DOI: 10.1111/jdv.16890 JEADV

GUIDELINES

European dermatology forum – updated guidelines on the use of extracorporeal photopheresis 2020 – part 1

R. Knobler,[1,*] P. Arenberger,[2] A. Arun,[3] C. Assaf,[4] M. Bagot,[5] G. Berlin,[6,7] A. Bohbot,[8] P. Calzavara-Pinton,[9] F. Child,[10] A. Cho,[11] L.E. French,[12] A.R. Gennery,[13] R. Gniadecki,[14] H.P.M. Gollnick,[15] E. Guenova,[16,17] P. Jaksch,[18] C. Jantschitsch,[19] C. Klemke,[20] J. Ludvigsson,[21] E. Papadavid,[22] J. Scarisbrick,[23] T. Schwarz,[24] R. Stadler,[25] P. Wolf,[26] J. Zic,[27] C. Zouboulis,[28] A. Zuckermann,[29] H. Greinix[30]

[1]Department of Dermatology, Medical University of Vienna, Vienna, Austria
[2]Third Faculty of Medicine, Charles University, Prague, Czech Republic
[3]FRCPath, The Rotherham NHA Foundation Trust, Rotherham, UK
[4]Department of Dermatology and Venerology, Helios Klinikum Krefeld, Krefeld, Germany
[5]Hospital Saint Louis, Université de Paris, Paris, France
[6]Department of Clinical Immunology and Transfusion Medicine, Linköping University, Linköping, Sweden
[7]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
[8]Onco-Hematology Department, Hautepierre Hospital, Strasbourg, France
[9]Dermatology Department, University of Brescia Italy, Brescia, Italy
[10]FRCP, St John's Institution of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[11]Department of Dermatology, Medical University of Vienna, Vienna, Austria
[12]Department of Dermatology, University Hospital, München, Germany
[13]Translational and Clinical Research Institute, Newcastle University Great North Children's Hospital Newcastle upon Tyne, Newcastle University, Newcastle upon Tyne, UK
[14]Division of Dermatology, University of Alberta, Edmonton, AB, Canada
[15]Dept. Dermatology & Venereology, Otto-von-Guericke University, Magdeburg, Germany
[16]Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
[17]Department of Dermatology, Lausanne University Hospital CHUV, Lausanne, Switzerland
[18]Department of Thoracic Surgery, Medical University Vienna, Vienna, Austria
[19]Department of Dermatology, Medical University of Vienna, Vienna, Austria
[20]Hautklinik Städtisches Klinikum Karlsruhe, Karlsruhe, Germany
[21]Crown Princess Victoria Children's Hospital and Division of Pediatrics, Department of Biomedical and Clinical Sciences, University Hospital, Linköping University, Linköping, Sweden
[22]National and Kapodistrian University of Athens, Athens, Greece
[23]University Hospital Birmingham, Birmingham, UK
[24]Department of Dermatology, University Clinics Schleswig-Holstein, Kiel, Germany
[25]University Clinic for Dermatology Johannes Wesling Medical Centre, UKRUB, University of Bochum, Minden, Germany
[26]Department of Dermatology, Medical University of Graz, Graz, Austria
[27]Department of Dermatology, Vanderbilt University Medical Center, Nashville, TN, USA
[28]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane, Dessau, Germany
[29]Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria
[30]Division of Haematology, LKH-Univ. Klinikum Graz, Medical University of Graz, Graz, Austria
*Correspondence: R. Knobler. E-mail: robert.knobler@meduniwien.ac.at

Abstract

Background Following the first investigational study on the use of extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma published in 1983, this technology has received continued use and further recognition for additional earlier as well as refractory forms. After the publication of the first guidelines for this technology in the JEADV in 2014, this technology has maintained additional promise in the treatment of other severe and refractory conditions in a multi-disciplinary setting. It has confirmed recognition in well-known documented conditions such as graft-versus-host disease after allogeneic bone marrow transplantation, systemic sclerosis, solid organ transplant rejection including lung, heart and liver and to a lesser extent inflammatory bowel disease.

Materials and methods In order to further provide recognized expert practical guidelines for the use of this technology for all indications, the European Dermatology Forum (EDF) again proceeded to address these questions in the hands of the recognized experts within and outside the field of dermatology. This was done using the recognized and approved guidelines of EDF for this task. All authors had the opportunity to review each contribution as it was added.

Results and conclusion These updated 2020 guidelines provide at present the most comprehensive available expert recommendations for the use of extracorporeal photopheresis based on the available published literature and expert consensus opinion. The guidelines are divided in two parts: PART I covers cutaneous T-cell lymphoma, chronic graft-versus-host disease and acute graft-versus-host disease while PART II will cover scleroderma, solid organ transplantation, Crohn's disease, use of ECP in paediatrics practice, atopic dermatitis, type 1 diabetes, pemphigus, epidermolysis bullosa acquisita and erosive oral lichen planus.

Received: 24 June 2020; Accepted: 6 August 2020

Conflict of interest

Dr. Arun reports research from Mallinckrodt Ltd and personal fees from Mallinckrodt Ltd, outside the submitted work.Dr. BAGOT reports personal fees from Kyowa Kirin, Takeda, Helsinn and Innate Pharma, outside the submitted work. In addition, Dr. BAGOT has a patent Anti-KIR3DL2 antibody licensed. Dr. Bohbot reports other from Therakos during the conduct of the study. Dr. Gennery reports grants from Mallinkrodt, during the conduct of the study. Dr. Gniadecki reports personal fees from Mallinckrodt, during the conduct of the study; personal fees from Lilly; personal fees and other from AbbVie; grants and personal fees from Sanofi; personal fees from Sun Pharma; and personal fees from Janssen, outside the submitted work. Dr. Prof.Dr. Gollnick has nothing to disclose. Dr. Greinix reports personal fees from Mallinckrodt, Novartis, Roche, Amgen and Celgene, during the conduct of the study. Dr. Guenova reports personal fees from Mallinckrodt, outside the submitted work. Dr. Knobler reports Speaker fees from Mallinckrodt-Therakos. Dr. Wolf reports grants and other from AbbVie, other from Almirall, other from Amgen, other from Celgene, other from Eli Lilly, other from Janssen-Cilag, other from Kwizda, other from Leo Pharma, other from Merck Sharp & Dohme, other from Novartis, other from Sanofi-Aventis, grants and other from Pfizer, and personal fees from Therakos, during the conduct of the study. Dr. Zouboulis reports personal fees from AccureAcne, Allergan, Almirall, Bayer Healthcare, General Topics, GSK/Stiefel, Idorsia, Incyte, Jafra Cosmetics, Janssen, Jenapharm, L'OREAL, Regeneron, and Sobi; personal fees and honoraria to his employer for his participation to clinical studies from AbbVie, Galderma, Novartis, InflaRx, NAOS-BIODERMA, Pierre Fabre, PPM and UCB; and honoraria to his employer for his participation to clinical studies from AOTI and AstraZeneca. Dr. Zuckermann reports personal fees from Therakos-Mallinckrodt, outside the submitted work. Dr. Arenberger, Dr. Assaf, Dr. Berlin, Dr. Calzavara-Pinton, Dr. Child, Dr. Cho, Dr. French, Dr. Prof.Dr. Gollnick, Dr Peter Jaksch, Dr. Jantschitsch, Dr. Klemke, Dr. Ludvigsson, Dr. Papadavid, Dr. Scarisbrick, Dr. Schwarz, Dr. Stadler and Dr. Zic have nothing to disclose.

Funding source

None declared.

Introduction

Extracorporeal photopheresis (ECP, also known as extracorporeal photochemotherapy, extracorporeal photoimmunotherapy or just photopheresis) is a leukapheresis-based therapy that is available at more than 200 centres worldwide.[1,2] During ECP, the patient's whole blood is processed outside the body: blood is collected via an antecubital vein, or a permanent catheter if vein access is cumbersome; white blood cells are then separated from red blood cells and plasma by centrifugation in a device that is specially constructed for this procedure. White blood cells are exposed to ultraviolet A (UVA) light in a separate plastic chamber and then returned to the patient.[3] In the past, patients treated with ECP were given oral 8-methoxypsoralen (8-MOP; methoxsalen) before the blood was leukapheresed.[1] Thus, during the ECP treatment, patients typically experienced untoward gastrointestinal effects such as nausea and vomiting, or the visual side-effects of psoralen. Moreover, differences in gastrointestinal absorption due to individual variability resulted in unpredictable blood concentrations of 8-MOP.[1,4] To avoid the problems of oral 8-MOP administration, a liquid formulation of 8-MOP (UVADEX®, Therakos®) that is added directly to the buffy-coat/blood fraction was developed. This method of dosing circumvents the potential side-effects of systemic 8-MOP administration and eliminates the need to measure for target blood levels.[5]

The first investigational study of ECP in patients with cutaneous T-cell lymphoma (CTCL) was completed in 1983. The first

Table 1 ECP devices in current use in adults and children (adapted from Wong and Jacobsohn)[7]

Methodology	Automated	Weight limit	Cell separator Extracorporeal volumes	Cell separator technology
One-step methods				
CELLEX® (Therakos®)*	Yes (double needle)	RBC prime needed if >115% ECV	Variable, dependent on Hct, blood volume processed, return bag threshold (lower than UVAR XTS)	IFC (continuous buffy coat collection with intermittent fluid return) (Latham Bowl)
	Yes (single needle)	RBC prime needed if >115% ECV	Variable, dependent on Hct, blood volume processed, return bag threshold (higher than double-needle method)	CFC (Latham Bowl)
UVAR XTS® (Therakos®) (not available in U.S and Europe)	Yes (single needle)	>40 kg (need to satisfy ECV limits)	Variable, dependent on Hct, number of cycles, and bowl size (225 or 125 mL)	IFC (Latham Bowl)
Two-step methods†				
Spectra OPTIA® (Terumo BCT) and **UVA irradiator**	Yes (only cell separation)	None	253 mL (Continuous mononuclear cell collection (CMNC), version 1.3); 147 mL (AutoPBSC procedure, Version 3.8)	CFC
Mini-buffy coat and **UVA irradiator**	No	Smaller children	None, but limited to 5–8 mL/kg whole blood draw	Standard manual buffy centrifugation technique
Three-step methods‡				
Spectra OPTIA® (Terumo BCT) & **UVAR XTS**® (Therakos®)	Yes (only cell separation)	None	See above for MNC and AutoPBSC procedure	CFC

Suitable for low bodyweight patients.

