell clone was found in the blood.

Blood involvement was shown in 28 of 36 (78%) patients before the start of ECP.

All patients received oral methoxsalen.

Most patients were treated with ECP alone or in combination with low dose interferon. Four patients received ECP for maintenance after other treatments were given.

For erythrodermic patients, the overall status of the skin was based on the extent of skin surface involvement and the discernible severity of inflammation (erythema intensity, edema and degree of scaling/fissuring of the skin) [subjective]. Erythema intensity was compared with an Erythema Scale (progressive layering of Kodak red filter film). The scale provided "E scores" on most patients (patients with dark pigmentation could not be measured) that ranged between 0 (normal skin hue) and 60 (deep red colour). For patients with no erythroderma, the overall skin status was judged from the extent of involvement and the average degree of infiltration among patch, plaque or tumour lesions on the skin.

Blood samples were also taken to determine the Sezary cell count.

Treatment responses using an overall assessment of skin status, lymph node size and Sezary cell counts relative to baseline were categorized according to a 6 point scale:

0=no disease detectable

1=disease manifestation much improved

2=disease manifestation somewhat improved

3=no significant change

4=disease manifestation somewhat worse

5=disease manifestation much worse

Relative global response scores of 0, 1 and 5 that lasted 4 or more weeks corresponded to the definition of clinical complete response, partial response and disease progression respectively.

Global severity scores of 0 or 1 lasting at least 4 weeks occurred in 12 (33%) patients. Five patients attained a clinical complete response and the duration ranged from 12 to more than 172 weeks (median >68 weeks) (one patient from ECP alone, one after interferon was added to ECP, one after palliative EB was given after the sixth ECP session, and 2 from initial radiotherapy followed by ECP to maintain the response). The other 7 patients had partial responses lasting 4 to 52 weeks (median 12 weeks) (2 from

ECP alone, 1 from initial radiotherapy followed by ECP, and 4 patients from ECP combined with nitrogen mustard ointment, methotrexate, interferon or a combination of these therapies). In 4 of these patients ECP was discontinued because of disease progression. Relatively stable disease during ECP occurred in 11 (31%) patients and ECP was stopped because of progressive disease in 1 patient. The remaining 13 patients exhibited steadily progressive disease despite ECP.

The median survival for all patients from the start of ECP was 36 months.

Sezary cell count was not reported for patients post-treatment.

Limitations to the study by Vonderheid et al. included:

- Concurrent treatment
- The main goal of the study was to determine the utility of serum interleukin 2 receptor as a test in monitoring of patients with advanced CTCL.
- Blinded skin score assessment?

In a prospective pilot cohort study, Quaglino et al. (35) examined the clinical efficacy of fludarabine monophosphate (FAMP) monotherapy in advanced CTCL and to evaluate if the sequential association of ECP to FAMP in selected patients may improve the response rate and or lengthen the remission duration.

Forty-four CTCL patients (17 SS and 26 MF, stage IIB-IV or with peripheral blood involvement: 1 MF associated with lymphomatoid papulosis) were enrolled from 1995-2002. SS diagnostic criteria consisted of:

Erythroderma and peripheral lymphadenopathies

Peripheral blood involvement with circulating Sezary cells

Cutaneous biopsy proven CTCL confirmed by the finding of a clonal T cell receptor gene

Eligibility criteria consisted of:

>18 years

stable IIB-IV according to the TNM staging **or** presence of peripheral blood involvement

Eastern Cooperative Oncology Group performance status 0-2

Adequate bone marrow function

Normal hepatic/renal and pulmonary functions

Twelve patients (7 MF and 5 SS: 27.3%) were previously untreated while 13 (9 MF and 4 SS: 29.5%) were previously treated with polychemotherapy. The remaining 20 patients underwent PUVA. Low dose interferon or thymopentin.

All patients received FAMP 5 days monthly. A first response evaluation was carried out after 2 full cycles. Responding or stable disease patients were treated until progression for up to 8 cycles (mean number of cycles per patient, 5; range 2-8). Nineteen patients (43.2%) underwent ECP after FAMP was discontinued. For MF patients, ECP was performed in 2 patients with erythrodermic disease, in 4 with peripheral blood involvement (1 stage Ib, 1 stage Iib and 2 stage IV) and in the patient with MF associated with LyP. ECP was not performed in 5 SS patients (3 developed rapidly progressive disease after FAMP and their clinical conditions worsened and 2 achieved a long standing CR after FAMP). Patients were considered members of the combination FAMP-ECP group when they received at least 6 ECP courses. The interval between FAMP and ECP did not exceed 6 months (median 3.1 months; range 2-6).

Response rate was based on the measurement of clinically apparent disease in the skin, lymph nodes and peripheral blood according to the pretreatment staging.

After a median follow-up of 4.2 years (range 6 months to 7.5 years), all 44 patients were evaluable for response. The overall response rate (RR) to FAMP evaluated before starting ECP was 29.5% (13/44); a higher RR was obtained in SS (35.3%) than in MF patients (25.9%). According to the pretreatment group, the RR of the FAMP-ECP group (63.2%) was significantly higher than that of the FAMP monotherapy group (24%,  $p=0.021$ ).

No statistically significant difference was found in time to progression (TTP) or survival by therapy group. The median overall survival was 19.3 months (range 3-91+ months) with a 5 year overall survival of 23.4%. The median survival of MF patients was 30.1 months (range 3-73) and for SS patients was 17 months (range 3-91). The TTP of the FAMP-ECP group was higher (median 13 months, range 3-91) than that of the FAMP only group (median 7 months, range 2-83); this was not statistically significant. No difference in survival was found between FAMP treated (median 25.5 months; range 2-84) and FAMP-ECP treated patients (median 20.1 months; range 8.5-91).

The main toxicities in the study were related to FAMP. Two ECP patients showed transient hypotension during treatment.

Limitations included:

- Low number of patients
- Nonrandomized patient accrual.
- ECP inclusion criteria in the institutions changed over the course of time. Once it was given only to SS patients with active disease, while the criteria at the time of publication included erythrodermic MF, MF with peripheral blood involvement and LyP patients. In addition, ECP has been given as maintenance treatment after chemotherapy induced remissions.
- The authors stated “Even if the low number of patients treated and the nonrandomized patient accrual do not allow us to reach definite conclusions, we do, however, feel that the response rate increase in the selected group of advanced CTCL patients treated with the combined FAMP-ECP schedule could well be the basis for the planning of randomized multicentre trials on larger groups of patients to investigate further these promising preliminary results.” (35)

Using a retrospective study design over a 14-year period, Suchin et al. (36) examined the efficacy of combination therapy for 47 consecutive patients with CTCL. Most patients had advanced disease at the time treatment was initiated: 32 (68%) of the 47 patients had stage III or IV disease; 42 (89%) of the 47 patients had peripheral blood involvement as determined by the presence of more than 5% atypical cells detected by...analysis of peripheral blood buffy coats. Most patients had analysis performed on peripheral blood for the cell surface markers CD3/4/7 and 8 and/or analysis of the T cell receptor gene to determine whether a clonal population of T cells was present.

A complete response to therapy was defined as the regression of all evidence of disease for at least 3 months, including skin disease, disappearance of Sezary cells from the peripheral blood if present before therapy and a change in the clonal population of T cells. Therefore, patients who did not have clonal T cells measured and did not have Sezary cells before therapy could have been classified as having a complete response based on skin surface area alone. A partial response was designated as at least a 50% reduction in skin surface area involvement and in numbers of circulating Sezary cells. Therefore some patients who did not have clonal T cells measured could have been classified as having a partial response based on skin surface area alone. Patients who experienced less than 50% clearance of skin and peripheral blood disease were classified as nonresponders.

Some patients received courses of local gamma irradiation to cutaneous tumours or lymph nodes and/or focal treatment to affected skin with topical chemotherapeutic agents or topical steroids and/or concurrent treatment with PUVA or UVB irradiation. The authors stated that “since these forms of therapy do not produce systemic immune enhancing effects, they were not considered forms of adjuvant therapy.” (36)

Thirty-one (66%) of the 47 patients received combination therapy compared to 15 (34%) patients who received ECP monotherapy. At baseline, differences between the 2 groups were statistically significant for the mean CD4+/CD8+ratio ( $p=0.006$ ). Although there appears to be a trend toward higher Sezary counts seen in patients who received combination therapy, there was no statistically significant difference noted ( $p=0.18$ ).

All 47 patients received a minimum of 6 months of ECP. Some of the patients received focal treatment with topical nitrogen mustard or carmustine ( $n=35$ ), topical steroids ( $n=43$ ), gamma irradiation ( $n=11$ ), PUVA ( $n=5$ ) or UVB ( $n=1$ ) treatment.

The clinical response by therapeutic group is shown in Table 4. Twenty-six of the 31 patients in the combination group experienced either a complete or partial clinical response. Of the 16 patients who

received ECP monotherapy, 12 (75%) had a positive response.

**Table 4: Clinical Response by Therapeutic Group**

Response	Combination Therapy (n=31)	ECP Monotherapy (n=16)	P value
Complete	6 (19)	6 (38)	
Partial	20 (65)	6 (38)	
<b>Total Response</b>	<b>26 (84)</b>	<b>12 (75)</b>	<b>0.47</b>
No response	4 (13)	3 (19)	
Progression	1 (3)	1 (6)	

*Used with permission. Suchin KR, Cucchiara AJ, Gottlieb SL, Wolfe JT, DeNardo BJ, Macey WH et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Archives of Dermatology 2002; 138(8):1054-1060 Copyright © 2002 American Medical Association. All rights reserved.*

Patients with late stage (III and IV) disease experienced a median survival of 55 months (4.6 years) versus patients with early stage (I and II) disease had a median survival of 92 months (7.7 years), p=0.03.

The median survival of for the patients undergoing combination therapy was 74 months (6.2 years) whereas the median survival for the monotherapy group was 66 months (5.5 years), p=0.51.

The authors stated that none of the patients experienced greater than grade I toxic effects according to the common toxicity criteria of the National Cancer Institute.

Limitations to the study by Suchin et al. included:

- Documented T cell clonality was not an inclusion criterion for all patients.
- Sezary cells may resemble activated lymphocytes. Both large and small variants have been described. (22) Large Sezary cells have been reported previously in association with CTCL. (22) However, the small variant can be difficult to distinguish from normal lymphocytes. (22) Morphologic interpretation is subjective and susceptible to interobserver variability. (22) The study by Suchin et al. was retrospective over a 14 year period.
- The authors stated that “present criteria for receiving ECP included extensive skin involvement and more than 5% circulating Sezary cells detected on buffy coat analysis. However, when ECP was in its early development, patients with any stage of cutaneous disease with or without peripheral blood involvement were eligible for treatment. Responses in some of these early patients are included in the present study and served to establish the current treatment criteria.”
- Unknown how many patients in each group received therapy that were not considered forms of “adjuvant therapy” by the authors.
- Some patients without Sezary cell count/T cell clonality may have been considered responders by skin score alone. This is important considering some topical treatments were not considered “adjuvant therapy”. The topical treatments alone may have changed the skin scores.
- “...further investigation is needed to better establish the effectiveness of multimodality biologic response therapy for the treatment of CTCL...”.
- Comparison to historical controls.

### **Studies Including Some Patients Having Peripheral T Cell Clonality and No Concomitant Therapy**

Stevens et al. (37) reported a case series of 17 patients who received ECP as first line treatment for SS (n=15) and erythrodermic MF (n=2). Although the study by Stevens et al. did not require all patients to have T cell clonality the authors reported T cell clonality for 14/15 SS patients. Significant blood

involvement was documented in the 15 patients with SS: 14 showed positive findings for clonality in the peripheral blood as shown by TCR analysis.

The procedure was performed on 2 consecutive days twice monthly for the first 2 months and monthly thereafter. Patients who maintained a complete remission for 1 year continued treatment every other month.

Four of the SS patients were moribund on presentation and underwent only 1 to 2 cycles of ECP (died within the first 2 months of therapy). For all 15 SS patients, the median survival was 34 months (similar to the survival of SS patients reported in the literature). The median survival was 56 months for the remaining 11 patients with SS.