CFC, continuous flow centrifugation; ECV, extracorporeal cell volume; Hct, haematocrit; IFC, intermittent flow centrifugation; MNC, mononuclear cell; PBSC, peripheral blood stem cell; RBC, red blood cell.

†Only cell separation is automated, while the UVA irradiator is operated manually. Other dedicated continuous or intermittent T-cell separators may also be used, such as Amicus (Fenwal, MNC kit) and AS104 (Fresenius Kabi) which have extracorporeal volumes of 163 and 175 Ml, respectively.

‡Three-step methods involve standard mononuclear cell collection using dedicated continuous cell separators followed by red blood cell priming of the UVAR-XTS instrument and photoactivation treatment of the 8-methoxypsoralen treated mononuclear cells within the UVAR-XTS instrument after programming the instrument that the last ECP cycle has occurred.

ECP apparatus that was approved by the United States Food and Drug Administration in 1988 was a closed system (UVAR®; Therakos®). National approvals in Europe and elsewhere followed. Although ECP was initially developed for use in CTCL patients, it has also shown promising efficacy in a number of other severe and difficult-to-treat clinical conditions such as graft-versus-host disease (GvHD), Crohn's disease, systemic sclerosis and for the prevention and treatment of rejection in solid organ transplantation, particularly in the areas of lung and heart transplantation.[6]

Several closed and open ECP apparatuses are currently available for clinical use and are compared in Table 1.[7] Their clinical efficacy in the treatment of a variety of T-cell-mediated diseases is well established. However, the two techniques have not been directly compared in a clinical setting. In a closed ECP apparatus (one-step method), the blood cell separation, drug photoactivation, and reinfusion stages are fully integrated and automated, and all elements are approved for their combined use, including methoxsalen, a photoactivating agent (Table 2). There is no risk of improper reinfusion when used according to the labelling, and the risk of infection and contamination associated with the medical device itself is very low.

From a technical aspect, an open apparatus is any disconnected process using a cell separator in combination with a light-box and a drug. Although the individual components may be Communauté Européenne (CE) marked, they are not explicitly approved for use together in the process of photopheresis. To obtain proper CE marking for photopheresis use, all the components of an apparatus must undergo a validation process prior to being used together in controlled clinical trials and routine therapy. This technology falls under the regulations of cell therapy according to the federal agency *L'Agence Nationale de Sécurité du Médicament* (ANSM) in France.[8] Open apparatuses can only be used by centres that are certified for cell therapy. To obtain the certificate, ANSM requires the filing of a record of authorization describing the entire ECP procedure, including the drug and material to be used, transport, quality controls, traceability, the structure of cell manipulation and much more. Closed apparatuses do not have these restrictions. A closed apparatus is a one-step method (UVAR-XTS® and CELLEX®; Therakos®). Critical steps, such as cell separation, drug photoactivation, and reinfusion, are fully integrated and automated processes. All the components are validated for

Table 2 European CE mark and FDA approval status of 'one-step' closed photopheresis apparatuses and various cell separation and drug photoactivation devices used in 'Multistep' photopheresis procedures

	Company	European CE mark	FDA approval
Closed photopheresis apparatuses			
CELLEX®†	Therakos®	✓ For photopheresis	✓ For photopheresis
UVAR XTS®	Therakos®	✓ For photopheresis	✓ For photopheresis
Tubing set (XTS® and CELLEX®)	Therakos®	✓ For photopheresis	✓ For photopheresis
UVADEX	Therakos®	✓ For photopheresis	✓ For photopheresis
Cell separation system (standard apheresis device)			
Spectra Optia®	Terumo BCT	✓ For therapeutic plasma exchange, RBC exchange, and WBC collection	✓ For therapeutic plasma exchange, leucocyte collection, and RBC exchange
Com. Tec®	Fresenius Kabi	✓ For therapeutic plasma exchange and WBC collection	✓ For therapeutic plasma exchange and WBC collection
MCS® plus	Haemonetics®	✓ For therapeutic plasma exchange and leucocyte collection	✓ For therapeutic plasma exchange and leucocyte collection
AMICUS	Fenwal	✓ For therapeutic plasma exchange and leucocyte collection	✓ For therapeutic plasma exchange and leucocyte collection
Drug photoactivation system			
PUVA light system	Macopharma	CE marked (indicated to treat psoriasis, not dedicated to ECP)	No
MACOGENIC	Macopharma	UVA illumination machine CE 0459	No
MACOGENIC G2	Macopharma	UVA illumination machine CE 0459	No
XUV bag	Macopharma	UVA illumination machine CE 0459	No
8-MOP	Macopharma	AMM PTA 07.10.109 (indicated for nuclear cell photosensibilization)	No
UVA PIT system	MedTech Solutions	Medical System for photoimmune therapy (body MDC 0483)	No
UVA PIT Kit	MedTech Solutions	Medical System for photoimmune therapy (body IMQ 0051)	No
PUVA Combi-Light	Cell.Max	CE marked medical device	No
UVA Illuminator	GMBH		

CE, Conformité Européenne; RBC, red blood cell; WBC, white blood cell.
†Suitable for low bodyweight patients.

their combined use, including the use with 8-methoxypsoralen Table 2. Components of closed ECP apparatuses are approved and certified as one functional unit, which may be operated by a single trained person.

One of the critical elements of both open and closed ECP apparatuses is the photoactivation chamber. Closed photopheresis apparatuses are equipped with a microprocessor that allows for a dynamic recirculation of photoactivated cells. All photoactivation elements have a fixed thickness and are tested by UV spectrophotometry to ensure the retention of photodynamic properties (optimal UV transmittance). Adsorption of 8-methoxypsoralen to the disposable plastic kit is measured and compensated for to ensure proper dosing. Components that are used in open ECP apparatuses are not designed or manufactured for the process of photopheresis, and, therefore, need to be certified prior to their use.

Inconsistent light exposure to targeted cells because of nonvalidated plastic films, variation in the fluidity of the solution in the treatment bag, unknown or variable drug adsorption onto plastic components, or stasis of the cells during UVA irradiation could cause partial DNA damage to the cells.

Regardless of the apparatus used, ECP is usually well-tolerated. There are no reports of grade III-IV side-effects (as rated by the World Health Organization (WHO)) following treatment. Transient hypotension or mild anaemia (after multiple treatments) may occur, and thrombocytopenia has also been reported. ECP should not be used as a therapy in patients with a known sensitivity to psoralen compounds such as methoxsalen, or comorbidities, including photosensitivity, a history of heparin-induced thrombocytopenia, a low haematocrit or cardiocirculatory failure (note: in some selected patients with cardiocirculatory failure, the therapy is actually well-tolerated as response to therapy contributes to stress reduction). It is also contraindicated in pregnancy. Methoxsalen containing ready-to-use sterile solutions are contraindicated in patients with aphakia because of the significantly increased risk of retinal damage. In patients with low bodyweight, children, and those with problematic venous access, implantable venous access devices with a proper blood flow per minute should be used. In this regard, peripheral venous catheters appear to be advantageous over central venous devices. In addition, it should be noted that the use

of Hickman catheters among erythroderma patients can be quite hazardous due to the high rate of infection with staphylococcus aureus.[9]

Ideally, ECP should be initiated as soon as clinically indicated, which in most cases is as a second-line therapy when other first-line therapies have failed. In general, currently, many centres in Europe perform ECP treatment as inpatient therapy. Monitoring of efficacy before and during ECP treatment should be based on the standards of care for each indication. The use of either heparin or acid citrate dextrose as anticoagulation during ECP depends on the preference of different centres. While the use of UVA protective glassware is recommended during PUVA in combination with oral methoxsalen, it may be unnecessary during ECP therapy due to the very low doses of psoralen used. With the use of UVADEX, there is usually a low to unmeasurable level of 8-MOP in the blood thus making it unnecessary to completely avoid UVA exposure post-therapy.

Mode of action

Although ECP has been in clinical use for more than 35 years, its mode of action remains elusive. Current doses and treatment intervals remain almost identical to regimens used in the 1980s. Early studies indicated that ECP induced lymphocyte apoptosis contributed to the therapeutic effect.[10,11] More recent studies have shown that the mechanism of action of ECP is primarily due to an immunomodulatory effect. The principal mechanisms of action comprise of the modulation of dendritic cells, alteration of the cytokine profiles, and induction of particular T-cell subpopulations.[12,13] ECP, like psoralen plus UVA (PUVA), induces psoralen-mediated DNA crosslinks that cause apoptosis in lymphoid cells, particularly in natural killer (NK) cells and T cells.[14]

However, the therapeutic effect of ECP in Sézary syndrome (SS) cannot be explained by the depletion of malignant cells, as only a relatively low proportion of the entire lymphocyte pool is treated in a photopheresis cycle. Monocytes, which appear to be more resistant to apoptosis, undergo a differentiation process within 2 days, and express surface markers such as CD83, X-11, α-V, beta- V, or CD1a.[15-17] This differentiation process appears to be independent of the psoralen-induced photoactivation and is mostly driven by direct contact of the cells with plastic and other synthetic materials during the passage through the ECP apparatus. Apoptotic lymphocytes are phagocytosed and eliminated by immature dendritic cells, which subsequently undergo maturation and present antigenic peptides — a process that has been designated transimmunization.[18] Thus, it has been suggested that transimmunization may induce an immune response against lymphoma cells, which might explain the beneficial effects of ECP observed in the therapy of SS.

Use of immunosuppressive agents does not have a positive effect on the course of CTCL and may even be hazardous. ECP-initiated cellular mechanisms of differentiation in contrast are associated with the release of a variety of cytokines including tumour necrosis factor (TNF) and interleukin (IL)-6, which induce the activation of CD36-positive macrophages.[19]

Long-term, beneficial immunologic alterations can be gained through the use of continuous ECP. The severity of CTCL is directly related to the imbalance of the ratio of T-helper cells 1 to T-helper cells 2 (Th1/Th2), which leads to the increased release of IL-4 and IL-5, the reduced activity of NK cells, and the diminished cytotoxic activity of CD8-positive T cells. In a study performed in patients with early-stage CTCL (stage IB) undergoing ECP therapy for 1 year, Di Renzo *et al.* observed not only an increase in CD36-positive monocytes in the blood but also a change in the cytokine reaction profile of peripheral blood lymphocytes upon stimulation with phytohaemagglutinin.[20] Both observations imply that ECP reverses the pathologic shift towards a Th2 immune response and restores the Th1/Th2 balance in CTCL patients. Also, anti-inflammatory cytokines appear to be induced by ECP, whereas blood levels of pro-inflammatory cytokines are lowered.[21]

In relation to neutrophils, these also undergo apoptosis resulting in mobilization of neutrophilic myeloid-derived suppressor cells (MDSC) into the circulation which can dampen Th1 and Th17 responses.[22]

Over the last two decades, ECP has been shown to be beneficial in patients with CTCL, GvHD, transplant rejection, and various autoimmune diseases. The findings mentioned above, however, cannot explain the effects of ECP in these patients, and because these conditions respond to immunosuppressive therapies, it was surmised that ECP might also exert immunosuppressive effects. Furthermore, in patients with GvHD, ECP was shown to induce IL-10 via the modulation of arginine metabolism.[23] In contrast to classic immunosuppressive therapy, ECP is not associated with significant side-effects such as opportunistic infections. It has been postulated that the therapeutic effect of ECP is due to the induction of regulatory T (T-reg) cells, without causing general immunosuppression. Using a murine contact hypersensitivity model, Maeda *et al.*[24] demonstrated that T-reg cells could be induced successfully by an ECP-like procedure (intravenous injection of leukocytes exposed to 8-MOP and UVA *in vitro*). T-reg cells induced by the combination of 8-MOP and UVA express CD4, CD25, CTLA-4, and the transcription factor Foxp3, similar to T-reg cells induced by UVB. Foxp3 suppresses the activity of other lymphocytes.[25] Furthermore, the release of IL-10 appears to be involved in this process.[26] The levels of serum B-cell activating factor (BAFF) were measured in a recent study of 46 patients with chronic GvHD (cGvHD). Serum levels of BAFF determined at 1 month after the start of ECP therapy were predictive of the 3-month and 6-month skin responses. Serum levels of BAFF lower than 4 ng/mL were associated with a significant improvement of the skin.[27] In addition, monocytes showed immunoregulatory capacity on CD4+ T cells in a human in vitro model of ECP. Reduced proliferation rates

of T cells after co-culture with ECP-treated monocytes was dependent on cell-contact between monocytes and T cells.[28] Also, there is evidence that infusion of lymphocytes treated with 8-MOP and UVA light induces CD19+ IL-10+ regulatory B cells and thereby promotes skin allograft survival.[29]

The manifestation of acute GvHD (aGvHD) in patients with allogeneic grafts was associated with a low number of T-reg cells.[30,31] Hence, several research groups have studied the effects of ECP on counts of T-reg cells. In a model of murine GvHD, regulatory T cells were shown to be induced by ECP.[32] In the majority of CTCL and GvHD patients, an increase in T-reg cells was observed after ECP therapy. Also, T-reg cells showed an enhanced immunosuppressive activity.[33-38] These findings could explain, at least in part, the beneficial effects of ECP detected in GvHD and autoimmune diseases. In patients with SS, however, reduced counts of T-reg cells have been reported, and their suppressive activity appears to be impaired.[36,39,40] These observations have led to the notion that T-reg cells could exert a suppressive impact on CD4-positive tumour cells in patients with SS.

ECP slightly increases or stabilizes counts of peripheral CD4+ CD25+FoxP3+ T-reg cells in lung transplant recipients.[41] Overall, the reinfusion of ECP-treated leukocytes induced suppression of the humoral and cellular immune responses, and thereby improved and extended the tolerance and survival of transplanted tissues and organs. The mechanism by which ECP counteracts cardiac transplant rejection was studied using a murine model of ECP.[41] Splenocytes exposed to the combination of 8-MOP and UVA were injected into syngeneic mice before and after heterotopic cardiac allograft transplantation. None of the mice received immunosuppressive agents. The treatment group showed extended cardiac allograft survival and increased counts of FoxP3-expressing CD4+ CD25+ T cells when compared to controls. The authors concluded that the murine model of ECP extends graft survival in fully histoincompatible strain combinations with no immunosuppressive agent added.[41]

In Crohn's disease, reinfusion of ECP-treated apoptotic leukocytes to the patient is hypothesised to induce a tolerogenic response via T-reg cells. Indeed, recirculation of DNA-adduct-positive cells to the intestinal mucosa has been described following ECP.[26,42] Murine models of inflammatory bowel disease have provided information on the potential therapeutic role of T-reg cells in overcoming inflammation in the intestine in humans.[43]

The effects of ECP on the immune system were studied in a randomized, double-blind, placebo-controlled trial in children with type 1 diabetes.[44] No significant effects of ECP on lymphocyte populations were observed. However, in the placebo group, the proportions of activated CD4+ (T-helper cells) and CD8+ cells increased over time, whereas such changes were not seen in the ECP-treated group. These findings probably reflect the activation of lymphocytes as a part of the natural course of type 1 diabetes and suggest that ECP may exert immunosuppressive effects by preventing lymphocyte activation.[45,46] Patients treated with placebo showed reduced T-reg cell-associated activity, which seems to be counteracted by ECP because ECP-treated patients showed preserved T-reg cell activity. These data indicate that ECP may help maintain T-reg cell-associated activity in recent-onset type 1 diabetes.[47]

Although distinct aspects of the mode of ECP action, such as the induction of T-reg cells, are well understood today, we are still far from a complete understanding of how ECP works. Animal models help us to optimize currently used treatment regimens with respect to the number of cycles, concentrations of 8-MOP, doses of UVA, and the number of cells treated in one clinical setting. Also, an enhanced understanding of the mechanism of action will finally enable ECP therapy to be directed towards those patients who will most benefit from it.

Methods

The present updated guidelines on the use of ECP were developed based on best medical practices, web review of relevant medical databases and literature, and collected expert opinions on the appropriate use of ECP.

In general, ECP is employed for the therapy of severe refractory disease courses or in situations in which other treatments have failed. However, ECP availability is limited, and evidence for its efficacy is derived from retrospective data, and small cohort or case-controlled studies. There is a lack of randomized, controlled clinical trials in the literature. Double-blind trials are challenging to perform and using sham photopheresis may be unethical for patients with severe diseases.

The present guidelines were drawn up to display the indications for which ECP is currently considered useful, as well as other indications where studies have shown promising results. For the main indications of ECP, namely CTCL and GvHD, the recommendations were developed by peers and leaders in the respective diseases. For minor indications, members of expert committees collaborated to examine all available evidence and to make appropriate recommendations. The aim was to answer clinical questions as follows:

- What are the potential indications for the treatment with ECP?
- Are there currently any guidelines/consensus statements on the use of ECP in this indication?
- Which patients should be considered for ECP treatment?
- What is the optimal treatment schedule, and how long should ECP treatment be continued?
- How can therapeutic efficacy be assessed?

For these recommendations, the individual experts in their area of expertise were consulted for their written contribution by email. In addition, individual co-authors were personally contacted during meetings (St. Gallen, Switzerland, January 26, 2018; Lisbon, Portugal, March 19, 2018; Vienna, Austria, March 22, 2018; Orlando, USA, May 17, 2018; Paris, France, September

15, 2018; St. Gallen, Switzerland, September 28, 2018; Montreux, Switzerland, January 25, 2019) or by email if a meeting in person was not feasible. The document was circulated among all members of the Guidelines Subcommittee before it was submitted to the Guidelines Committee for final approval according to the standard operating procedures of the European Dermatology Forum (EDF).

Cutaneous T-cell lymphoma

CTCL describes a heterogeneous group of rare lymphoproliferative disorders that are characterized by the accumulation of malignant T-cell clones that are localized to the skin.[48] The most common variants are mycosis fungoides (MF), which accounts for about 60% of CTCL cases, and Sézary syndrome (SS), which accounts for 5% of cases. MF is characterized by the presence of a clonal T-cell population in the cutaneous environment and, in the early stages of the disease, presents as scaly patches or plaques, which may resemble eczema or psoriasis in appearance and are often associated with pruritus. As the disease progresses, patients may experience the growth of nodular lesions and large tumours, also with severe pruritus, which may ulcerate and result in chronic septicaemia, thrombosis, and pain.

SS is the 'leukaemic' form of CTCL, in which the dominant T-cell population also circulates in the peripheral blood and may affect internal organs such as the lungs and spleen. MF/SS is classified into clinical stages from IA (the earliest stage) to IVB according to the degree of skin, lymph node, peripheral blood, and visceral organ involvement.[49,50]

Except for allo-transplantation which can be curative in some patients, there are no curative therapies for CTCL. Treatment is usually directed towards palliation and the induction of long-term remissions. The aim is to reduce or clear skin lesions, including tumours, and reduce pruritus, thereby providing symptom relief and improving patient quality of life.[48] In the early stages of MF, treatment usually involves skin-directed therapies such as topical corticosteroids, topical chemotherapy (nitrogen mustard or bis-chloronitrosourea), or phototherapy (narrow-band UVB or PUVA). Systemic therapies, including chemotherapy and biological response modifiers (interferon [IFN]-α, bexarotene), brentuximab vedotin or mogamulizumab, are used if the disease progresses or for those who present with more advanced-stage disease, often in combination with skin-directed therapies.[51]

PUVA, in which patients take an oral formulation of 8-MOP to induce photoactivation followed by exposure of their skin to UVA radiation, is a widely used and effective skin-directed therapy for early-stage, skin-localized CTCL, which can produce relatively long-lasting remissions.[51] It is, however, associated with the short-term side-effects of oral psoralen intake and possible long-term complications such as photosensitivity and the potential for the development of skin cancer.[4] ECP has enabled the safety profile of PUVA to be improved, avoiding the potential complications associated with long-term skin exposure to UVA. Thus, the benefits of ECP therapy can be extended to patient populations with more advanced disease stages, including those patients with malignant clones in the peripheral blood.[4] Many studies have demonstrated that ECP is of significant value for the treatment of CTCL.[52]

However, due to the low prevalence of CTCL and the fact that ECP therapy is only available in specialized centres, there are no prospective, placebo-controlled, randomized clinical trials that evaluate the impact of ECP treatment on survival available in the literature. Thus, comparisons are usually made with historical controls. The initial ECP study in patients with CTCL resistant to other treatments was reported by Edelson *et al.* in 1987 and showed it to be a promising therapy.[2] Among thirty-seven patients, twenty-seven (73%) responded to treatment, with an average decrease of 64% in cutaneous involvement; nine of these patients had a complete response (CR). Data from this study have recently been reanalysed using currently accepted international criteria. The skin overall response rate was 74%; 33% of patients were achieving ≥50% partial skin response, and 41% of patients were achieving ≥90% improvement.[53] An update on the overall survival (OS) of these patients was also provided. Overall survival times were 9.2 and 6.6 years from disease onset and initiation of ECP, respectively.