The 2 MF patients were not included in the survival analysis. One of them was in complete remission at the time of manuscript writing, and the other died after 39 months of ECP, secondary to chronic obstructive pulmonary disease.

No major adverse effects were noted during the course of ECP.

Limitations to the study by Stevens et al. included:

- Unclear if study was retrospective or prospective
- Small sample size.
- All patients received oral methoxsalen.
- Emphasis on the results for the 11 patients rather than the full sample size of 15 patients.
- Patients were said to have had ECP as initial therapy, but no discussion was provided as to if the patients received concomitant therapy.
- The authors make claims without evidence to support their beliefs. E.g., “We do not view ECP as salvage therapy; therefore, we do not believe that including results from moribund patients is appropriate.” (37) In addition, “However, we believe that the benefit of ECP accrues over months of treatment.....thus exclusion of moribund patients is appropriate.” (37)

### **Studies Including Patients Having Refractory Cutaneous T-Cell Lymphoma and No Concomitant Therapy**

In 1987 Edelson et al. (9) reported outcomes of 41 patients with CTCL who were treated with ECP. Thirty-three patients had generalized erythroderma, 8 had localized plaques, and all had diagnostic skin biopsies and circulating atypical mononuclear cells. Studies of disease status included histologic evaluation of peripheral lymph nodes and identification of clonal rearrangements of the T cell receptor genes of blood and lymph node lymphocytes.

Methoxsalen was administered orally and an earlier version of the device, the UVAR I, was used which had a treatment time of 6 to 7 hours (irradiation was not started until all buffy coat collection was complete). Since the trial of Edelson et al., the UVAR II system has been used in studies (e.g., Heald et al. (23) ) which has a treatment time of 3 to 4 hours. (23)

Patients received adjunctive therapy; this was limited to 1% hydrocortisone.(23)

The main outcome was skin response. A minimally successful skin response was defined as a 25% reduction in the baseline overall skin lesion score maintained for 4 consecutive weeks.

Four patients withdrew voluntarily before reaching a clinical endpoint. No further information about the patients was reported by the authors. Twenty-eight of the remaining 37 patients had either not responded to a course of systemic chemotherapy or had subsequently had a relapse, as had the other 9 patients given

EB radiotherapy, topical mechlorethamine or methoxsalen photochemotherapy directed at the skin.

On the basis of skin scores, 27 patients were judged to have had a positive response to treatment (the mean [SD] time to a positive response was 22.4 [9.6] weeks).

Twenty-four of the 29 patients with exfoliative erythroderma responded to the treatment compared to 3 of 8 patients with more localized plaques and tumours.

Limitations to the study by Edelson et al. included:

- Unknown if the patients were enrolled consecutively.
- The four patients who withdrew were excluded from subsequent data analyses.
- No details regarding the extent of treatment resistance of the 28 patients (how many different prior treatments, duration). Heald et al. reported that the cohort “included patients who had failed at least one conventional modality.”
- According to the authors, “...this study is a preliminary step in the development of clinically efficacious treatments of blood by photoactive drugs and the follow-up period is too short to reveal the long-term effect of photochemotherapy on the natural course of CTCL.”
- Were any of the patients on any concurrent therapy during the trial? Yes – unpublished literature from the manufacturer stated that patients concurrently received systemic and topical therapy during the trial.
- Blinded assessment of skin scores?

Heald et al. (28) followed up the 29 erythrodermic CTCL patients who were originally studied by Edelson et al. (9). According to the authors, 6 of the 29 erythrodermic CTCL patients had a complete remission. Another 6 patients had more than 50% improvement of skin scores and 5 patients had either no change or deterioration of their skin status. The remaining patients had an improvement in skin score associated with a “variable improvement in the quality of life.” The authors did not discuss or report any standardized and validated quality of life scale used to determine the quality of life outcome.

Survival statistics were calculated by the actuarial or life-table method. Two patients were lost to follow-up. The median survival of the erythrodermic CTCL patients was 60.3 months from the time of diagnosis. From the time that ECP was initiated, the median survival was 47.9 months. The range was not reported.

Four of the 6 responders maintained complete remissions. Five patients had no response to therapy. Of these patients, one elected to continue ECP and was still alive at the time the manuscript was written. The other 4 responders died. Cause of death was not reported. ECP was continued for the remaining 18 patients with intermediate responses. Nine of the patients were continuing maintenance therapy with monthly ECP at the time the manuscript was written. The outcomes of the other 9 patients with intermediate responses were not reported.

The authors stated that the largest series comparable to that reported by Heald et al. is 42 patients with “generalized erythema” in CTCL. (38;39) In those historical controls from 1979 and 1981, the median survival was 30 months. (38;39) Another report from 1988 that reviewed tumour registry data noted that Sezary syndrome (not defined) had a median survival of 2.6 years from diagnosis. (40)

Limitations to the study by Heald et al. included:

- Limitations to the study by Edelson et al.
- Definition of an intermediate response?
- Details of the causes of deaths?
- No details about the outcome of non-erythrodermic CTCL patients?



- Blinded assessment of skin scores?
- Comparison to historical control groups.

Heald et al. (23) examined the skin scores of 32 CTCL patients who received ECP. It is unclear if these were the same patients who received ECP treatment in Edelson et al. (9). The device was different, however, it is unknown if some of the same patients received treatment with the newer device. Oral methoxsalen was administered to the patients.

There were 3 groups of patients: erythroderma (n=22), tumour stage (n=9) and those with widespread disease in relapse for more than 1 year after therapy (n=3). The majority were of patients were those with erythroderma receiving photopheresis as their first line of therapy (n=19). Skin responses were graded into 3 categories: patients clearing either 75% of their surface involvement; patients involving more than 25% of their involvement but less than 75%; and those with less than 25% involvement.

Adjunctive therapy was considered for patients with responses that were incomplete (stable but not acceptable improvement in response to ECP).

Twenty-two patients with erythroderma were treated; 19 of these had ECP as the first line therapy. Five of the patients cleared over 75% of their skin involvement. Ten patients cleared 25% to 75% while 4 patients had less than 25% improvement.

The preliminary results of treating tumour stage disease with ECP alone showed that tumours did not resolve within a few months of therapy.

Limitations to the study by Heald et al. include:

- Case series design.
- It is unknown if the skin score assessment was blinded.
- Comparison to historical cohorts – Edelson et al. (9)
- Details regarding dropouts/deaths were not reported.
- The total number of patients assessed is unclear – the text reports 32, but the table in the journal article reports 34.

### **Studies Including Patients Having Refractory Cutaneous T-Cell Lymphoma With Concomitant Therapy**

Two studies by the same author (one study was a follow-up of the same patients) matched these inclusion criteria.

In 1992 Zic et al. (41) reported on 24 patients with CTCL who received ECP. Most patients were judged to have disease refractory to standard therapy at the time of referral and demonstrated progressive disease before ECP. The authors stated that their series included only those patients who had undergone at least 6 months of ECP. Patients were excluded because they had less than 6 months of ECP at the time of evaluation (n=2); withdrew or personal reasons (n=1); were unable to tolerate repeated venipunctures (n=1). Patients were not excluded on the basis of stage of disease or extent of prior therapy.

A complete response was defined as the disappearance of all lesions for at least 1 month. A partial response was defined as more than 50% disappearance of all lesions for at least 1 month. Stabilization was defined as less clearing of lesions than a partial response but no evidence of new lesions. Progressive disease was defined as the appearance of new skin lesions.

Adjunctive therapy was considered on an individual basis depending on the severity of the disease and

initial response to ECP. However, the authors then state that adjunctive therapies were not used for the initial 4 to 6 months of the ECP treatment period. The response to the agents used adjunctively was compared before and after ECP to determine additive or synergistic effects.

Eleven patients showed a partial or complete response to ECP. The disease stabilized in 4 patients and progressed in 5 patients. Ten of 14 patients with generalized patch/plaque stage disease responded. Neither of the 2 patients with tumour stage disease improved. One of the 3 patients with refractory exfoliative erythroderma responded.

The CTCL patients who responded did so usually within the first 6 months of therapy.

The authors did a t test to determine which variable was associated with outcome (response versus no response). The number of ECP sessions was the only variable that was significantly associated with outcome ( $p=0.03$ ). To determine whether this difference was associated with other variables, logistic regression was also performed. The authors stated that the number of ECP sessions was the variable that best predicted outcome ( $p<0.05$ ). No additional or separate beneficial effect of adjunctive chemotherapy ( $p>0.5$ ) or preceding electron beam therapy ( $p>0.1$ ) was found.

In combination with ECP, 10 of 20 patients were able to be maintained with minimal additional therapy: topical steroids alone ( $n=3$ ), PUVA alone ( $n=1$ ), nitrogen mustard alone ( $n=3$ ), topical steroids and nitrogen mustard ( $n=1$ ), topical steroids and methotrexate ( $n=1$ ), topical steroids combined with chlorambucil and prednisone (patient 19).

In 1996 Zic et al. (29) reported on 20 patients (16 had MF, 2 had SS, 1 had T cell anaplastic large cell lymphoma, and 1 had angiocentric T cell lymphoma) who received at least 6 months of ECP. All had progressive disease before initiating ECP and most were judged to have disease that was refractory to standard therapy.

Sezary cell counts were available in 19 patients. T cell subset evaluations on peripheral blood samples were performed and available for 11 of 20 patients. Ten patients had samples obtained after initiation ECP, and in 1 patient, the sample was obtained before ECP.

Adjunctive therapy was considered on an individual basis depending on the severity of the disease and initial response to ECP. These consisted of topical nitrogen mustard ( $n=9$ ), oral chlorambucil and prednisone ( $n=6$ ), methotrexate ( $n=6$ ), electron beam radiotherapy ( $n=4$ ), PUVA ( $n=7$ ), combination chemotherapy ( $n=4$ ), retinoids ( $n=2$ ), and topical or intralesional steroids ( $n=13$ ).

ECP was discontinued on an individual basis in patients demonstrating progressive disease or no benefit from the combined ECP treatments and adjunctive therapies.

Before ECP, 13 patients showed progression of disease after electron beam radiation therapy. Thirteen patients also showed progression after topical nitrogen mustard therapy before ECP.

Cutaneous T-cell lymphoma had transformed to a large cell lymphoma in 3 patients before ECP and in 2 patients at 43 and 25 months after ECP.

The mean period of follow-up for all living patients since initiating ECP was  $69.3 \pm 9.2$  months (range 54 to 85).

Ten patients responded and 10 patients showed either stabilization or progressive disease while receiving ECP. Of the responders, 5 showed a complete and 4 showed a partial response. Eleven patients were

alive at the time of manuscript writing (2 with progressive disease). Seven patients died of causes directly related to their lymphoma and 2 due to causes unrelated to their disease.

Of the 10 patients who responded, 7 were weaned from ECP. Two partial responders were not weaned due to new skin lesions that developed as the treatment intervals were increased to 8 weeks. One partial responder discontinued ECP for personal reasons and progressive disease developed about 3 years after her last treatment.

Of the 7 patients weaned from ECP, 2 patients relapsed 23 and 24 months after their last treatment. The median time to clearing for the 7 patients who did show a complete response was 11 months (range 5 to 14 months). The mean number of ECP treatments received by the complete responders was  $26 \pm 4$  treatments or  $13 \pm 2$  day cycles. The mean relapse free interval of all 7 patients weaned from ECP was  $44.7 \pm 21.1$  months (range 20 to 64 months). The mean relapse free interval of the 6 living patients weaned from ECP was  $48.8 \pm 19.8$  months (range 23 to 64 months). Remissions continued to be maintained in 4 patients receiving no ECP treatment.

Extracorporeal photophoresis was discontinued in 3 patients due to progressive disease. Six patients with refractory disease died during the time they continued to receive ECP.

The 5-year survival rate for all patients receiving ECP regardless of state was 75% (95% CI, 0.56 to 0.94). The median survival for the 5 patients with an advanced skin stage, tumour and erythrodermic was 54 months and 40 months respectively.