Since 1987, numerous studies employing ECP have been conducted. A meta-analysis of nineteen studies covering more than 400 patients at all stages of CTCL reported a combined overall response (OR) rate of 56% for ECP monotherapy and 56% when used in combination with other agents, and a CR rate of 15% and 18%, respectively.[54] For erythrodermic disease, the OR rate was 58%, and the CR rate was 15%. Importantly, ECP was effective in SS, showing an OR rate of 43%, with a CR rate of 10%. Table 3, adapted from the UK consensus statement on the use of ECP for the treatment of CTCL and GvHD, provides a summary of the published response rates with ECP in the treatment of CTCL from 1987 to 2011.[55] Based on the 30 separate studies in 689 patients published from 1987 to mid-2007 that were analysed in the UK consensus statement, the mean OR rate in the studies was 63% (range 33–100%), and response rates were generally higher among patients with erythrodermic CTCL.[55] The CR rates, where recorded, ranged from 0% to 62% (mean 20%). More recent studies published from late 2007 to 2011 report OR rates ranging from 42% to 80%, with CR rates ranging from 0% to 30%.[56-62]

ECP is beneficial in the treatment of CTCL.[52] However, it is also apparent that there are considerable differences in response rates between centres and the type of device used. Differences in the selection of patients, stage of the disease, prior treatments, treatment schedule of ECP, and the definition of response used might explain the large variability in the study results.[55] Similar considerations apply to studies reporting on survival rates of patients with CTCL treated with ECP. Variable median survival

Table 3 Summary of studies using extracorporeal photopheresis as monotherapy or in combination with other therapies for the treatment of cutaneous T-cell lymphoma (adapted from Scarisbrick *et al*.[55])

	Patients (*n*)	OR (%)	CR (%)	PR (%)	MR (%)
Edelson *et al*., 1987[2]	37 (erythrodermic 29)	73 (27/37) 83 (24/29)	24 (9/37)	35 (13/37)	14 (5/37)
Heald *et al*., 1989[64]	32 (erythrodermic 22)	NK 86 (19/22)	23 (5/22)	45 (10/22)	18 (4/22)
Nagatani *et al*., 1990[151]	7	43 (3/7)	NK	NK	
Zic *et al*., 1992[152]	20	55 (11/20)	25 (5/20)	30 (6/20)	
Koh *et al*., 1994[153]	34 (erythrodermic 31)	53 (18/34)	15 (5/34)	38 (13/34)	
Prinz *et al*., 1995[154]	17 (erythrodermic 3)	71 (12/17)	0 (0/17)	41 (7/17)	29 (5/17)
Duvic *et al*., 1996[155]	34 (erythrodermic 28)	50 (17/34)	18 (6/34)	32 (11/34)	
Gottlieb *et al*., 1996[65]	28 (erythrodermic NK)	71 (20/28)	25 (7/28)	46 (13/28)	
Stevens *et al*., 2002[156]	17 (erythrodermic)	53 (9/17)	29 (5/17)	24 (4/17)	
Zic *et al*., 1996[66]	20 (erythrodermic 3)	50 (10/20)	25 (5/20)	25 (5/20)	
Konstantinow *et al*., 1997[157]	12 (erythrodermic 6)	67 (8/12) 50 (3/6)	8 (1/12) 0 (0/6)	42 (5/12) 50 (3/6)	17 (2/12)
Miracco *et al*., 1997[158]	7	86 (6/7)	14 (1/7)	71 (5/7)	
Russell-Jones *et al*., 1997[159]	19 (erythrodermic)	53 (10/19)	16 (3/19)	37 (7/19)†	
Vonderheid *et al*., 1998[160]	36 (erythrodermic 29)	33 (12/36) 31 (9/29)	14 (5/36) 10 (3/29)	19 (7/36) 21 (6/29)	
Zouboulis *et al*., 1998[161]	20	65 (13/20)	NK	NK	
Jiang *et al*., 1999[162]	25 (erythrodermic)	80 (20/25)	20 (5/25)	60 (15/25)	
Bisaccia *et al*., 2000[69]	37	54 (20/37)	14 (5/37)	41 (15/37)	
Crovetti *et al*., 2000[163]	30 (erythrodermic 9)	73 (22/30) 66 (6/9)	33 (10/30) 33 (3/9)	40 (12/30) 33 (3/9)	
Wollina *et al*., 2000[164]	20	65 (13/20)	50 (10/20)	15 (3/20)	
Wollina *et al*., 2001[165]	14	50 (7/14)	29 (4/14)	21 (3/14)	
Bouwhuis *et al*., 2002[166]	55 SS	80 (44/55)	62 (34/55)	18 (10/55)	
Knobler *et al*., 2002[167]	20 (erythrodermic 13)	50 (10/20) 85 (11/13)	15 (3/20) 15 (2/13)	54 (7/13)	15 (2/13)
Suchin *et al*., 2002[67]	47	79 (37/47)	26 (12/47)	53 (25/47)	
Quaglino *et al*., 2004[168]	19	63 (12/19)	NK	NK	
De Misa *et al*., 2005[169]	10 (advanced SS)	60 (6/10)	10 (1/10)		
Rao *et al*., 2006[170]	16	44 (7/16)	NK	NK	
Gasova *et al*., 2007[171]	8 (2 with CTCL)	100 (2/2)	NK	NK	
Tsirigotis *et al*., 2007[56]	5 (SS 2)	80 (4/5)	20 (1/5)	60 (3/5)	
Arulogun *et al*., 2008[57]	13 (all SS; 12 erythrodermic)	62 (8/13)	15 (2/13)	46 (6/13)	
Booken *et al*., 2010[58]	12 (all SS)	33 (4/12)	0 (0/12)	33 (4/12)	
McGirt *et al*., 2010[59]	21 (18 erythrodermic)	57 (12/21)	14 (3/21)	19 (4/21)	24 (5/21)
Quaglino *et al*., 2013[62]	48 (all erythrodermic;12 MF, 36 SS)	60 (29/48)	13 (6/48)	48 (23/48)	
Raphael *et al*., 2011[61]	98 (all erythrodermic)	74 (73/98)	30 (29/98)	45 (44/98)	
Talpur *et al*., 2011[60]	19 (all early-stage MF)	63 (12/19)	11 (2/19)	53 (10/19)	

CR, complete response; MF, mycosis fungoides; MR, minor response (>25% improvement in skin scores); NK, not known; OR, overall response (CR + PR); PR, partial response (>50% improvement in skin scores); SS, Sézary syndrome; CTCL, cutaneous T-cell lymphoma.
†Combined PR and MR.

data have been reported for SS, ranging from 30 to 60 months. Much longer median survival times for CTCL patients treated with ECP have been reported, but not all patients in these studies had the erythrodermic disease, or they had received other therapies in combination.[63-66]

In most case series, ECP was used as monotherapy or in conjunction with other treatments. Such combination therapies have been investigated to further improve response rates, particularly in patients with a high tumour burden. Raphael *et al*.[61] published the most extensive case series of CTCL patients treated with ECP. The group reported on their 25-year experience from a total of 98 erythrodermic CTCL patients treated with ECP for a minimum of 3 months. A significant clinical improvement was obtained in 75% of patients with a multimodality therapy;

30% achieved CR. Previously, Suchin *et al.* reported on 47 patients who had received at least six cycles of ECP. In these patients, stage III or IV CTCL was diagnosed in 68%, and malignant T cells were detected in the blood of 89%.[67] Thirty-one patients received treatment with ECP plus other drugs, including IFN-α, IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) or systemic retinoids for 3 months at least. Overall, 79% of the patients responded well to therapy; 26% were achieving CR. Among patients receiving combination therapy, 84% responded well to therapy, and 20% were attaining CR; the OR rate with ECP monotherapy was 74% (CR rate was 38%). The median survival times were 74 months for the combination therapy and 66 months for ECP monotherapy; the difference was not statistically significant.

A prospective observational study of 48 patients with erythrodermic CTCL (thirty-six with SS) reported a response rate of 58% for ECP alone, compared with 64% for combination therapy in patients with more adverse prognostic factors.[62] Similarly, Duvic *et al.*[68] reported on a slightly higher response rate among 32 patients treated with ECP in combination with IFN-α, bexarotene, or GM-CSF compared with 54% for ECP monotherapy. A number of other studies with ECP plus IFN-α have been published that report an increased response rate compared with ECP monotherapy.[65,69] However, none of these studies was controlled or randomized, making it difficult to assess how much of the clinical benefit is due to IFN-α and ECP and what the magnitude of potential synergistic effects is.

In the USCLC review of the 34 patients presenting with SS treated with ECP, IFN, and bexarotene, 30 patients (88.2%) responded to the combined therapy, including eleven patients with CR (32.4%).[70] Bexarotene oral dosages ranged from 75 to 450 mg per day. Subcutaneous dosages of IFN-α and IFN-γ ranged from 1.5 to 6 MU given three times a week and 40 to 100 μg given five times a week, respectively.

A total of 97 CTCL patients included in five UK sites (2010–2015) were investigated.[71] Patients tended to be treated early in the course of their disease (median time from diagnosis of CTCL to ECP therapy was 4.6 months). In 45.4% of cases, ECP was used as first-line systemic therapy. Most patients had advanced disease stage IIIA-IVA2 at the start of treatment, but three had early-stage MF (treated for 2, 34 and 148 cycles, respectively). The intention to treat response rate at 6 months was 61.2% (60/97 patients). The median duration of ECP therapy was 9 months (range 1–118 months), and the median number of treatments was 16 cycles (range 1–148). Most patients (72%) were receiving concurrent systemic therapy at the start of treatment. The authors concluded that distinct long-term responders might have improved survival. However, these results may be confounded by other prognostic factors.

Extracorporeal photopheresis has also been used in combination with total skin electron beam (TSEB) therapy. A retrospective study of 44 patients with erythrodermic MF/SS treated with TSEB with or without ECP reported an overall CR rate of 73%; the 3-year disease-free survival rate was 63%.[72] Among those patients who were receiving TSEB plus ECP, the 3-year disease-free survival rate was 81% compared to 49% for TSEB monotherapy. Based on these data, further studies using the combination of TSEB and ECP are warranted.

Most of the studies with ECP in CTCL have primarily included patients with advanced stages of the disease. Recent guidelines recommend ECP as first- or second-line therapy for erythrodermic MF and SS.[51,55,73-76] Its use in early stages of CTCL is controversial but warrants further investigation. A literature review of data from 16 studies with ECP or ECP plus adjuvant therapy performed between 1987 and 2007 included a total of 124 patients with early-stage CTCL (stage IA, IB, IIA). This study revealed that response rates ranged from 33% to 88% for ECP monotherapy and 50–60% for ECP plus adjuvant therapy.[77] Furthermore, many early-stage patients treated with ECP achieved long-lasting regression of the disease. In a recent prospective clinical trial, 19 patients with early-stage MF were treated with one ECP cycle every 4 weeks for 6 months.[60] Patients with a partial response (PR) continued with ECP monotherapy for another 6 months, whereas non-responders were allowed to receive additional therapy with oral bexarotene and/or IFN-α. The OR rate for ECP monotherapy was 42% (8/19, including 1 CR; 7 PRs), with an overall duration of response of 6.5 months (range 1–48). Seven patients with stable disease at 3 months received additional bexarotene and/or IFN-α, and four of these patients (57%) responded to therapy. For all 19 patients, the OR rate was 63% (2 CRs, 10 PRs). Most guidelines do not indicate the use of ECP in early-stage disease, but the National Comprehensive Cancer Network (NCCN) Guidelines recommend ECP in patients with stage IA, IB, and IIA refractory disease.[76]

In summary, ECP administered as monotherapy or in combination with other immunotherapies can be alternative treatment options that have proven effective and might beneficially impact survival rates in patients with advanced CTCL, i.e., a patient population who is typically resistant to conventional treatments and, therefore, shows poor prognosis. Given the favourable side-effect profile of ECP compared with other therapies and its demonstrated efficacy in late-stage CTCL, this treatment modality might also be useful in earlier stages of the disease as recently suggested by Talpur *et al.* and others.[52,60] However, there is substantial intersubject variability in response to ECP therapy in CTCL disease. Therefore, attempts have been made to characterize and identify those patients who are most likely to respond to therapy.

Baseline predictors of response to photopheresis have recently been summarized (see Table 4).[78] Although these criteria are useful in identifying responders to ECP, these criteria consistently need to be adapted and improved.[79] A critical factor for the success of ECP therapy is that the patient's immune system

Table 4 Baseline predictors of response to photopheresis in the treatment of CTCL

Low tumour load of malignant T cells	Parameter	Reference
Skin	Erythroderma	62,172
	Plaques <10–15% total skin surface	173,172
Blood	Lower percentage of elevated circulating Sézary cells	174,61,59
	Lower CD4/CD8 ratio <10–15	174,175,61,62
	Lower % CD4+ CD7− <30%	156,61
	Lower % CD4+ CD26− <30%	61
	Normal LDH levels	175,62
	B0 or B1 blood-stage	62
	Lymphocyte count <20 000/μL	173
Lymph nodes	Lack of bulky adenopathy	173
Visceral organs	Lack of visceral organ involvement	173
Peripheral blood involvement		
	B1 blood stage > B2 blood stage	62,81,173
	Presence of a discrete number of Sézary cells (10–20% mononuclear cells)	172
Relatively intact immune system		
	Higher % monocytes >9%	61
	Increased eosinophil count >300/mm^3	59
	No previous intense chemotherapy	176,173
	Short disease duration before ECP (<2 years from diagnosis)	173,62
	↑ NK cell count at 6 months into ECP therapy	154,62
	Near-normal NK cell activity	172
	Normal CD3+ CD8+ cell count >200/mm^3	62
	High levels of CD4+ Foxp3+CD25− cells at baseline	177
Other monitored factors		
PBMC microRNA levels	↑ miR-191, ↑ miR-223, ↑ miR-342 at 3 months into ECP monotherapy	178
Soluble IL-2 receptor	↓sIL-2R at 6 months into ECP	170
Neopterin	↓ neopterin at 6 months into ECP	170
Beta^2-microglobulin	↓ beta^2-microglobulin at 6 months into ECP	170
Response at 5-6 months of ECP	Predicts durable response and long-term survival	156,66

LDH, lactate dehydrogenase, NK natural killer, ECP, extracorporeal photopheresis, PBMC, peripheral blood mononuclear cell.
Adapted from Zic JA. Extracorporeal photopheresis in the treatment of mycosis fungoides and Sézary syndrome.[78]

must be capable of responding appropriately to malignant cells that have undergone photoactivation.[80,81]

Existing clinical guidelines

Several professional organizations have set up guidelines on the management of CTCL and the use of ECP. In 2006, the European Organisation for Research and Treatment of Cancer (EORTC) recommended ECP for the first-line treatment of SS and MF stage III with a C-strength of recommendation (on a scale from A to D).[51,73] In MF, the level of evidence was rated 4 (evidence from case series, poor-quality cohort or case-control studies), and in SS, 2b (evidence from individual cohort study or poor-quality, randomized, controlled trial). Although not recommended by EORTC, it was mentioned that ECP treatment is usually performed on two consecutive days at 4-week intervals, continued for up to 6 months, and followed by maintenance therapy.

The UK Photopheresis Expert Group consensus statement recommends ECP for the treatment of patients with CTCL if they fulfil the criteria of erythroderma and stage III or stage IVA CTCL and at least one of the minor criteria, which are: (i) circulating clonal disease (circulating T-cell clone proven by polymerase chain reaction or Southern blot analysis), (ii) evidence of circulating Sézary cells (>10% of circulating lymphocytes), and (iii) a CD4/CD8 ratio higher than 10.[55] The recommended ECP treatment schedule is one cycle on two consecutive days every 2–4 weeks. It may be administered more frequently in symptomatic patients and those with a high blood tumour burden. At the maximum clinical response, ECP treatment should be tapered to one cycle every 6–12 weeks before it is completely stopped. However, in a very recent update from 2017, the UK Photopheresis Expert Group revised its recommendations and suggested continuing with ECP treatment in patients with complete, partial, or minimal clinical response.[82] This revised recommendation is in keeping with other treatments for advanced MF/SS. They should be continued for as long as a clinical benefit is detectable including improvements leading to better quality of

life which may encompass improved functionality, reduced symptoms and improved well-being. Despite not reaching a partial response (better by 50%) in skin diseases, continuous treatment is recommended. However, in some patients, a durable response of more than five years has been observed with ECP, which is markedly better than conventional therapy with a median survival time of about three years in advanced-stage patients.[82]

Guidance on the monitoring of treatment success is also provided. Assessments at 3-month intervals will allow non-responders to be offered a combinatory or alternative therapy to ensure that ECP treatment is not unnecessarily prolonged.

In 2006, the British Photodermatology Group and the UK Skin Lymphoma Group reported on the use of ECP in a variety of clinical conditions based on data that were derived between 1987 and 2001.[83]. These groups concluded that there is (i) 'fair' evidence of the clinical benefit of ECP in patients with erythrodermic MF/SS (stage III/IVA/B1/0), with a strength of recommendation B (on a scale from A to E) based on a level of evidence of II1 (i.e. derived from well-designed, non-randomized, controlled trials); (ii) 'fair' evidence that supports the use of TSEB plus ECP for erythrodermic MF/SS patients, with a strength of recommendation B, level of evidence II2 (i.e. well-designed cohort or case-control studies); and (iii) 'poor' evidence that supports the use of IFN-α plus ECP for erythrodermic MF/SS, with a strength of recommendation C, level of evidence II2. Per standard protocol, ECP treatments should be performed on two consecutive days per month, continued for up to 6 months, and followed by tapering or maintenance treatment in those patients who have adequately responded. The treatment intervals can be shortened to biweekly cycles in poor responders, or ECP can be combined with other therapeutic agents such as IFN-α. Recommended time points on patient assessments and appropriate efficacy parameters are also listed. These recommendations have also been updated and adopted in the 2018 British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas.[84]

The US National Cancer Institute recommends ECP for the therapy of MF and SS.[75] ECP is offered as an option for the treatment of stage III MF/SS and, either alone or in combination with TSEB, for the treatment of stage IV MF/SS. For patients with recurrent MF/SS, it is noted that ECP has produced tumour regression in those patients who were resistant to other therapies. No information was given on the appropriate monitoring of therapy or outcomes.

In 2012, the NCCN clinical guidelines on MF/SS stated that their recommendations are all based on category 2A evidence (lower level evidence). ECP was recommended as first-line therapy for stage IV SS alone, or in combination with interferon or bexarotene. The guidelines also suggest that ECP may be used in relapsed or refractory stage III disease, and stages IA, IB-IIA, which are refractory to skin-directed therapy.[76]

The United States Cutaneous Lymphoma Consortium (USCLC) reviewed available therapeutic options for SS.[70] Based on level II2 evidence, ECP was classified as category A systemic monotherapy. Level II2 evidence means that information was obtained from at least one prospective, well-designed cohort or a case-control study, preferably from more than one centre or research group. Similarly, TSEB plus ECP, alone and in combination with IFN-α, IFN-γ, or bexarotene and ECP plus bexarotene, IFN-α, IFN-γ, or low-dose methotrexate alone or in combination are alternative therapeutic options.

Finally, the German Association of the Scientific Medical Societies (AWMF) provides guidance on the staging, assessment, diagnosis, and therapy of cutaneous lymphomas.[85,86] ECP was recommended as first-line therapy for stage III erythrodermic MF and for SS. Their guidelines stated that ECP could be combined with IFN-α, methotrexate, bexarotene, or PUVA. The AWMF also commented on the excellent safety profile of ECP. No rating of the grade of recommendation or level of evidence was given, and no information was provided on how these guidelines were prepared.

Recommendations

Patient selection ECP should be considered as first-line therapy for patients with MF/SS as follows:

- Erythrodermic MF stages IIIA or IIIB (B0 or B1) according to the revised International Society for Cutaneous Lymphomas (ISCL)/ EORTC classification).[49]

Even though case series have suggested that there is a potential benefit of ECP in patients with early-stage disease (stage IA, IB, IIA), the consensus decision was that this application should only be considered for clinical trial purposes, as a variety of other effective, safe, and easily accessible treatment options are available for use at these stages.[60]

- MF/SS Stage IVA1 (T1-T4, N0-2, M0, B2)
- MF/SS Stage IVA2 (T1-T4, N3, M0, B0-2)

Treatment schedule The recommended ECP treatment schedule is one cycle (i.e. one ECP procedure per day on two consecutive days) every 2 weeks for the first 3 months followed by an ECP cycle every 3–4 weeks. However, there is no optimal therapy, and other published guidelines have recommended one cycle every 2–4 weeks followed by tapering after the maximum response has been achieved.[55]

Currently, there are no data in the literature that support the concept of increased clinical efficacy if the frequency of ECP cycles rises. However, based on common clinical experience, it is assumed that an initially higher frequency of ECP treatments may result in a significant improvement of subjective symptoms, particularly in CTCL patients suffering from itchiness and those

with B2 staging. Based on the patient's compliance, a standard treatment regimen could also be performed, according to the policies and possibilities at the centre. Treatment of CTCL patients should be continued for 6 months at minimum before the response to ECP is evaluated. At maximum response, treatment should slowly be tapered to one treatment cycle every 4–8 weeks for maintenance therapy. In patients with a favourable response or disease stabilization and good quality of life, ECP treatment should be extended to more than 2 years. Treatment intervals should be progressively prolonged to up to 8 weeks. Patients who do not respond to ECP as first-line therapy should be considered for combination therapies (i.e. ECP plus other drugs or interventions). IFN and/or bexarotene should be used in combination with ECP. Skincare and topical medications, including topical steroids and emollients, should also be prescribed to help alleviate ongoing symptoms.