Limitations to the study by Zic et al. (29) included:

- Case series
- It is unknown if patients were consecutively enrolled.
- No controls
- Only 2 patients had SS
- 2 patients didn't have CTCL
- Most patients were judged to be refractory to standard therapy. The authors defined refractory as "progressive disease after receiving at least 2 standard therapies for CTCL". Is 2 therapies considered resistant? One patient's prior therapy consisted of only nitrogen mustard. Another patient's prior therapy consisted of only steroids. A third patient's prior therapy consisted of only herbs and vitamins.
- ECP was discontinued in 3 patients because of progressive disease. ECP was discontinued in another patient with only bone marrow involvement due to no response.
- Sezary cell count/T cell clonality not assessed/reported post treatment.
- Unknown how adjunctive therapy contributed to outcomes. Complete responders in the study were all concurrently on nitrogen mustard, steroids and PUVA.
- The authors attempted to identify predictors of response by using Fisher's exact test, not regression analysis.
- The authors stated that their results "indicate an assessment of early response after 6 to 8 cycles of ECP as having a sensitivity of 100% and a specificity of 90% for predicting long-term (greater than 4 years) outcome." It is unclear how this was calculated.

Wilson et al. (42) conducted a retrospective study to examine survival in patients with erythrodermic MF who received TSEB radiation plus combination ECP (ECP could be administered before TSEB, concurrently with TSEB, or after TSEB therapy) versus patients administered TSEB only. Forty-four patients received TSEB, of which 21 patients also received ECP treatment 2 days per month for a median of 6 months. Seventy-three percent of patients had received other therapies before TSEB, including 75 courses that failed to control the disease (n=15 systemic therapy, 16 biologicals, 44 topical therapies).

When patients received TSEB, 59% had hematologic involvement (B1), 30% were stage IVA (N3), and 13% were IVB (M1). Median follow-up was for 2 years (range 0.3-13.9 years) subsequent to TSEB and 3.7 years from diagnosis (range 0.8 to 16.8 years).

All patients responded to TSEB within 2 months of completion, with a cutaneous CR rate of 73%. For the 32 complete responders, the 3-year disease free survival was 63%; 49% for the 17 patients who received only TSEB compared with 81% for those 15 patients who received TSEB and ECP.

Cox regression analysis showed that ECP was associated with prolonged remission (disease free survival,  $p=0.024$  adjusting for B1 and stage). The 2-year progression free survival, cause free survival, and overall survival for the TSEB group were 36%, 69% and 63% respectively compared with 66%, 100% and 88% for the combination group. Cox regression also showed that ECP was associated with cause specific survival ( $p=0.048$ , adjusting for B1 and stage). Finally, multivariate Cox regression analysis failed to show a significant improvement ( $P = 0.14$ ) after adjustment for stage and B1.

For patients who progressed, a total of 49 subsequent courses of therapy were administered (n=20 chemotherapy, 10 biologicals, and 19 topical therapies).

Thirteen patients died from MF related causes and 8 died from other causes.

Acute and chronic toxicities were consistent with those previously reported. (42)

Limitations to the study by Wilson et al. (42) included:

- Retrospective multicentre study
- No specific, explicit detail as to if the patients had documented peripheral T cell clonality.
- Arguable if  $p=0.048$  (~ 0.05) is considered statistically significant.
- “future study needs to explore the most appropriate sequencing of ECP in combination with TSEB...”

### **Studies Including Patients Having Cutaneous T-Cell Lymphoma - Treatment Resistance Unclear, No Peripheral T Cell Clonality**

Duvic et al. (26) examined 47 patients with histologic proof of MF or SS who were treated with ECP regardless of the number and type of previous therapies. ECP was given for at least 6 months unless there was rapid progression of disease or adverse side effects. Patients who achieved a CR or PR continued to receive maintenance therapy every 1 to 2 months for 1 year or until relapse. Therapy was gradually tapered during the second year.

The method used by Duvic et al. differed from the standard ECP in that the authors used an accelerated protocol in which mononuclear cells were collected for 9 cycles instead of the usual 6 and acid citrate dextrase A instead of heparin was used for extracorporeal anticoagulation.

Complete response was defined as the disappearance of all erythema and scaling, completely normal skin,

no adenopathy, skin score of zero.

A partial response was defined as a 50% to 99% reduction in the skin score recorded at the onset of therapy. No lesions increased in size and no new lesions appeared.

Patients must have received at least 4 months of therapy (usually 8 ECP treatments) to be able to be assessed for response.

Thirteen patients did not receive 4 months of ECP and were not evaluated by the authors for response. No further details about these patients were provided by the authors.

Twenty-eight of the 34 patients (84%) whose responses were evaluated had erythroderma. Twenty patients (59%) had extracutaneous disease that “involved Sezary cells”.

Six patients (18%) had a CR and 11 (32%) had a PR. According to the authors, the overall response rate was 50%. The median time to response was 6 months, mean time was 10 months (range 29 days to 32 months). All responders had erythroderma except for 1 patient. Thirteen of the 17 responders and all of the nonresponders had previous therapy.

The authors reported that there was “no meaningful difference was found in the mean skin scores between the responders and nonresponders. After ECP, responders had a decrease of 75% in mean skin scores compared to nonresponders who had a mean increase of 21% in the skin score (no p values were reported).

The Kaplan Meier survival estimate at 3 years was 55.7% (95% CI 34.4 to 77.0%) and at 4 years was 47.7% (95% CI 24.2 to 71.2%).

Limitations to the study by Duvic et al. included:

- Unclear if concomitant therapy was administered.
- Different ECP procedure used.
- Patients not accounted for in the analysis.
- 13 patients were not evaluated.

Wollina et al. (43) conducted a prospective study of 14 patients with MF stage IIa/IIb treated with ECP twice a month for 6 months in combination with interferon  $\alpha$ . Patients with histologic proof of CTCL stage IIa or IIb and relapse or unresponsiveness to previous treatments were eligible.

After 6 months, there was a CR in 4 patients, a PR in 3 and stable disease in 7 of the 14 patients (overall response rate CR+PR=50%). In responders, the time to best response was  $4.3 \pm 1.4$  months.

The next 6 months, 9 patients were kept on combination therapy. Their final outcome after 12 months was CR in 1 patient, PR in 2 patients and stable disease in 6 patients. Another patient with CR was given low dose interferon – it is unclear which group this patient is from.

Two patients were in remission without any treatment. One patient was kept on ECP alone. One patient with stable disease dropped out 7 months after initiation and was treated with chemotherapy.

After 12 months, the total response rate was 46.2% (6/13 patients): 5/9 with stage IIa (55.6%) and 1/4 with stage IIb (25.0%).

The authors stated that “generally the treatment was well tolerated”. (43)

Limitations to the study by Wollina include:

- It is unknown if these were consecutive patients or how they were selected.
- Definition of controlled study. The authors stated that “Response criteria were applied and controlled by a second skin biopsy after 6 and 12 months of treatment...”
- Unclear reporting of data.
- “Long term studies are necessary to evaluate the final outcome after response”. (43)

Crovetti et al. (3) reported on a 5 year experience with ECP in 33 patients with CTCL. Six patients received ECP with interferon  $\alpha$ . Sterile solution methoxsalen was injected into the buffy coat bag. Survival was defined as the time between the beginning of ECP therapy and death for any cause.

Thirty patients completed at least 3 ECP cycles and were evaluable. A favourable clinical response was obtained in 80.9% (16/21) of MF patients (CR 33.3%, PR 47.6%) and in 66% (6/9) of SS patients (CR 33.3%, PR 33.3%).

Median survival of responders was 18 months (range 4-58 months).

Crovetti et al. reported that all patients tolerated ECP well without significant side effects.

Limitations to the study by Crovetti et al. included:

- Unknown if the patients were the total consecutive number within the study timeframe or how they were selected.
- Small sample size.
- Case series.

Gottlieb et al. (27) conducted a retrospective chart review for 41 patients who received ECP for treatment of CTCL. The majority of the patients had stage III/IV disease with the presence of circulating malignant T cells.

Ten of the patients included in the study by Gottlieb et al. were also included in the ECP study reported by Edelson et al. (9) in 1987.

Thirty one of the 41 patients were treated for 6 or more cycles. Ten patients were treated with less than 6 cycles due to rapidly progressing disease (n=6), death unrelated to CTCL (n=2), or withdrawal from treatment (n=1).

Twenty-eight of the 31 patients treated for 6 or more cycles received ECP monotherapy. Among the 28 patients, 7 (25%) had a complete remission, 13 (46%) had a partial remission defined as more than 50% clearing of skin disease, and 8 (29%) did not respond to treatment.

The median survival from initiation of therapy was 77 months and from the time of diagnosis exceeded 100 months.

According to the authors, the presence of Sezary cells in the peripheral blood was associated with a favourable response. “Twenty-four of the 28 patients had circulating Sezary cells at the start of treatment with ECP...these patients had a significantly better response to ECP than the 4 patients without circulating cells (p=0.003).” “The presence of circulating Sezary cells was the best predictor of a satisfactory clinical response to ECP.” The authors did not use appropriate statistics to arrive at that conclusion.

Limitations to the study by Gottlieb et al. were:

- Lack of standardization regarding the psoralen dose. “...if a patient failed to respond after 4 to 5 cycles of ECP, we occasionally measured plasma psoralen levels or empirically increased the dose.”
- Concomitant therapy. “If the patient showed no improvement or the disease had progressed at the end of 6 months, adjuvant treatment was usually added. Three of the 41 patients received adjuvant therapy at the time of their first treatment because their pretreatment assessments strongly suggested that they had particularly advanced disease defined by a markedly elevated leukocyte count,...and high numbers of circulating Sezary cells.” Therefore patients with advanced CTCL did not receive ECP monotherapy.
- Strange definitions of concomitant therapy. “Because local gamma radiation is not a systemic treatment, it was not considered an adjuvant treatment nor was treatment with topical corticosteroids.”
- ECP was discontinued if the patient’s disease progressed.
- Patients who did not respond were excluded from statistical analyses.
- Fisher’s exact test was used to determine the significance of the presence or absence of Sezary cells with respect to clinical response. Regression/multivariate/univariate analysis was not used.

## **Unpublished Cutaneous T-Cell Lymphoma Studies Submitted to US FDA**

Three studies (CTCL 1, 2 and 3) were submitted to the US FDA in order to obtain approval of UVADEX Sterile solution for the extracorporeal administration of methoxsalen with ECP. (44-49) CTCL 1 is the identical study as Edelson et al. (9) from 1987, but was reanalyzed to allow comparison of the results to CTCL 3. CTCL 2 is a 5 year post approval follow-up of patients to evaluate long-term safety. CTCL 3 is an open label, single arm study that examined the use extracorporeal administration of

methoxsalen during photopheresis (CTCL 1 and 2 used oral methoxsalen).

The following is a summary and critique of the 3 unpublished studies (Table 5). The US FDA also reviewed these trials and their comments and critiques are included as well. (44;46-49)

**Table 5: Characteristics of the Three Unpublished Studies Examined by the FDA**

	CTCL 1	CTCL 2	CTCL 3
New data?	No – Edelson et al. 1987	Yes	Yes
Administration	Oral	Oral	Extracorporeal
Study type	Open label, single arm		
Sample size	39	57	51
Patient type	Patch/plaque or extensive plaque or erythrodermic disease		
Treatment resistance?	Yes – few details as to <u>how</u> treatment resistant – comparability among patients		
Consecutive enrollment?	?	?	?
Concomitant therapy?	Systemic & topical steroids	No restriction	Only topical steroids permitted (soles of feet/palms of hands)
	Patients who developed skin tumours >1.5 cm in diameter received 1 or a combination of radiotherapy, surgical excision or cryotherapy		
Body surface area assessed the standard way?	Yes	No	Yes
Treatment schedule	2 consecutive days every 4-5 weeks. 3 types of accelerated treatment		2 consecutive days every 4-5 weeks. 1 type of accelerated treatment

### CTCL 1

- Same study as Edelson et al. 1987; single arm, open label study that assessed ECP using oral methoxsalen.
- To allow comparison of the results to CTCL 3, other analyses were conducted with patient subsets.
- It is unclear if there was consecutive enrollment of patients.
- Four patients who withdrew were excluded from subsequent data analyses.
- No details regarding extent of treatment resistance.
- Patients were included who had patch plaque, extensive plaque or erythrodermic disease.
- Systemic steroids allowed (and topical steroids).
- Patients who developed skin tumours >1.5 cm diameter received 1 or a combination of radiotherapy, surgical excision, or cryotherapy.
- Variable treatment; patients were treated on 2 consecutive days every 4-5 wks.
- If no response after 4 cycles, treatment accelerated to 2 consecutive days every other week.
  - If no response after 4 cycles, treatment on 2 consecutive days every week.
  - If no response after 4 cycles, treatment on 3 consecutive days every week for 3 cycles.