In CTCL, patients with leukemic involvement and high white blood cell counts (i.e. >20 000 mm^3), a cytoreductive treatment (debulking chemotherapy or alemtuzumab) aimed at decreasing the number of leukemic peripheral cells can be performed prior to the start of ECP therapy (potentially blunting and thus reducing the immune response). Also, local radiotherapy can be performed either before or during ECP to treat localized infiltrated skin lesions. While the combination of ECP with histone deacetylase inhibitors appears potentially useful, there are no published data available which support this approach at present. HDAC inhibitors may also blunt the immune response and might likely inhibit the generation of an optimal response to ECP.

Systemic concurrent therapies can be initiated at any time point. However, the consensus is that ECP monotherapy should be continued for at least 3 months before another drug or therapy is added. If patients are already on other therapies (bexarotene and/or IFN), ECP can be added without the withdrawal of the previous treatment.

Response assessment Response assessments should be performed every 3 months according to the ISCL/EORTC/USCLC consensus statements.[49,70,87] Based on clinical experience, responses to ECP therapy are not immediate and may take 3–6 months before a clinical response is observed. Thus, it was agreed that there should be at least 6 months of treatment and evaluation of the response to ECP before conclusions on its efficacy are being drawn. If CR is observed in CTCL patients, ECP treatment should not be stopped. Instead, ECP intervals should be extended to up to 8 weeks. If PR or stable disease is observed, the consensus statement suggests that the efficacy of combining ECP therapy with other treatments or increasing the frequency of ECP treatments should be evaluated. Similar recommendations are made for the case of progressive CTCL disease. Alternatively, ECP may be stopped in favour of other CTCL therapies.

Chronic graft-versus-host disease

Chronic GvHD (cGvHD) is a multisystem disorder occurring in the range of 30 to 50% of patients after allogeneic transplant.[88]

The likelihood of cGvHD rises with the use of unrelated, mismatched, older, or multiparous donors, in older recipients, and with the application of reduced-intensity conditioning (RIC). RIC transplants are recognized for having haematological malignancies; notably, due to myeloid leukaemia, the number of patients with cGvHD has increased in recent years.[89] Non-myeloablative and RIC treatment regimens enable older patients or comorbid patients presenting with myeloid malignancies to be treated by allogeneic haematopoietic cell transplantation (HCT).

The difficulty of finding the optimal treatment vs. risk balance between cGvHD relapse, significant morbidity, and non-relapse mortality has been addressed by Kuzmina *et al.*[90] The first report on the successful treatment of cGvHD by use of ECP was published in 1994.[91] A more recent prospective multicentre study by Arora *et al.* performed between 2011 and 2014 at thirteen locations in the US reports on a cohort of 911 HCT patients (55% RIC). The authors of this study detected an incidence of 47% (95% confidence interval [CI]: 44%–51%) for cGvHD 2 years after the start of HCT.[92] The median time to the onset of cGvHD was 7.4 months or 222 days (range: 0.8–45.1 months). Oral mucosa was the most common site involved (59%), followed by skin (57%) and liver (56%). According to the National Institutes of Health (NIH) Consensus Conference, cGvHD symptoms were classified as mild in 19%, moderate in 53%, and severe in 28% of the patients. Among the 428 cGvHD patients, non-relapse mortality was 12% (95% CI: 9%–16%). The probability of overall survival was 81% (95% CI: 76%–85%) 2 years after the diagnosis of cGvHD. The 2-year non-relapse mortality was 11% (95% CI: 5%–24%) for mild, 8% (95% CI: 5%–13%) for moderate, and 18% (95% CI: 12%–28%) for severe cGvHD. Among all patients with cGvHD, only 11% (95% CI: 8%–16%) were able to discontinue the entire immunosuppression 1 year after cGvHD diagnosis. Patients with severe GvHD were less likely (9%) to discontinue immunosuppression as compared to those with moderate (12%) or mild GvHD (18%).

The pathogenesis of cGvHD remains poorly understood. cGvHD is an immune-mediated disease resulting from the interactions between the donor graft and the recipient's immune system. The donor T cells are the primary aggressors causing antibody-mediated damage. There is increasing recognition that B cells may have a role in the initiation and progression of cGvHD pathogenesis by altered B-cell homeostasis and disruption of tolerance mechanisms.[93] Cytokine dysregulation is implicated with high levels of IL-6, IFN-γ, TNF-α, IL-12, IL-17, and low levels of IL-10.[94]

The varied manifestations of cGvHD make the diagnosis and monitoring of the multisystem disorder difficult and comparing

different clinical studies can be challenging. Criteria for the diagnosis and staging of clinical trials in cGvHD have recently been updated by Jagasia *et al.* to standardize diagnosis and assessment of response to treatment. Established first-line treatment of cGvHD is with glucocorticosteroids (~1 mg/kg bodyweight of prednisone equivalent).[95] An established first-line treatment of cGvHD uses the administration of glucocorticosteroids (~1 mg/kg bodyweight of prednisone equivalent). The addition of a calcineurin inhibitor may be considered, if appropriate.[96] In some patients, second-line therapy must be initiated. However, the choice of second-line agent varies considerably between centres and is often selected on an individual patient basis. Second-line treatment options include the administration of ECP, mycophenolate mofetil, mTOR inhibitors, methotrexate, imatinib, rituximab and ruxolitinib.[97]

Extracorporeal photopheresis is an attractive treatment option exerting glucocorticosteroid-sparing effects and showing response rates of approximately 60% in cGvHD patients.[82] In 2008, Scarisbrick *et al.*[55] reviewed 23 studies, including a total of 633 patients presenting with cGvHD who underwent ECP treatment between 1987 and 2001. Response rates were determined based on organ involvement. The mean response rate was 68% (range, 29%–100%) in cutaneous cGvHD as derived from eighteen studies (patients evidencing CR were included in this analysis). In patients with hepatic involvement, the mean response rate was 63% (10 studies). Likewise, the mean response rate was 63% (9 studies) in patients presenting with mucosal involvement. An updated review of the literature reveals that thirteen additional investigations, comprising a total of 492 patients, are available for the analysis of response rates of the skin, liver, and oral manifestations in cGvHD patients. Response rate ranges were 31%–93% for the skin, 29%–100% for the liver, 21%–100% for oral disease, resulting in an overall response rate ranging from 36% to 83% (Table 5).

These data suggest that ECP is an effective treatment option for patients with cGvHD affecting skin, liver or oral mucosa. However, differences in the selection criteria of patients, and the use of different first-line therapies, and second-line treatment combinations may be the reason for the large variability in reported response rates. Alfred *et al.* investigated the results of 725 adult patients with either steroid-resistant, steroid-intolerant or steroid-dependent cGvHD.[82] Response rates for cutaneous cGvHD were available from 23 studies showing a mean response rate of 74%. Response rates for hepatic cGvHD were available from fifteen studies that resulted in a mean response rate of 62%. Also, another twelve studies reported on mucosal cGvHD response rates resulting in a mean value of 62%. Response rates for pulmonary, ocular, and gastrointestinal involvement were 46%, 60%, and 46%, respectively. The overall response rate from a cross-section of fourteen studies was 68% (Table 6).

Jagasia *et al.* recently reported on a randomized, prospective study investigating ECP use as first-line therapy in cGvHD, based on the 2015 NIH consensus criteria for diagnosis and response assessment. The addition of ECP to standard of care was compared to standard of care alone. ORR at week 28 was 74.1% (ECP arm) vs. 60.9% (control arm). Patients in the ECP arm tolerated the treatment well while maintaining quality of life (QoL).[98] QOL is an important facet of survival post-HSCT, and scores in cGvHD are comparable to other chronic conditions such as multiple sclerosis and scleroderma.[99] Maintaining or improving QoL has also been demonstrated in other ECP studies of cGvHD.[100-103] There is also emerging evidence to suggest that ECP helps maintain response to viral infections while also not increasing the risk of relapse, which is of clinical importance in this group of patients.[104,105]

Flowers *et al.*[103] published the first multicentre, randomized, controlled, prospective phase II trial of ECP in 95 patients with steroid-refractory/-dependent/-intolerant cGvHD. The primary efficacy end-point of the study was a blinded quantitative comparison of percentage change from baseline in Total Skin Score (TSS) of 10 body regions at week 12. The median percentage improvement in TSS at week 12 was 15% for the ECP arm compared with 9% for the control arm – a non-significant difference.

Table 5 Extract of studies using extracorporeal photopheresis in adult patients with chronic graft-versus-host disease

	Patients (*n*)	CR/PR skin (%)	CR/PR liver (%)	CR/PR mouth (%)	OR (%)
Greinix *et al.*, 1998[119]	15	80	70	100	NK
Apisarnthanarax *et al.*, 2003[179]	32	59	0	NK	56
Seaton *et al.*, 2003[180]	28	48	32	21	36
Foss *et al.*, 2005[181]	25	64	0	46	64
Rubegni *et al.*, 2005[182]	32	81	77	92	69
Couriel *et al.*, 2006[183]	71	57	71	78	61
Greinix *et al.*, 2006[184]	47	93	84	95	83
Flowers *et al.*, 2008[103]	48	40	29	53	
Dignan *et al.*, 2012[185]	82	92	NK	91	74
Greinix *et al.*, 2011[186]	29	31	50	70	NK

CR, complete response; NK, not known; OR, overall response; PR, partial response.

Table 6 Summary of studies using extracorporeal photopheresis in paediatric patients with chronic graft-versus-host disease

	Patients (*n*)	CR/PR skin (%)	CR/PR liver (%)	CR/PR mouth (%)	Comment
Rossetti *et al*., 1995[187]	7	33 (2/6)	100 (1/1)	-	50% (2/4) lung CR
Dall'Amico *et al*., 1997[188]	4	67 (2/3)	-	-	67% (2/3) lung improved
Salvaneschi *et al*., 2001[114]	14	83 (10/12)	67 (6/9)	67 (8/12)	79% OS
Halle *et al*., 2002[189]	8	88 (7/8)	67 (4/6)	-	100% OS
Perseghin *et al*., 2002[190]	9	88 (7/8)	100 (2/2)	67 (2/3)	-
Perutelli *et al*., 2002[191]	7	-	-	-	43% (3/7) CR; 57% (4/7) improved
Messina *et al*., 2003[115]	44	56 (20/36)	60 (12/20)	-	77% OS
Duzovali *et al*., 2007[192]	7	-	-	-	43% (3/7) improved; 43% (3/7) died
Kanold *et al*., 2007[116]	15	75 (9/12)	82 (9/11)	86 (6/7)	67% (10/15) alive
Perseghin *et al*., 2007[193]	25	67 (4/6)	67 (4/6)	78 (7/9)	76% (19/25) alive
Gonzales-Vicent *et al*., 2008[117]	3	100 (2/2)	100 (2/2)	-	100% (3/3) alive
Perotti *et al*., 2010[118]	23	96 (22/23)	100 (4/4)	80 (4/5)	83% (19/23) alive at 5 years

CR, complete response; PR, partial response; OS, overall survival.

However, significantly more patients in the ECP arm had a complete or partial skin response, as assessed by the clinical investigators ($P < 0.001$). At week 12, the proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease in TSS was 8% in the ECP arm vs. 0% in the control arm ($P = 0.04$).

The safety profile of ECP is excellent, with only minimal side-effects and no long-term complications. When compared to other immunosuppressive therapies currently available for the treatment of cGvHD, ECP is not associated with organ toxicities, the occurrence of opportunistic infections, treatment-emergent adverse events or underlying disease relapse.[97,98,104,105]

Review of recent guidelines

Extracorporeal photopheresis is recommended as second-line therapy for steroid-intolerant, steroid-refractory or steroid-dependent cGvHD including but not limited to skin, oral mucosa, and liver involvement.[55,97,106,107] ECP should be performed weekly or every 2 weeks for a minimum of 3 months. The updated NIH criteria for measuring response in cGvHD patients should be used, and treatment should be tapered in responders.[82,108]

In 2013, an update of the ECP guidelines was provided by the *Societa Italiana di Emaferesi e Manipolazione Cellulare* (SIdEM) and the *Gruppo Italiano Trapianto Midollo Osseo* (GITMO) for both adult patients and paediatric patients with steroid-resistant or steroid-dependent cGvHD, irrespective of the extent and severity of the disease.[101] Also, it was noted that ECP might exert a potentially steroid-sparing effect and improve the quality of life in responding patients. SIdEM and GITMO recently published a review article on the assessment of best practices among twenty-four Italian centres investigated.[100]

In 2017, the UK Photopheresis Society published an update of its 2008 Guidelines.[82] For cGvHD of the skin, liver, and oral mucosa, they recommend ECP as second-line therapy in steroid-refractory, steroid-intolerant or steroid-dependent patients. Two treatments per week (one cycle) performed at 2-week intervals and a monitoring schedule according to the updated NIH criteria are stipulated.[108]

The American Society for Apheresis recommends ECP for second-line therapy of cutaneous and non-cutaneous cGvHD (level of evidence cII), either as monotherapy or in conjunction with other therapies.[109]

Recommendations

Patient selection Extracorporeal photopheresis should be considered as second-line therapy in patients with steroid-dependent, steroid-intolerant or steroid-resistant cGvHD and those with recurrent infections or a high risk of relapse of their underlying disease.

Patients ineligible for ECP include those with leucocyte counts below 1.0 G/L, intolerance to methoxsalen, heparin, or citrate products, and haemodynamic instability due to life-threatening infections.

Treatment schedule Extracorporeal photopheresis cycles are recommended weekly (two treatments; one cycle) for the first 3 months (or until GVHD stabilizes) followed by one cycle twice per month and then tapered depending on clinical response. The time schedule is largely dependent on the severity of cGvHD and the documented response. If cGvHD progresses, a change in the treatment strategy should be considered.

Response assessment Serial response assessments should be carried out using NIH assessment criteria and performed by appropriately trained staff.[108]

Serial quality of life assessments, in addition to clinical response criteria, are recommended. Concurrent steroid and other immunosuppressive drug doses should be recorded at each assessment.

Acute graft-versus-host disease

Acute GvHD is a serious complication of allogeneic Haematopoietic Stem Cell Transplantation (HSCT) and a fundamental cause of transplant-related morbidity and mortality, mainly due to severe infections and organ toxicities.[110] Furthermore, aGvHD is an important risk factor and determinant for the development of cGvHD. Currently, the standard first-line therapy comprises the application of corticosteroids. However, <50% of patients respond to corticosteroid therapy, and thus a substantial proportion of patients presenting with aGvHD require salvage treatment.[110-113] So far, not a single immunosuppressive agent has been approved by regulatory agencies for the treatment of steroid-refractory aGvHD; as a consequence, there is large variation in its management and treatment. Martin *et al.* published recommendations by the American Society of Blood and Marrow Transplantation (ASBMT) for the treatment of aGvHD based on a comprehensive and critical review of published reports.[110] Across the 67 studies selected, a total of nineteen different agents or medical devices were investigated. Besides horse anti-thymocyte globulin (ATG), ECP was the most frequently studied therapeutic intervention. ECP was applied in approximately 300 patients with steroid-refractory aGvHD, and these numbers have been increasing over time.[114-135]

Overall, the median rates for CR and PR of cutaneous manifestations of patients are 75% each (range 50–100%). Accordingly, the median rates for CR and PR of patients with hepatic involvement are 47% each (range 0–100%), while the median rates for CR and PR of gastrointestinal manifestations are 58% each (range 0–100%). ECP was tolerated excellently as the side-effects observed were only mild in severity, consisting primarily of reversible, temporal drops in peripheral blood cell counts after the first courses of ECP.

The results of studies that employed ECP as second-line treatment of aGvHD are summarized in Table 7.[114-119,122,126-128,130] Promising first results from a preliminary study were confirmed by a pilot study performed on twenty-one aGvHD patients.[119,136]. Subsequently, Greinix *et al.* conducted a phase II study on ECP in fifty-nine steroid-refractory or steroid-dependent adult patients with severe aGvHD.[126]

In contrast to the pilot study, an intensified schedule of ECP was applied in the respective phase II study, consisting of 2–3 treatments per week until a maximum response was observed.[125,126] By using this 'intensified' ECP schedule, CR rates improved in patients with grade IV aGvHD (60% vs. 12%) and gastrointestinal involvement (73% vs. 25%) compared to results from the pilot study.[125,126,136]. The best response rates to ECP were observed after a median treatment duration of 1.3 months (range 0.5–6), and no flare-ups were detected after tapering and discontinuation of corticosteroid therapy. In ECP-responders, corticosteroid therapy was discontinued after a median of 55 days (range 17–284 days) after the start of ECP. In subsequent univariate analyses, the following parameters were identified as significantly affecting the outcome of aGvHD patients treated with ECP: (i) the grade of aGvHD, (ii) the number of organs involved at the start of ECP and first-line therapy with corticosteroids, and (iii) the cumulative corticosteroid dose given prior to ECP. However, in logistic regression analyses, a low grade of aGvHD at the start of ECP therapy and the late onset of corticosteroid drugs after HSCT were the only variables that affected CR outcomes positively. Three months after the start of ECP, the cumulative incidence of transplant-related mortality at 4 years was 14% in patients achieving CR of steroid-refractory aGvHD, compared to 73% in patients without CR ($P < 0.0001$). Patients with CR of steroid-refractory aGvHD with ECP had a significantly improved OS rate of 59%, compared to 11% in patients without CR ($P < 0.0001$). The cumulative incidence of relapse at 4 years was 28%, which was thus not increased when compared

Table 7 Summary of studies using extracorporeal photopheresis in the second-line treatment of acute graft-versus-host disease

	Patients (*n*)	CR skin (%)	CR liver (%)	CR gut (%)	OS (%)
Salvaneschi *et al.*, 2001[114]	9	67 (6/9)	33 (1/3)	60 (3/5)	67
Dall'Amico *et al.*, 2002[122]	14	71 (10/14)	57 (4/7)	60 (6/10)	57
Messina *et al.*, 2003[115]	33	76 (25/33)	60 (9/15)	75 (15/20)	69 at 5 years
Garban *et al.*, 2005[127]	12	67 (8/12)	0 (0/2)	40 (2/5)	42
Greinix *et al.*, 2006[126]	59	82 (47/57)	61 (14/23)	60 (9/15)	47 at 5 years
Kanold *et al.*, 2007[116]	12	90 (9/10)	56 (5/9)	83 (5/6)	75 at 8.5 months
Calore *et al.*, 2008[130]	15	92 (12/13)	–	100 (14/14)	85 at 5 years
Gonzales-Vicent *et al.*, 2008[117]	8	100 (8/8)	100 (2/2)	57 (4/7)	38
Perfetti *et al.*, 2008[128]	23	65 (15/23)	27 (3/11)	40 (8/20)	48 at 37 months
Perotti *et al.*, 2010[118]	50	83 (39/47)†	67 (16/24)†	73 (8/11)†	64 at 1 year
Jagasia *et al.*, 2013[139]	57	67 (38/57)†	67 (38/57)†	67 (38/57)†	59 at 2 years
Calore *et al.*, 2015[133]	72	78 (50/64)	84 (10/12)	76 (42/55)	71 at 5 years

CR, complete response; OS, overall survival; PR, partial response.
†Combined CR and PR.

with HSCT patients not receiving ECP. In general, treatment with ECP was well-tolerated.