### CTCL 2

- Single arm study; N=57; oral methoxsalen.
- 5 year post approval follow-up of patients to evaluate long-term safety.
- Target was to enroll first 50 patients with CTCL treated with ECP after receiving market approval in the US.
- To allow comparison of these results to CTCL 3, other analyses were conducted with patient subsets.



- No specific inclusion/exclusion criteria.
- No concomitant medication restriction.
- No criteria for removal of a patient from therapy or exclusion of results from assessment were listed in the protocol.
- No formal statistical analyses.
- Treatment pattern same as CTCL 1.

### **CTCL 3**

- Open label, single arm study, 12 months duration
- Extracorporeal administration of methoxsalen.
- Eligible patients N=53. Target sample size calculated N=42. Following consultation and agreement with the FDA, a 25% lower binomial confidence limit was allowed to define a positive study outcome. The 25% target was derived from the assumption of a 10% spontaneous remission rate and a 15% treatment related improvement.
- Patients had patch plaque, extensive plaque or erythrodermic disease.
- The success of the trial was based on statistical inference.
- Only topical steroids permitted (only for treatment of fissures on soles of feet/palms of hands).
- Treatment = 1 ECP on 2 consecutive days every 4 to 5 weeks.
- Patients who developed skin tumours >1.5 cm in diameter received 1 or a combination of radiotherapy, surgical excision, or cryotherapy.
- Most common reason for terminating therapy: to receive oral methoxsalen or other therapies that were not allowed in the study.
- Patients who did not respond to therapy did not have follow-up photographs taken.
  - Not possible to confirm skin lesion scores/response.

## Analysis for Primary Endpoint

The primary endpoint for CTCL 1, 2 and 3 was the ITT analysis for a 25% reduction in skin score maintained for 4 consecutive weeks within 6 months of treatment. According to the protocol for CTCL 3, if the lower 95% CI > 25%, treatment considered effective. As indicated in the Table 6, the lower 95% CI for the response rate within 6 months (using an ITT analysis) means that ECP did not significantly reduce skin scores. Similarly, ECP did not reduce skin scores anytime during treatment (using ITT analysis).

**Table 6: Intent to Treat Analysis for 25% Reduction in Skin Score Maintained for Four Consecutive Weeks (successful response) Within Six Months of Treatment**

Study (Unpublished)	Response rate <u>within 6 months</u> (ITT)	Lower 95% binomial confidence interval	Response rate <u>at anytime</u> during treatment (ITT)	Lower 95% binomial confidence interval	Median survival from date of diagnosis (months)
<b>CTCL 1 (oral)</b>	<b>21/39 (54%)</b>	<b>37%</b>	<b>29/39 (74%)</b>	<b>58%</b>	<b>127</b>
Time until start of response (median)	103 d		126 d		
Duration of response (median)	419 d		365 d		
<b>CTCL 2 (oral)</b>	<b>16/57 (28%)</b>	<b>17%</b>	<b>25/57 (44%)</b>	<b>31%</b>	<b>-</b>
Time until start of response (median)	71 d		153 d		
Duration of response (median)	104 d		152 d		
<b>CTCL 3 (extracorporeal)</b>	<b>17/51 (33%)</b>	<b>21%*</b>	<b>19/51 (37%)</b>	<b>24%*</b>	<b>125</b>
Time until start of response (median)	84 d		86 d		
Duration of response (median)	140 d		169 d		

\* For CTCL 3, if lower 95% CI > 25% treatment considered effective.

## **Summary and Conclusions from the Food and Drug Administration Statistical Review and Evaluation of CTCL 3**

- Uncontrolled and small sample size.
- No formal statistical testing could be conducted.
- Claims of effectiveness should be viewed cautiously.

## **Cutaneous T Cell Lymphoma Trials Underway or Unpublished**

The ClinicalTrials.org website listed the following trials related to CTCL in progress. (50)

### **Origin and Course of Cutaneous T Cell Lymphoma. NCT00075322**

Study Design: Observational, natural history. N=100. Sponsored by National Cancer Institute.

### **Stem Cell Transplant Therapy with Campath 1H for Treating Advanced Mycosis Fungoides and Sezary Syndrome. NCT00042640**

Study design: Interventional, treatment, safety. N=58. Sponsored by National Heart, Lung and Blood Institute.

### **Photopheresis as an international therapy for the treatment of CTCL (mycosis fungoides) Stage 1A, 1B, 2A. NCT00221039**

Study design: nonrandomized, open label, historical control, single group assignment. N=50

Duration of treatment: 2 treatment periods, a 6 month initial period and a 6 month follow-up period where ECP therapy may continue. Sponsored by a manufacturer.

## **Summary of cGvHD Findings: International Health Technology Assessments**

### **Blue Cross Blue Shield Technology Evaluation Centre, November 2001**

The objectives of the Blue Cross Blue Shield (BCBS) assessment were to review the available evidence on outcomes of ECP in patients with GvHD including:

- Previously untreated patients or those responding to established therapies; or
- Patients who are refractory to established therapy.

Based on the evidence, BCBS made the following judgments about whether ECP meets the BCBS Technology Evaluation Center criteria as treatment for GvHD.(51)

1. *The technology must have final approval from the appropriate governmental regulatory bodies.*
  - The UVAR photopheresis system (Therakos, Inc.) is indicated for palliative treatment of skin manifestations from CTCL in persons who have not been responsive to other therapy. The UVAR system is the only ECP device with premarket application approval for the FDA. No device has FDA approval for treatment of GvHD. Therefore, use of the UVAR ECP system for GvHD is an off label use of an FDA approved device.
  - Use of UVADEX for GvHD is an off label use of a FDA approved drug. (51)

2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.*
  - No studies were identified that met selection criteria and reported results of ECP alone or in combination with other therapies for acute or chronic GvHD in previously untreated patients or in those responding to conventional therapy. Therefore, no conclusions are possible on the effects of this therapy on health outcomes in previously untreated or responsive patients.
  - 6 studies reported outcomes for 112 patients with extensive chronic GvHD that was refractory to 1 or more lines of therapy with steroids and other immunosuppressive drugs. These reports provided sufficient evidence to permit conclusions on the health outcomes of ECP for treatment of refractory extensive chronic GvHD. No studies reported on patients with limited chronic GvHD.
  - 3 studies reported outcomes for 58 patient with acute GvHD that was refractory to standard treatment with steroids and other immunosuppressive drugs. Patients with Grade IV disease were generally unresponsive to ECP. A single study (n=21) reported responses in a majority of patients with Grade III disease. This evidence is insufficient to permit conclusions on the outcomes of ECP for treatment refractory acute GvHD. (51)
  
3. *The technology must improve the net health outcome and be as beneficial as any established alternatives.*
  - Evidence is insufficient to determine whether ECP alone or in combination with other therapies improves the net health outcome or is as beneficial as any established alternatives for patients with acute or chronic GvHD that is previously untreated or responding to standard drug therapy.
  - Evidence is insufficient to determine whether ECP improves net health outcome or is beneficial as any alternative for patients with treatment refractory acute GvHD or limited chronic GvHD.
  - 2 studies reported complete resolution of all skin, mouth and liver lesions and discontinuation of immunosuppressive drug treatment for 13/25 patients with extensive cGvHD refractory to steroids and other immunosuppressive drugs.
  - 3 additional studies (n=69) reported marked symptomatic improvements in most patients (50% to >90%) but did not report full resolution of lesions in any.
  - Another study (n=18) showed that lesions improved for half of those with de novo onset but only one fourth of those with prior acute GvHD.
  - Adverse effects were consistently infrequent, mild and transient in studies that added a sterile solution of methoxsalen directly to cell suspensions after leukapheresis and avoided use of orally administered drug.
  - BCBS concluded that ECP improves the net health outcome for patient with cGvHD that is refractory to standard immunosuppressive drug therapy (no alternative available). (51)
  
4. *The improvement must be attainable outside the investigational settings.*
  - BCBS stated that the improvements in net health outcomes reported by studies of ECP for treatment refractory extensive chronic GvHD are achievable outside the investigational setting at centres with experience using the FDA approved device to treat patients with refractory GvHD and providing supportive care and symptom management to these patients. (51)

*Overall, BCBS concluded that:*

- ECP meets the TEC criteria as therapy for cGvHD that is refractory to established therapy. (51)
- ECP does not meet TEC criteria as therapy for acute GvHD or cGvHD that is either previously untreated or is responding to established therapies. (51)

A detailed discussion of the methodological limitations of the studies examining cGvHD was not reported. How ECP met the TEC criteria as therapy for cGvHD that is refractory to established therapy

despite not having final approval from the appropriate governmental regulatory bodies (off label use) was not discussed.

## Catalan Agency for Health Technology Assessment and Research, July 2001

The following is a summary of the Catalan report. (16)

Similar to the FDA in the United States, ECP is approved by the Spanish Ministry of Health and Consumption for the treatment of SS, but not for GvHD. (16)

- From 1994, the first studies of ECP in GvHD make particular reference to the effect of ECP in the cutaneous manifestations of the disease. (16)
- Since then, 5 studies (all small sample size case series) have been identified and assessed the benefit of ECP for the treatment of acute and cGvHD. (16)
- Overall, ECP mainly improved cutaneous and mucous manifestations (from 48% to 80% in the chronic form). (16)
- An improvement was also noted in hepatic manifestations, albeit at a lower proportion. (16)
- As far as other relevant result measurements are concerned, such as mortality and survival, assessment has been “scant, very variable and it is difficult to make comparisons between studies”. (16)

Table 7 summarizes the Catalan report.

**Table 7: Results of Extracorporeal Photopheresis in the Treatment of cGvHD**

Study (year)	Patients (N)	Complete Remission of Manifestations		Mortality (%)	Survival (%)
		Cutaneous (%)	Hepatic (%)		
Smith 1997	18	60	15.4	61.1	39 <sup>a</sup>
Greinix 1998	15	80	70	-	98 <sup>b</sup>
Child 1999	11	48 <sup>c</sup>	16	-	-
Zic 1999	9	55	50	33	-

<sup>a</sup> Survival 4 years after the beginning of treatment with ECP

<sup>b</sup> Survival 15 months after treatment

<sup>c</sup> According to a scale developed by the authors of the study

*From: Almazan C, Espallargues M, Catalan Agency for Health Technology Assessment and Research. Extracorporeal phototherapy (photopheresis) for the treatment of Sezary syndrome and graft versus host disease. 2001. Available from: [www.aatm.es](http://www.aatm.es)*

## Updated Summary of Findings – cGvHD

A tabulated summary of the studies published since the Blue Cross Blue Shield assessment is presented in Appendix 2.

Couriel et al. (52) through a retrospective chart review evaluated 71 patients with severe chronic cGvHD

treated with ECP. Patients had received an allogeneic transplant for hematologic malignancies (n=67) benign hematologic disorders (n=3) and breast cancer (n=1). The main endpoints of the study were response to therapy, nonrelapse mortality and overall survival.

At the time of initiation of ECP, all patients were steroid refractory. cGvHD was considered refractory if: a) patients had stable disease (no response NR) after 1 month of treatment, b) no more than a partial response (PR) occurred after 2 months of treatment, or c) progressive disease occurred after 2 weeks of initiation of steroid treatment or during the tapering of corticosteroids.

CR was defined as resolution of all manifestations of cGvHD. PR was defined as at least a 50% improvement of clinical manifestations without a CR. No response was no change in cGvHD. Patients who experienced early deaths due to cGvHD prior to assessment of response were considered NR. Progressive disease (PD) was any worsening while on treatment or steroid taper.

Timing of response was analyzed as best response of at least 2 weeks duration, occurring within 3 months after initiation of therapy and response at 6 months following initiation of therapy.

At the time of initiation of ECP, 59/71 (83%) patients were still on steroids. Six patients (8%) achieved an initial CR or PR prior to initiation of ECP. Thirty-one patients (44%) received more than 2 lines of immunosuppression including steroids and tacrolimus prior to ECP.

Patients received a median of 32 ECP procedures (1-259 procedures) over a median of 14.5 weeks (1-333 weeks). Chronic cutaneous GvHD was the leading indication for ECP (n=56, 79%), followed by liver (n=21, 30), pulmonary (n=11, 15%), oral (n=9, 13%), ocular (n=6, 8%), and GI (n=3, 4%) GvHD.

The overall response rate was 61% (n=43) and 14 patients had complete responses. The cumulative incidence of CR/PR at 1 year since initiation of ECP was 83% (standard error 9). A total of 33 patients (59%) with skin GvHD responded to ECP. Responses were also seen in liver (n=15, 71%), oral mucosa (n=7, 77%), eye (n=4, 67%), pulmonary (n=6, 54%), and GI (n=2, 66%).

A total of 42 patients (59%) died, with a median follow-up of 34 months (4-66 months) among survivors. At 5 years after initiation of ECP, the overall survival was 19% (2-49%) and the cumulative incidence of nonrelapse mortality was 46% (standard error 7).

Limitations to the study by Couriel et al. included:

- Retrospective chart review.
- Small sample size.
- The authors stated “our results warrant further evaluation of ECP in prospective, controlled clinical trials to document its effect on response, survival, immune function, infections and relapse of the underlying disease.” (52)

Foss et al. (53) enrolled 25 patients with extensive steroid refractory cGvHD in a prospective trial to evaluate the efficacy of ECP in both skin and visceral cGvHD. Two patients were under the age of 18 years. Patients were selected based on a body weight of at least 40kg, ability to tolerate the ECP procedure, and the presence of refractory cGvHD after treatment with steroids, cyclosporin A, tacrolimus and/or MMF. All patients had been steroid refractory or steroid intolerant prior to the institution of other immunosuppressive agents. At the time of the study entry, patients had ongoing refractory skin and /or visceral cGvHD.

Extracorporeal photopheresis was performed on an outpatient basis and was administered using current techniques; i.e., methoxsalen injected directly into the recirculation bag of the ECP circuit. The median

time from transplant to initiation of ECP was 790 days. Extracorporeal photopheresis was administered for 2 consecutive days every 2 weeks in 17 patients and once a week in 8 patients until the best response or stable disease was observed. The median duration of therapy was 9 months (range 3-24 months).

The overall response rate was (response in at least one site of disease) was 64%. Overall, 20 patients had improvement in cutaneous GvHD and 6 had healing of oral ulcerations.

In all, 15 patients developed serious adverse events during therapy. However, the individual complications listed by the authors, do not sum to 15 patients.

- 5 - pneumonia
- 2 - complications related to indwelling venous catheter
- 1 - Cytomegalovirus associated colitis
- 1 - gastrointestinal bleeding associated with gastrointestinal GVHD
- 1 - urosepsis with subsequent renal failure from Tobramycin therapy
- 1 - recurrence of acute myelogenous leukemia

The median survival of the study group was 51 months from day 0 of allogeneic transplantation. Of the 10 patients who died, the median number of cycles of ECP that they received was 5 whereas in the survivors it was 12. The median survival for responders versus nonresponders was 55 versus 39 months ( $p=0.3$ ).

Although the protocol did not stipulate a precise algorithm for decreasing or stopping immunosuppression, corticosteroids were tapered first. In all, 11 patients had a decrease in corticosteroid dose while on ECP, 12 had a reduction or discontinuation of MMF and 5 reduction or discontinuation of tacrolimus. Four patients who had stable disease (no documented change in skin or visceral manifestations) had reduction in immunosuppressive medications during ECP without evidence of disease flare.

Response rates were similar between patients receiving treatment weekly versus every 2 weeks and in patients commencing ECP less than versus greater than 18 months from transplant (70% versus 66%).

According to Foss et al. (53), currently there is a multinational randomized trial underway which will examine ECP in patients with cGvHD.

Seaton et al. (54) examined 28 adult patients with cGvHD who failed conventional immunosuppressive therapy. ECP treatment was only considered if the following criteria were met:

- Histologically established cGvHD
- Adequate hemodynamic and cardiac function
- Body weight more than 40 kg
- Hemoglobin count higher than 90 g/l
- Platelet count higher than  $20 \times 10^9/L$
- Neutrophil count higher than  $1 \times 10^9/L$

Extracorporeal photopheresis was initiated approximately 2 years after onset of cGvHD and 3 years following allogeneic stem cell transplantation. Patients received treatment on 2 consecutive days, every 2 weeks for the first 4 months and then monthly. At 6 months a decision was made whether to continue treatment depending upon the clinical response, the inconvenience of traveling long distances and the patients' own preferences. Whenever possible, changes in systemic immunosuppressive medication during treatment were avoided. Response was assessed using quantifiable disease measures, including skin score, liver function tests, blood counts and lung function tests.

Twenty-seven patients had extensive cGvHD and a single patient had limited cGvHD.

Of the patients, 25 completed 3 months of treatment, 21 completed 6 months of treatment and 6 completed 12 months of treatment. Median duration of treatment was 6 months (range 1-58 months).

Systemic immunosuppression was stable or reduced in 86% of patients.

After 6 months, median skin scores were 53% lower ( $p=0.003$ ) in sclerodermoid and lichenoid disease. Of 6 patients with mucosal ulceration, 3 improved. There was no statistically significant improvement of liver function tests.

Regression analysis showed that no baseline parameters predicted a favourable response to ECP.

#### Adverse Events

Five patients developed serious complications, including 4 who died. After 0.5, 3, and 20 months of treatment, 3 patients died from advanced cGvHD – these deaths were not clearly treatment related. One patient died from renal failure and sepsis after 4 months of treatment having developed acute invasive pulmonary aspergillosis. Another patient completed 1 cycle of ECP having developed acute dyspnea and hypoxia several hours after the first treatment and developed acute respiratory distress syndrome and required transfer to intensive care unit. Investigators failed to identify an infective cause and the patient recovered fully.

Extracorporeal photopheresis was discontinued in 2 patients who had become unwell between treatments: one had pulmonary cGvHD and developed pneumothorax with pleural effusions after 3 cycles of treatment; another developed symptomatic exercise induced ischemic heart disease.

Having improved and stabilized, 4 patients discontinued treatment after lengthy courses. Of the remaining patients, the reasons for discontinued treatment were as follows:

- Deterioration of cGvHD (n=2)
- Poor response to treatment (n=2)
- Severe difficulties with venous access (n=1)
- Inconvenience of treatment schedules (n=2)
- External funding difficulties (n=1)
- Lung transplantation (n=1)

At the time of manuscript writing, 8 patients were continuing to receive treatment.

During ECP treatment, systemic immunosuppression was stable in 15 patients reduced in 9 patients, and increased in 4 patients.

Limitations to the study by Seaton et al. (54) included:

- small sample size

Messina et al. (55) examined 44 children with cGvHD resistant to conventional immunosuppressive therapy who were treated with ECP in 4 Italian hospitals. Inclusion criteria consisted of:

- Confirmed diagnosis of either steroid resistant cGvHD failing to respond to at least 2 lines of treatment (specifically steroid resistance was defined as lack of stable clinical improvement after treatment with prednisolone)
- Complete hematological remission and full donor chimerism
- White blood cell count  $>1 \times 10^9/L$



- Body weight greater than 10 kg
- No concomitant treatment with either ATG or monoclonal antibodies causing lymphocyte lysis.
- All patients enrolled for ECP after day 100 of GvHD.

Forty four patients had cGvHD which was extensive in 38 patients and limited in 6 patients. Progressive cGvHD evolved directly from active aGvHD in 26 patients whereas the quiescent form of the disease was diagnosed in 13 children. The median Lansky/Karnofsky play performance score at the start of treatment was 60% (range 30%-90%) (a play performance scale records usual play activity as the index of performance in pediatric cancer patients). The median age of the patients at the time of ECP was 8.2 years (0.3-20.5 years). The median interval from diagnosis of cGvHD to time of ECP was 8.9 months (0.4-109 months) and the median interval from BMT to ECP was 1.5 years (0.3-9.2 years).

Patients were treated with ECP on 2 consecutive days at 1 week intervals for the first month ever 2 weeks during the second and third month and then at monthly intervals for at least 3 further months.

Progressive tapering and discontinuation of ECP was decided upon evaluation of individual response. Any concomitant immunosuppressive therapy was initially maintained, then modified or discontinued according to the clinical response.

Complete organ response was defined as complete regression of skin, liver, gastrointestinal, lung oral, joint or eye manifestations. Patients with greater than 50% response in terms of organ involvement were considered as partial responders, irrespective of their original overall clinical stage. An evaluated response of less than 50% in organ involvement was judged as stable disease irrespective of any changes in immunosuppressive therapy; worsening of organ involvement as well as onset of new GvHD related signs or symptoms was defined as progressive disease. Patients with either stable or progressive disease were considered nonresponders.

Clinical evaluation of the patients was registered at baseline, after 1, 2, 3, and 6 months and when ECP was discontinued.

## Results

The median duration of treatment was 74 days (range 8-467 days) for a median number of 8 cycles (range 2-20 cycles). Out of 44 patients, 34 (77%) survived and 59% experienced a significant improvement after ECP. The median improvement in the extent of skin surface involved (ESS) and skin severity score (SSS) was 26% and 8 points respectively.<sup>1</sup> At the end of ECP treatment, 15 (44%) and 10 (29%) of the 34 surviving patients had a complete and partial response respectively.

As a result of treatment, it was possible to discontinue immunosuppressive therapy in 15 (44%) patients and to reduce it in 10 (29%) of these patients respectively.

The median Lansky/Karnofsky score improved from 60% to 90% (range 60-100%).

The 5-year overall survival was significantly better ( $p=0.04$ ) in patients responding to ECP than in nonresponders, namely 96% (95% CI 89-100) versus 58% (95% CI 34-82). A clinical response was more frequently (64%) observed in patients who started ECP earlier (before the median time of 8.9 months)

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<sup>1</sup> ESS was recorded on a body diagram used to calculate surface burns in children, with scores ranging from 0% to 100%. ESS of 0-33%, 34-66%, or 67-100% were considered as having mild, moderate or severe skin involvement respectively. SSS was rated from 0 to 45, obtained by measuring skin thickness in 15 areas, using a scale from 0 to 3. A rating of 0 was attributed to normal skin, and 3 in case of severe thickening; intermediate skin involvement was rated as 1 or 2.

after cGvHD diagnosis. Age, sex, diagnosis, type of donor and source of stem cells did not influence the outcome in univariate analysis.

Ten patients died while being treated with ECP: 6 of GvHD, 2 of CMV pneumonia and 2 of gram negative sepsis.

Side effects observed during ECP were generally mild, but were more frequent in children with low body weight.

Limitations to the study by Messina et al. included:

- Variable treatment schedule and duration of ECP.
- Retrospective study.
- "...the role of ECP in the treatment of GvHD needs to be confirmed by larger prospective randomized studies." (55)

Rubegni et al. (56) evaluated ECP in 32 patients with steroid refractory cGvHD. It is reported unclearly whether the study was retrospective or prospective. Extracorporeal photopheresis was administered using the current technique; i.e., methoxsalen injected directly into the recirculation bag of the ECP circuit. The patients underwent a total of 1,128 cycles of ECP with minor side effects reported (e.g., slight hypotension, hematomas at venepuncture sites), none of which required interruption of treatment.

For the overall outcome, the contribution of ECP was considered:

“Determinant” when CR was observed in all organs involved after the start of ECP and when the dose of immunosuppressants could be reduced by at least 50% with respect to initial therapy.

“Ineffective” when progression was observed in one of the organs involved when it was necessary to increase the dose of immunosuppressants or when CR was not observed in any organ and immunosuppressants were not reduced by more than 50%

“Good” in all other cases.

Extracorporeal photopheresis was “determinant” in 22% of cases, “good” in 56% and “ineffective” in 22% of patients. (56)

Limitations to the study by Rubegni et al. (56) included:

- Small sample size
- Unknown how patients were selected

Apisarnthanarax et al. (57) retrospectively analyzed all allogeneic stem cell transplantation patients who received ECP for the management of steroid dependent or steroid refractory cutaneous cGvHD during a 36 month period. Patients who were steroid refractory or steroid resistant who were treated by ECP after day 100 and who received at least 4 weeks of ECP were considered evaluable for the study.

Out of 64 transplant patients, 32 patients met the inclusion criteria. All 32 patients had been previously treated with systemic corticosteroids with 11(34%) being steroid resistant and 21 (66%) steroid dependent. The evaluated patients had received a median of 3 prior therapies before ECP.

Patients received a median of 36 ECP sessions (range 12-98) over a median of 5.3 months (range 1-28) with a median of 6 sessions per month.

The CR rate was 22% (n=7) and the PR rate was 34% (n=11). Twenty-eight patients were on systemic corticosteroid therapy at the start of ECP and 18 patients achieved a 50% dose reduction while on ECP, yielding a 64% steroid sparing response rate.

At the time of manuscript writing, a total of 11 (34%) patients died after ECP with all cases due to visceral cGvHD or cGvHD related infectious complications. All 21 surviving patients remained on at least some immunosuppressive cGvHD therapy (including ECP in 8 patients).

Limitations to the study by Apisarnthanarax et al. (57) included:

- Retrospective study design.
- Multiple concomitant therapies
- “Every effort should be made to carry out further study of ECP in a prospective randomized trial setting.”

## **cGvHD Trials Underway or Unpublished**

The ClinicalTrials.org website listed the following trials related to cGvHD in progress. (50)

### **Safety and efficacy study of photopheresis plus standard therapy to treat cGvHD. NCT00054613**

Study design: randomized, single blind, active control, parallel assignment. N=72

Duration of treatment: not stated. Sponsored by a manufacturer. This RCT completed recruiting patients

### **ECP in patients with extensive cGvHD refractor or intolerant to standard therapy. NCT00248365**

Study design: randomized, open label dose comparison, parallel assignment. N=20. Sponsored by a manufacturer.

### **Extracorporeal photopheresis to treat cGvHD. NCT00048789**

Study design: not stated. N=25. Sponsored by a manufacturer.

## **GRADE Quality of the Evidence**

According to the GRADE Working Group criteria, the quality of the trials was examined. (15)

Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up. (15)

Consistency refers to the similarity of estimates of effect across studies. (15) If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect and the significance of the differences guide the decision about whether important inconsistency exists. (15)

Directness refers to the extent to which the people interventions and outcome measures are similar to those of interest. (15) For example, there may be uncertainty about the directness of the evidence if the people of interest are older, sicker or have more comorbidity than those in the studies. (15)

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence. (15)

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

## **Cutaneous T Cell Lymphoma**

- Overall, there is low quality evidence that ECP improves patient response rates and survival (Table 8).
- The reported CR range is ~ 16% to 23% and the overall reported CR/PR range is ~ 33% to 80%.

- The wide range in reported responses to ECP appears to be due not only to the variability of the patient treated but also to the way in which the data were presented and analyzed.
- Many patients in mostly retrospective case series were concurrently on other therapies and were not assessed for comparability of diagnosis, disease stage (MF versus SS; erythrodermic versus not erythrodermic) and other prognostic factors. Blood involvement in patients receiving ECP (e.g., T cell clonality) was not consistently reported, especially in earlier studies. The definitions of partial and complete response also are not standardized.
- The Catalan assessment did not attempt to stratify patients according to type of CTCL, peripheral T cell clone requirement upon study entry, or type of concomitant therapy. As a result, the Medical Advisory Secretariat also reexamined the studies that were included in the Catalan assessment.
- Quality of life was reported in one study by Bisaccia et al. (58) However, the scale was developed by the authors and is not a standard validated scale.
- Adverse events associated with ECP appear to be uncommon and most involve catheter related infections and hypotension caused by volume depletion.

**Table 8: GRADE Quality of Studies – Extracorporeal Photophoresis for Erythrodermal CTCL**

Outcome	Design	Quality	Consistency	Directness	Overall Quality
<b>Response rates</b>	1 small crossover RCT	Unbalanced arms Unclear biometry Not blinded No details regarding interim analysis. Results based on 8 patients	Worsening of skin scores	Uncertainty regarding diagnostic and outcome criteria	Low
	Case series	Treatment heterogeneity Disease stage/acuity variation Concomitant treatment No blinded assessment	Wide range of responses		
<b>Survival</b>	Retrospective case series	Same as above	Wide range of survival results	Same as above	Low

### Chronic Graft-Versus-Host Disease

- Overall, there is low quality evidence that ECP improves patient response rates and survival (Table 9).
- Patients in the studies had stem cell transplants due to a variety of hematological disorders (e.g., leukemias, aplastic anemia, thalassemia major, Hodgkin’s lymphoma, non Hodgkin’s lymphoma).
- In 2001, The Blue Cross Blue Shield Technology Evaluation Centre concluded that ECP meets the TEC criteria as treatment of cGvHD that is refractory to established therapy. (51)
- The Catalan assessment (also published in 2001) concluded that ECP is a new but experimental therapeutic alternative for the treatment of the erythrodermal phase of CTCL and cGvHD in allogenic HPTC and that this therapy should be evaluated in the framework of a RCT. (16)
- Quality of life (Lansky/Karnofsky play performance score) was reported in 1 study. (55)
- The patients in the studies were all refractory to steroids and other immunosuppressive agents, and these drugs were frequently continued concomitantly with ECP.
- Criteria for assessment of organ improvement in cGvHD are variable, but PR was typically defined as >50% improvement from baseline parameters and CR as complete resolution of organ involvement.
- Follow-up was variable and incomplete among the studies.

**Table 9: GRADE Quality of Studies – Extracorporeal Photophoresis for cGvHD**

Outcome	Design	Quality	Consistency	Directness	Overall Quality
<b>Response rates</b>	Case series	Treatment heterogeneity Concomitant treatment No blinded assessment Lack of consistent scoring Different lengths of follow-up Quality of life reported in 1 pediatric case series	Wide range of responses (~50-90%)	Uncertainty regarding diagnostic and outcome criteria	Low
<b>Survival</b>	Case series	Same as above	Wide range of survival results (~39%-98%)	Same as above	Low

## Economic Analysis

### Literature Review

No economic analysis of ECP treatment for CTCL or cGvHD was identified in the literature.

### Ontario Context

Out-of-country funding for ECP has been approved for patients with CTCL. (Since the Ministry of Health and Long-Term Care does not direct patient care, decisions relating to patient treatment, including location, are determined by the patient's physician.)

In 2004/05, the ministry approved 8 applications for 7 distinct patients for Ontario Health Insurance Plan-funded ECP treatment in the United States. The average amount paid per patient was \$US 136,061.

The annual budget impact for CTCL patients is shown in Table 10.

- Annual Budget Impact: \$1.5 M Cdn based on 30 patients
- Current Expenditure: \$1.3M Cdn (out of country for 7 patients)
- Potential cost savings based on 30 patients: \$3.8 M Cdn (annual)
- The annual budget impact for CTCL and cGvHD patients would be \$3M Cdn based on 60 patients.

**Table 10: Annual Budget Impact for CTCL Patients**

<b>Treatment Costs</b>	<b>Canadian Dollars</b>
Procedural Kit	\$1,200
Instrument Operator	\$144
Cost of Methoxsalen	\$63
Cost of saline & supplies	\$121
Total (per treatment)	\$1,528
OHIP	
Estimated OHIP costs (12 to 30 treatments)	\$1,074 to \$2,433
Fixed Costs	
Cost of Machine (10 year lifetime)	\$80,000
Light Assembly	\$2,000
Training/Assembly	\$8,000
Service Agreements	\$26,000
Total Fixed costs	\$116,000
Annual Fixed costs	\$11,600
Total annual cost per patient (low end estimate. Excludes setup and administrative costs)	<b>\$20,000 to \$40,000</b>

## **Existing Guidelines Regarding the Utilization of the Technology**

Very few guidelines exist regarding the management of MF or SS.

### **Australian Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma, Draft Document August 2005**

The Australian Clinical Practice Guidelines (6) state that:

“In general terms, the treatment of SS is similar to that of advanced stage MF.”

“The first trial reported that 83% of patients with erythroderma responded to ECP. Further large phase II studies have reported the therapeutic benefit of ECP in CTCL, though the response data have been variable, ranging from 30% to 80% depending on the study entry criteria, patient selection, and intervals between diagnosis and treatment.”

As ECP has been used in CTCL patients refractory to all other therapies, no phase III (RCT) trials have been performed.” (6)

### **British Photodermatology Group and UK Skin Lymphoma Group 2006**

The British Photodermatology Group and the United Kingdom Skin Lymphoma Group (59) reported the following:

#### **Strength of Recommendations**

- A Good evidence to support the use of the procedure.
- B Fair evidence to support the use of the procedure.
- C Poor evidence to support the use of the procedure.
- D Fair evidence to support the rejection of the use of the procedure.
- E Good evidence to support the rejection of the use of the procedure.

#### **Type of Evidence**

- I Evidence from at least 1 properly designed RCT.
- II Evidence from well designed controlled trials without randomization.
- III Evidence from well designed cohort or case control analytic studies preferably from more than one centre or research group.
- IIII Evidence from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III Options of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
- IV Evidence inadequate to problems of methodology (e.g., sample size or length or comprehensiveness of follow-up or conflicts of evidence).



The evidence for the efficacy of ECP was appraised by a combine British Photodermatology Group and UK Skin Lymphoma Group workshop on the basis of evidence published up to the end of 2001 and on the consensus of best practice. (59)

### **Extracorporeal Photophoresis for CTCL**

“There is good evidence to support the rejection of the use of ECP for the treatment of nonerythrodermic MF and fair evidence to support the use of ECP for erythrodermic MF/SS.” (59)

*CTCL nonerythrodermic (stage IA-IIB): Strength of recommendation E, Quality of evidence I*

*CTCL erythrodermic (stage III/IVA/B1/0): Strength of recommendation B, Quality of evidence II-i*

### **Extracorporeal Photophoresis and Interferon**

There is fair evidence to support the rejection of the use of IFN- $\alpha$  with ECP for nonerythrodermic disease. There is poor evidence to support the use of the latter for erythrodermic disease. Randomized studies are needed. (59)

*CTCL nonerythrodermic: Strength of recommendation D, Quality of evidence II-ii*

*CTCL erythrodermic: Strength of recommendation C, Quality of evidence II-ii*

### **Extracorporeal Photophoresis and Total Skin Electron Beam Therapy**

There is fair evidence to support the use of TSEB with ECP for erythrodermic MF/SS. (59)

*Strength of recommendation B, Quality of evidence II-ii*

### **Extracorporeal Photophoresis for cGvHD**

There is fair evidence to support the use of ECP in cGvHD with cutaneous or mucosal involvement, but the evidence in hepatic disease is poor. There is fair evidence to support the rejection of the use of ECP for gastrointestinal or pulmonary cGvHD. (59)

*cGvHD cutaneous/mucous membranes: Strength of recommendation B, Quality of evidence II-ii*

*cGvHD hepatic: Strength of recommendation C, Quality of evidence II-iii*

*cGvHD gastrointestinal/pulmonary: Strength of recommendation D, Quality of evidence II-ii*

## **Conclusion**

1. Overall, there is low quality evidence that ECP is effective for the treatment of refractory erythrodermic CTCL (Table 8). The wide range in reported responses to ECP appears to be due to the variability of the patients treated (e.g., past/concurrent therapy, disease severity and duration, refractory or not refractory to alternate forms of therapy, peripheral T cell clonality), and to the way in which the data were reported and analyzed (e.g., exclusion of patients, lack of intent-to-treat analyses).

Limitations in the literature related to ECP for the treatment of refractory erythrodermic CTCL are:

- Different treatment regimens.
- Variety of forms of CTCL (and not necessarily treatment resistant) – MF, erythrodermic MF, SS.

- SS with peripheral blood involvement → role of T cell clonality reporting?
- Case series (1 small crossover RCT with several limitations)
- Small sample sizes.
- Retrospective.
- Response criteria not clearly defined/consistent.
- Unclear how concomitant therapy contributed to responses.
- Variation in definitions of concomitant therapy
- Comparison to historical controls.
- Some patients were excluded from analysis because of progression of disease, toxicity and other reasons.
- Unclear/strange statistics
- Quality of life not reported as an outcome of interest.

Overall, there is low quality evidence that ECP is effective for the treatment of refractory cGvHD (Table 9). The patients in the studies were all refractory to steroids and other immunosuppressive agents, and these drugs were frequently continued concomitantly with ECP. Criteria for assessment of organ improvement in cGvHD are variable, but PR was typically defined as >50% improvement from baseline parameters and CR as complete resolution of organ involvement. Followup was variable and incomplete among the studies.

2. As per the GRADE Working Group, overall recommendations consider 4 main factors. (15)
  - The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates and the relative value placed on the outcome.
  - The quality of the evidence.
  - Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects such as proximity to a hospital or availability of necessary expertise.
  - Uncertainty about the baseline risk for the population of interest.

The GRADE Working Group also recommends that incremental costs of healthcare alternatives should be considered explicitly alongside the expected health benefits and harms. (15) Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. (15) The last column in Table 11 is the overall trade-off between benefits and harms and incorporates any risk/uncertainty.

For refractory erythrodermic CTCL, the overall GRADE and strength of the recommendation is “weak” – the quality of the evidence is “low” (uncertainties due to methodological limitations in the study design in terms of study quality and directness), and the corresponding risk/uncertainty is increased due to a budget impact of approximately \$1.5M while the cost-effectiveness of ECP is unknown and difficult to estimate considering that there are no high quality studies of effectiveness. The device is licensed by Health Canada, but the sterile solution of methoxsalen is not licensed.

With an annual budget impact of \$1.5 M Cdn (based on 30 patients), and the current expenditure is \$1.3M Cdn (for out of country for 7 patients), the potential cost savings based on 30 patients with refractory erythrodermic CTCL is about \$3.8 M Cdn (annual).

For refractory cGvHD, the overall GRADE and strength of the recommendation is “weak” – the quality of the evidence is “low” (uncertainties due to methodological limitations in the study design in terms of study quality and directness), and the corresponding risk/uncertainty is increased due to a budget impact of approximately \$1.5M while the cost-effectiveness of ECP is unknown and difficult

to estimate considering that there are no high quality studies of effectiveness. Both the device and sterile solution are not licensed by Health Canada for the treatment of cGvHD.

If all the ECP procedures for patients with refractory erythrodermic CTCL and refractory cGvHD were performed in Ontario, the annual budget impact would be approximately \$3M CDN

**Table 11: Overall GRADE and Strength of Recommendation (including uncertainty)**

	Licensed by Health Canada?	Quality	Estimated Incidence in Ontario	Cost-Effectiveness	Cost in Ontario	Overall Grade and Strength of Recommendation  (Including Uncertainty)
Treatment resistant Erythrodermic CTCL	Device - Yes  Drug solution - No	Low	~ 30	? Unknown	If all procedures done in Ontario ~ \$1.5M CDN  If all procedures done in the US ~ \$5M CDN	Weak
Treatment resistant cGvHD	Device - No  Drug solution - No	Low	~30	? Unknown	Same as above	Weak

# Appraisal

The UVAR XTS Photopheresis System is licensed by Health Canada as a Class 3 medical device (license # 7703) for the “palliative treatment of skin manifestations of CTCL.”

UVADEX (sterile solution methoxsalen) is not licensed by Health Canada, but can be used in Canada via the Special Access Program. (Personal communication, Therakos, February 16, 2006)

According to the manufacturer, the UVAR XTS photopheresis system licensed by Health Canada can also be used with oral methoxsalen. (Personal communication, Therakos, February 16, 2006) However, oral methoxsalen is associated with side effects, must be taken by the patient in advance of ECP, and has variable absorption in the gastrointestinal tract.

According to Health Canada, UVADEX is not approved for use in Canada. In addition, a review of the Product Monographs of the methoxsalen products that have been approved in Canada showed that none of them have been approved for oral administration in combination with the UVAR XTS photopheresis system for "the palliative treatment of the skin manifestations of cutaneous T-cell Lymphoma".

Two Ontario expert consultants jointly estimated that there may be approximately 30 new erythrodermic treatment resistant CTCL patients and 30 new treatment resistant cGvHD patients per year who are unresponsive to other forms of therapy and may be candidates for ECP.

## Survey of Provinces/Territories

The funding status of ECP reported by other Canadian provinces and territories is shown in Table 12.

**Table 12: Reported Funding Status of Extracorporeal Photopheresis in Canadian Provinces and Territories.**

Province/Territory	Funding Status
Newfoundland	“There is no listing for extracorporeal photopheresis in our Medical Payment Schedule and no formal decision has been made to cover it as an unlisted benefit on an interim basis.”
New Brunswick	“Not available in NB. Out of province funding is available.”
Nova Scotia	“Not available in NS.”
Prince Edward Island	No reply to date.
Quebec	Not available in Quebec. Out of province funding provided.
Ontario	Not insured. Out of province/country funding available.
Manitoba	“Not listed in The Payments for Insured Medical Services Regulation.”
Saskatchewan	No reply to date.
Alberta	“There is no fee code for this in Alberta. The bone marrow transplant program receives global funding through Province-Wide-Services.”
British Columbia	Contact unsure about funding status.
Yukon	No reply to date.
Northwest Territories	No reply to date.

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Nunavut

No reply to date.

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### Survey of Some Insurers in United States

The funding status of ECP by insurers in the United States is shown in Table 13.

**Table 13: Funding Status of Extracorporeal Photophoresis by Insurers in the United States.**

Insurer	Funding Status
CMS (60)	<ul style="list-style-type: none"><li>➤ Covered only when used in the palliative treatment of the skin manifestations of CTCL that has <u>not responded to other therapy</u>.</li><li>➤ There are reports of "individual consideration" coverage of its use in <u>treatment refractory</u> GvHD by individual local Medicare contractors.</li><li>➤ Reimbursement is approved for both inpatient and outpatient settings.</li></ul>
Blue Cross of California (61)	Medically necessary for: <ul style="list-style-type: none"><li>➤ Erythrodermic variants of CTCL (mycosis fungoides, Sezary syndrome)</li><li>➤ <u>Refractory</u> cGvHD (marrow or organ)</li></ul>
Aetna (62)	Medically necessary for: <ul style="list-style-type: none"><li>➤ Erythrodermic variants of CTCL (mycosis fungoides, Sezary syndrome)</li></ul> <p>Medical necessity of ECP for treatment of cGvHD (lung, kidney, bone marrow or stem cell transplantation) on a case-by-case basis.</p>
Cigna (63)	Medically necessary for: <ul style="list-style-type: none"><li>➤ <u>Advanced or refractory</u> CTCL</li><li>➤ <u>Refractory</u> systemic GvHD (allogenic hematopoietic stem cell transplantation, NOT solid organ graft rejection)</li></ul>

# Appendix 1

## Relative Frequency and Disease Specific 5-Year Survival of 1,905 Primary Cutaneous Lymphomas Classified According to the WHO-EORTC Classification.

WHO-EORTC Classification	Number	Frequency (%) <sup>*</sup>	Disease-specific 5 year survival (%)
<b>Cutaneous T Cell Lymphoma</b>			
<b>Indolent clinical behaviour</b>			
<b>Mycosis fungoides</b>	<b>800</b>	<b>44</b>	<b>88</b>
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	<1	100
Granulomatous slack skin	4	<1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T cell lymphoma	18	1	82
Primary cutaneous CD4+ small/medium pleomorphic T cell lymphoma	39	2	75
<b>Aggressive clinical behaviour</b>			
<b>Sezary syndrome</b>	<b>52</b>	<b>3</b>	<b>24</b>
Primary cutaneous NK/T cell lymphoma, nasal type	7	<1	NR
Primary cutaneous aggressive CD8+ T cell lymphoma	14	<1	18
Primary cutaneous $\tilde{\square}$ T cell lymphoma	13	<1	NR
Primary cutaneous peripheral T cell lymphoma, unspecified	47	2	16
<b>Cutaneous B Cell Lymphoma</b>			
<b>Indolent clinical behaviour</b>			
Primary cutaneous marginal zone B cell lymphoma	127	7	99
Primary cutaneous follicle center lymphoma	207	11	95
<b>Intermediate clinical behaviour</b>			
Primary cutaneous diffuse large B cell lymphoma, leg type	85	4	55
Primary cutaneous diffuse large B cell lymphoma, other	4	<1	50
Primary cutaneous intravascular large B cell lymphoma	6	<1	65

NR = Not reached

\* Data are based on 1905 patients with a primary cutaneous lymphoma registered at the Dutch and Austrian Cutaneous Lymphoma Group between 1986 and 2002.

*Reprinted with permission from the American Society of Hematology; From: Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105: 3768-3785 (2)*

### TNM Classification for MF/SS from the National Cancer Institute

Classification	Description
<b>T (skin)</b>	
T0	Clinically or histopathologically suspicious lesions
T1	Limited plaques, papules, or eczematous patches (<10% of total skin surface)
T2	Generalized plaques, papules, or eczematous patches (≥10% of total skin surface)
T3	Tumours
T4	Generalized erythroderma
<b>M (visceral organ involvement)</b>	
M0	No visceral organ involvement
M1	Pathologically confirmed visceral involvement
<b>B (peripheral blood)</b>	
PB0	No circulating atypical (Sezary) cells (<5% of total lymphocytes)
PB1	Circulating atypical (Sezary) cells (≥5% of total lymphocytes)
<b>N (nodes)</b>	
N0	No clinically abnormal peripheral lymph nodes; pathology negative for CTCL
N1	Clinically abnormal peripheral lymph nodes; pathology negative for CTCL
N2	No clinically abnormal peripheral lymph nodes; pathology is positive for CTCL
N3	Clinically abnormal peripheral lymph nodes; pathology is positive for CTCL

Above information available at: National Cancer Institute. *Mycosis fungoides and the sezary syndrome (PDQ): treatment. Stage information. 2006*; [www.nci.nih.gov/cancertopics/pdq/treatment/mycosisfungoides/healthprofessional/page3\(64\)](http://www.nci.nih.gov/cancertopics/pdq/treatment/mycosisfungoides/healthprofessional/page3(64))

### Staging Classification for MF/SS from the National Cancer Institute

Clinical Stage	Classification
IA	T1, N0, M0
IB	T2, N0, M0
IIA	T1-2, N1, M0
IIB	T3, N0-1, M0
III	T4, N0-1, M0
IVA	T1-4, N2-3, M0
IVB	T1-4, N0-3, M1

Above information available at: National Cancer Institute. *Mycosis fungoides and the sezary syndrome (PDQ): treatment. Stage information. 2006*; [www.nci.nih.gov/cancertopics/pdq/treatment/mycosisfungoides/healthprofessional/page3\(64\)](http://www.nci.nih.gov/cancertopics/pdq/treatment/mycosisfungoides/healthprofessional/page3(64))

## Appendix 2

### Update to Catalan Review – Studies Examining the Treatment of CTCL Using Extracorporeal Phorophoresis

Study (year)	Study Type	Inclusion Criteria	Treatment	Outcome	Results
<b>Update to Catalan Review - Prospective Studies ECP Monotherapy</b>					
Child et al. 2004	Prospective Randomized Crossover N=16	<b>T2 plaque stage MF</b> Detectable peripheral blood T cell clone, but no lymph node involvement. No active treatment (other than topical steroids and emollients) within 3 months of commencing study.	PUVA twice weekly for 3 months followed by ECP once monthly for 6 months	Monthly skin scores and peripheral blood T cell clonality	<u>8 out of original 16 patients completed the study.</u> Four dropped out: 2 prior to starting treatment 1 mildly hypotensive during ECP and couldn't tolerate it 1 disease progression  4 completed the first arm of the study but were subsequently withdrawn as the study was halted following interim analysis (no further details reported).  <b>Skin Scores:</b> Reduction in scores for all patients during PUVA, but with ECP the scores remained stable or increased. N=8, 3 months PUVA significantly reduced skin scores compared to 6 months ECP. (Difference in skin score 113 CI [42-184], p=0.002). T cell clones detected in peripheral blood <u>both before and after</u> PUVA and ECP.
<b>Update to Catalan Review Prospective Studies Combination Therapy</b>					
Quaglino et al. 2004	Prospective cohort N=44	CTCL (17 SS; 26 MF- stage IIB IV or with peripheral blood involvement; 1 MF associated with lymphomatoid papulosis)	FAMP monochemotherapy in advanced CTCL and if the sequential association of ECP (oral) to FAMP in selected patients may improve the response rate and or lengthen the remission duration.	Response rate based on measurement of clinically apparent disease in the skin, lymph nodes and peripheral blood according to pretreatment staging.	Overall response rate (RR) to FAMP evaluated before starting ECP was 29.5% (13/44); a higher RR was obtained in SS (35.3%) than in MF patients (25.9%). According to the pretreatment group, the RR of the FAMP-ECP group (63.2%) was significantly higher than that of the FAMP monotherapy group (24%, p=0.021).



		<p>SS diagnostic criteria: Erythroderma and peripheral lymphadenopathies. Peripheral blood involvement with circulating Sezary cells Cutaneous biopsy proven CTCL confirmed by the finding of a clonal Tcell recECPtor gene.</p> <p>12 patients were previously untreated while 13 were previously treated with polychemotherapy. The remaining 20 patients underwent PUVA, low dose interferon or thymopentin.</p>	<p>All patients received FAMP 5 days monthly. Responding or stable disease patients were treated until progression for up to 8 cycles.</p> <p>19 patients (43.2%) underwent ECP after FAMP was discontinued. Patients were considered members of the combination FAMP-ECP group when they received at least 6 ECP courses.</p>		<p><b>TTP</b> of the FAMP-ECP group was higher (median 13 months, range 3-91) than that of the FAMP only group (median 7 months, range 2-83); <b>not statistically significant.</b></p> <p><b>No difference in survival</b> was found between FAMP treated (median 25.5 months; range 2-84) and FAMP-ECP treated patients (median 20.1 months; range 8.5-91).</p>
Wollina et al. 2001	Prospective cohort N=14	MF stage IIa/IIb Relapse or unresponsiveness to previous treatments.	<p>ECP twice a month for 6 months in combination with interferon a.</p> <p>Oral methoxsalen.</p>	Skin biopsy	<p>After 6 months, there was a CR in 4 patients, a PR in 3 and stable disease in 7 of the 14 patients (<b>overall response rate CR+PR=50%</b>).</p> <p>9 patients were kept on combination therapy. Final outcome after 12 months was CR in 1 patient, PR in 2 patients and stable disease in 6 patients. Another patient with CR was given low dose interferon (??).</p> <p>After 12 months, total response rate was 46.2% (6/13 patients): 5/9 with stage IIa (55.6%) and 1/4 with stage IIb (25.0%).</p>
<b>Update to Catalan Review Retrospective Studies</b>					
Stevens et al. 2002	Case series Retrospective/ prospective? N=17	<p>SS n=15 (14 positive for clonality)</p> <p>Erythrodermic MF n=2</p>	<p>ECP First line treatment</p> <p>ECP performed on 2 consecutive days monthly for first 2 months, and monthly thereafter.</p>	Survival	<p>4 SS patients moribund on presentation – only underwent 1-2 cycles (died). <u>Median survival 56 months for remaining 11 patients with SS.</u> <b>If all 15 SS patients were considered, the median survival was 34 months.</b> 2 MF patients not included in analysis.</p>

			Oral methoxsalen.		1 in complete remission at time of manuscript writing. 1 died after 39 months of ECP (2° to chronic obstructive pulmonary disease)
Suchin et al. 2002	Case series Retrospective 14 years N=47	32/47 (68%) Stage II or IV  42/47 (89%) Peripheral blood involvement.	31/47 (66%) combination therapy  15 (34%) ECP monotherapy  All received minimum 6 months of ECP.	Clinical response	<u>Combination Therapy n=31</u> CR 6 (19) PR 20 (65) Total 26 (84) None 4 (13) Median survival 74 months  <u>ECP Monotherapy n=15</u> CR 6 (38) PR 6 (38) Total 12 (75) <b>p=0.47</b> None 3 (19) Median survival 66 months
Crovetti et al. 2000	Case series Retrospective N=33 How selected? Consecutive?	5 year experience	6 patients received ECP with interferon.  30 patients completed at least 3 ECP cycles.  3 dead?	Disappearance/ reduction of erythroderma, skin lesions.  Survival	Favourable clinical response: 16/21 (80.9%) MF patients 6/9 (66%) SS patients  Median survival of responders: 18 months (range 4-58 months)
Wilson et al. 2000	Case series Retrospective N=44	Erythrodermic MF 59% of patients had hematologic involvement.	TSEB only TSEB + ECP n= 21 (ECP before, during or after TSEB)  73% of patients had other therapies before TSEB.	Survival  Median follow-up 2 years (0.3-13.9 years) subsequent to TSEB.	All patients responded to TSEB within 2 months of completion, with a cutaneous CR rate of 73%.  For the 32 complete responders, the 3 year disease free survival was 63%; 49% for the 17 patients who received only TSEB compared with 81% for those 15 patients who received TSEB and ECP.
Prinz et al. 1995	Case series N=17 Consecutive patients?	3 erythroderma 14 plaque No strict inclusion criteria stated.	5 patients had concomitant therapy.	Skin clearing. Response defined as being >50% in skin clearing.	Overall response rate: n=7 (41%). No patients had 100% clearing of skin lesions.
Konstantinow et al. 1997	Case series N=12 Nonconsecutive patients	6 SS 6 MF No strict inclusion criteria stated.	6 patients had concomitant therapy.	Skin clearing. Response defined as >50% in skin clearing.	Overall response rate: n=6 (50%). 1 patient (8.3%) had 100% clearing of skin lesions.
Jiang et al. 1999	Case series Retrospective? Consecutive? N=41	Erythrodermic CTCL.  25 patients fulfilled inclusion criteria (completion of > 6	Emollients, topical corticosteroids and salicylic acid ointment.  "Only in patients with minimal	CR=disappearance of measureable disease for at least 1 month. PR= $\geq$ 50% clearance of measurable	5 patients (20%) had CR. 15 patients (60%) had PR. 5 patients (20%) had no response.  An intent-to-treat analysis should have

cycles of ECP)	or almost no clinical response after 6 cycles was systemic adjunctive treatment used, which was most commonly oral etretinate (n=5).	disease for at least 1 month.	included all 41 patients (including patients who withdrew for progression of disease or voluntary withdrawal.
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### Update to Catalan Review – Studies Examining the Treatment of cGvHD Using ECP

Study (year)	Study Type	Inclusion Criteria	Treatment	Outcome	Results
<b>Update to Blue Cross Blue Shield TEC Review - Prospective Studies ECP</b>					
Foss et al. 2005	Prospective Case series N=25	Extensive steroid refractory cGvHD. Body weight at least 40kg, ability to tolerate ECP.	Methoxsalen injected directly into buffy bag. Median time from transplant to ECP was 790 days. Median duration of therapy 9 months. ECP administered for 2 consecutive days every 2 weeks in 17 patients and once a week in 8 patients until the best response or stable disease was observed.	Efficacy of ECP in both skin and visceral cGvHD.	Overall response rate=64%.  20 patients had improvement in cutaneous GvHD and 6 had healing of oral ulcerations.  15 patients developed serious adverse events during therapy.  Median survival of study group was 51 months from day 0 of allogeneic transplantation.
Seaton et al. 2003	Prospective Case series N=28	Failed conventional immunosuppressive therapy. Body weight more than 40kg.	ECP started ~ 2 years after onset of cGvHD and 3 years after allogeneic stem cell transplantation. ECP administered on 2 consecutive days every 2 weeks for the first 4 months and then monthly. At 6 months, a decision was made whether to continue treatment depending upon the clinical response, long distance travel, and patient preferences.	Skin score, liver function tests, blood counts, lung function tests.	25 patients completed 3 months of treatment, 21 completed 6 months and 6 completed 12 months. Median duration of treatment was 6 months (range 1-58). Systemic immunosuppression was stable or reduced in 86% of patients. After 6 months, median skin scores were 53% lower (p=0.03) in sclerodermoid and lichenoid disease. Of 6 patients with mucosal ulceration, 3 improved. There was no statistically significant improvement of liver function tests.  5 patients developed serious

					complications, including 4 who died. Systemic immunosuppression was stable in 15 patients reduced in 9 patients and increased in 4 patients.
Salvaneschi et al. 2003	Prospective case series N=14 children	Refractory to at least one line of treatment.	ECP on 2 consecutive days at 2 week intervals for 3 months. If clinical signs and symptoms of cGvHD improved, patients were treated for 2 consecutive days at 3 week intervals for 3 additional months. Tapering and discontinuation of ECP depended on evaluation of individual clinical response.  Median interval between occurrence of cGvHD and start of ECP was 12 months (range 1-110).	CR=resolution of skin, liver, gut, lung, oral mucosa, joint or ocular manifestations.  PR=response greater than 50% in organ involvement.	9/14 responded to treatment: 4/14 had CR and 5/14 had PR. The remaining 5/14 had stable disease or disease that progressed during ECP.  3/5 nonresponding patients died (2 due to cGvHD, and 1 of carcinoma of the tongue – due to prolonged immunosuppression).
<b>Update to Blue Cross Blue Shield TEC Review - Retrospective Studies ECP</b>					
Rubegni et al. 2005	Retrospective? Prospective? case series N=32	Steroid refractory cGvHD.	8MOP injected directly into the buffy bag.	“Determinant” = CR observed in all organs and dose of immunosuppressants reduced by at least 50%. “Ineffective”=Progression observed in one of the organs involved, when it was necessary to increase dose of immunosuppressants or when CR was not observed in any organ and immunosuppressants were not reduced by more than 50%. “Good” =all other cases.	ECP was “determinant” in 22% of cases, “good” in 56% and “ineffective” in 22% of patients.
Apisarnthanarax et al. 2003	Retrospective Case series N=32	Steroid resistant or steroid dependent and treated after day 100 and who received	Median of 36 ECP sessions (range 12-98) over a median of 5.3 months (range 1-28)	CR=complete resolution of all active involvement with or without residual clinically	CR was 22% (n=7) and PR was 34% (n=11). Steroid sparing response rate=64%

at least 4 weeks of ECP. All 32 patients had been previously treated with systemic corticosteroids with 11 (34%) being steroid resistant and 21 (66%) steroid dependent.

with a median of 6 sessions per month.

inactive lesions. PR=improvement in skin rash and/or skin involvement on at least 50% of the body surface area. Steroid sparing response=50% or more decrease in the systemic corticosteroid requirement between the beginning and end of ECP therapy.

Couriel et al.  
2005

Retrospective  
chart review  
N=71

Steroid refractory if:  
a) stable disease (no response) after 1 month of treatment.  
b) no more than a partial response occurred after 2 months of treatment.  
c) progressive disease occurred after 2 weeks of initiation of steroid treatment or during tapering of corticosteroids.

Patients received a median of 32 ECP procedures (range 1-259 procedures) over a median of 14.5 weeks (range 1-333 weeks).

CR=resolution of all manifestations of cGvHD. PR=at least a 50% improvement of clinical manifestations without a CR. No response=no change in cGvHD.

The overall response rate was 61% (n=43) and 14 patients had CR. The cumulative incidence of CR/PR at 1 year since initiation of ECP was 83% (standard error 9). A total of 33 patients (59%) with skin GvHD responded to ECP. Responses were also seen in liver (n=15, 71%), oral mucosa (n=7, 77%), eye (n=4, 67%), pulmonary (n=6, 54%) and gastrointestinal (n=2, 66%).

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