Perotti *et al.*[118] recently reported on excellent response rates in 50 patients with steroid-refractory aGvHD and confirmed the corticosteroid-sparing effect of ECP. There was a policy of early intervention in place in patients with aGvHD, so the median time from onset of symptoms to the start of ECP therapy was only 9 days. The OR rate was 68% (32% CR and 36% PR), with almost similar response rates for skin (83%), liver (67%), and gastrointestinal tract (73%). Furthermore, the survival of ECP-responders was significantly improved (62% vs. 6%) in aGvHD patients compared to ECP non-responders ($P < 0.001$). The ability to decrease the corticosteroid dose 30 days after the start of ECP therapy was associated with a significantly reduced mortality rate, confirming the importance of sparing corticosteroid doses in aGvHD patients. Other authors have noted that the decrease of dose of corticosteroids after 30 days of therapy reflects a major advantage of ECP in the prevention of long-term complications in children.[115,116]

Several ECP studies conducted in paediatric patients with aGvHD have shown similar results to those obtained in adults. For instance, in a large, multicentre, retrospective study of thirty-three paediatric patients with steroid-refractory aGvHD, the overall rates were 54% for CR and 21% for PR.[115] The CR rates were 76% for skin symptoms, 75% for gastrointestinal manifestations, and 60% for liver involvement. The 5-year OS rate was significantly better for responders than for non-responders (69% vs. 12%; $P = 0.001$). Due to ECP therapy, immunosuppressive treatment was discontinued in eight out of nineteen survivors (42%) and reduced in another seven patients (36%). The median Karnofsky performance score improved significantly from 60% before ECP therapy to 100% (range 80–100%) after the completion of ECP therapy.

Supportive data were derived from subsequent small studies using a twice-weekly ECP treatment regimen.[117,137] In fifteen paediatric patients with steroid-refractory aGvHD, the strongest predictor of response to ECP treatment was the stage of the disease itself: there was a 100% response rate for stage II, 75% for stage III, and 0% for stage IV. The stage of aGvHD and the response to ECP therapy both turned out to be significant predictors of transplant-related mortality. A direct comparison of ECP and steroid therapy also showed somewhat better results for ECP in paediatric patients.[130] Following ECP treatment, 73% of fifteen patients showed CR; the remaining 27% showed PR. CR was recorded in 92% of patients with skin manifestations, 71% with gastrointestinal tract manifestations, and 100% with liver disease. In comparison, 56% of the 16 patients receiving steroid therapy showed CR and 31% had PR; two patients had persistent cGvHD after 1 year. CR rates were 46% for skin, 57% for gastrointestinal tract, and 67% for liver. Transplant-related mortality at day 100 of treatment was 6% for steroid therapy, but no patient died in the ECP group, and the 2-year OS rates were numerically, but not significantly, higher in the ECP groups (85%) as compared to the steroid therapy group (57%).[130]

Several authors have pointed out that the use of ECP in children might be challenging because of low bodyweight, difficult vascular access, high extracorporeal volume, metabolic and haematological problems, and psychological intolerance.[115,116,131] Nevertheless, Messina *et al.*[115] were able to treat patients with bodyweights as low as 10 kg without detecting significant side-effects. Kanold *et al.* reported on the follow-up with paediatric patients diagnosed with GvHD. The authors put particular emphasis on the technical aspects of the ECP therapy.[116] The efficacy results were similar to those from other studies (7/12 patients [58%] with aGvHD showed CR, and 3/12 [25%] showed PR). They observed good tolerability of the treatment in patients with low bodyweight and emphasized the importance of a dedicated paediatric environment and care team to manage challenges such as difficult vascular access and psychological intolerance.[116]

Calore *et al.* consecutively treated 72 paediatric patients (21 steroid-refractory, 42 steroid-dependent, 9 steroid-naïve) between 1997 and 2013, achieving CR in 72% and PR in 11% of the patients.[133] Transplantation-related mortality was 3% and 20% among responders and non-responders to ECP ($P < 0.0001$), respectively. The 5-year overall survival showed a significant difference between responders and non-responders (78% vs. 30%, $P = 0.0004$).[133]

The challenge of treating paediatric patients of low-bodyweight (as low as 15 kg) was addressed in a study of patients presenting with aGvHD or cGvHD.[131] In contrast to many groups that have used an 'offline' two-stage technique for mononuclear cell collection and irradiation, this group reported on the use of a sterile, closed-loop procedure in which patients received fluid boluses of normal saline or 5% albumin to boost blood volume before and, if needed, during the ECP treatment.[116-118] This procedure allows for the use of continuous flow ECP even in patients with low bodyweight.

In a retrospective analysis of 128 patients with steroid-refractory or steroid-dependent aGvHD treated with ECP as second-line therapy on a weekly basis, Das-Gupta *et al.* reported 6-month freedom from treatment failure of 77.3% and a 2-year survival rate of 56%.[138] Higher grades of aGvHD (grade 2 vs. grades 3-4) at the start of ECP were predictive of poor clinical outcome as determined by survival analysis (hazard ratio [HR] 2.78, $P < 0.001$); non-relapse mortality (HR 2.78, $P = 0.001$); and 6-month freedom from treatment failure (HR 3.05, $P < 0.002$). Jagasia *et al.*[139] compared ECP vs. anti-cytokine therapy as second-line treatment for steroid-refractory aGvHD in a retrospective analysis. Overall response rates were 66% and 32% in the ECP and the anti-cytokine cohort, respectively. The respective rates for CR were 54% and 20%. ECP was an independent predictor of response (HR 3.42, $P = 0.007$) and survival

(HR 2.12, $P = 0.018$). In patients with steroid-refractory aGvHD grade II, the use of ECP was associated with superior survival rates (HR 4.6, $P = 0.016$). Furthermore, the administration of ECP was associated with lower non-relapse mortality (HR 0.45, $P = 0.018$). These promising results warrant confirmation in a prospective clinical study.

In a systematic review of six prospective studies including a total of 103 patients with steroid-refractory aGvHD given ECP as salvage therapy, Abu-Dalle *et al.*[140] reported an overall response rate of 69%, including 84% for cutaneous, 65% for gastrointestinal, and 55% for hepatic manifestations. In a meta-analysis of seven prospective studies on ECP treatment in patients with steroid-refractory aGvHD, Zhang *et al.* included a total of 121 patients. The reported overall response rate was 71%, and the CR rate was 71%.[141] The efficacy rates of ECP on the skin, liver, and gut manifestations of aGvHD were 86%, 60%, and 68%, respectively.

To reduce the incidence of aGvHD, several studies investigated the use of ECP as part of the myeloablative conditioning regimen prior to HSCT. For instance, Miller *et al.* showed an unexpectedly low incidence of severe aGvHD if ECP was used as part of a novel 'reduced-intensity' conditioning regimen on –day 6 and –day 7 (prior HSCT). No disease relapse or negative effects on the engraftment were observed.[142] However, the results from a phase II study revealed that after the addition of ECP to cyclosporine and methotrexate (all given as aGvHD prophylaxis as part of a standard myeloablative regimen), the incidence of aGvHD was similar to that found by other studies.[143] The comparison of the ECP-treated group to historical controls indicated a somewhat lower incidence of aGvHD grades II-IV and improved OS of patients when ECP was introduced during the conditioning phase.[143]

Recently, Michallet *et al.* performed a prospective multicentre phase II study to evaluate the safety and efficacy of prophylactic ECP soon after the start of reduced-intensity conditioning (RIC)-HCT in 20 adult patients with haematological malignancies.[144] ECP was started on day twenty-one and was given twice per week for the first 2 weeks and then once per week for the following 4 weeks for a total of eight ECP courses. The cumulative incidence of aGvHD grades II-IV on day 100 was 15%. The 2-year OS and progression-free survival (PFS) were 84% and 74%, respectively. ECP was tolerated well, and no adverse effects related to ECP were reported.

Kitko *et al.* investigated the combination of etanercept and ECP for GvHD prophylaxis in a prospective phase II study in 48 patients undergoing RIC-HCT.[145] The cumulative incidence of aGvHD grades II-IV was 46% on day 100. The 1-year OS was 73% because of low rates of non-relapse mortality (21%) and relapse (19%). However, this strategy was ineffective in preventing chronic GvHD and late deaths. Therefore, the 2-year survival probability declined to 56%. The preventive use of ECP may have some benefits, but data from more patients with a longer duration of follow-up are needed for confirmation.

In conclusion, ECP is well-tolerated, shows an excellent safety profile in children and adults, and is highly effective in aGvHD. The early start and use of an intensified ECP schedule consisting of 2–3 treatments per week and rapid tapering of corticosteroids in steroid-refractory patients are necessary actions that might exert a significant impact on the patients' survival rate. However, more prospective clinical studies are warranted, including those studies investigating the use of ECP for prophylactic purposes.

Existing clinical guidelines

The American Society for Apheresis (ASFA) reviewed available data on ECP in aGvHD patients and concluded that OR rates for steroid-refractory aGvHD in paediatric and adult patients range from 52% to100%. Corresponding response rates for the skin, gastrointestinal tract and liver were ranging from 66% to 100%, 40% to 83%, and 27% to 71%, respectively.[146] ASFA recommends that ECP be used weekly on two consecutive days (one series) until disease response is maximized and then be tapered to every other week before discontinuation.

A joint working group established by the haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) provided guidelines on the diagnosis and management of aGvHD.[113] Based on the findings of this group, ECP is recommended as second-line therapy for the treatment of steroid-refractory aGvHD (level of evidence 2C). The BCSH/BSBMT commented on the excellent tolerability of ECP but concluded that the optimal treatment schedule and duration have not yet been established. However, Das-Gupta *et al.* reported on a regimen of weekly ECP cycles for a minimum of 8 weeks continued until maximum response or CR is observed.[147] Of note, no other immunosuppressive agent recommended by the BCSH/BSBMT obtained a higher level of evidence.

In a recent update of a consensus statement from the UK Photopheresis Society, the promising role of ECP in the treatment of steroid-refractory aGvHD was confirmed.[82] Based on expert opinions, analyses of current practices and published results, in 2007, Kanold *et al.*[116] released clinical practice guidelines for physicians caring for children with aGvHD. In this guideline article, ECP is recommended for paediatric aGvHD patients who are unresponsive to corticosteroids as defined by the absence of clinical and biologic improvement after 1 week of corticosteroid therapy (prednisolone or methylprednisolone up to 2–5 mg/kg/day). However, the authors commented that they were considering ECP as early as 48 h after the initiation of corticosteroid therapy in severe cases of aGvHD. Thus, ECP was suggested as second-line therapy of aGvHD in paediatric patients presenting

either with steroid-intolerant, steroid-refractory or steroid-dependent severe aGvHD. In detail, given the excellent safety profile of ECP, Kanold *et al.* considered ECP as first-line therapy for paediatric patients with grade IV aGvHD (in combination with conventional immunosuppressive therapies) and as second-line therapy in steroid-refractory aGvHD grades II-III. The authors recommended that ECP therapy be started at three times a week until a maximum response has been achieved, followed by individual progressive tapering of immunosuppressive treatment. Recommendations on vascular access and ECP technique in children were also provided.

Martin *et al.*[110] published the recommendations of the American Society of Blood and Marrow Transplantation (ASBMT) for the treatment of aGvHD based on a comprehensive and critical review of published reports. In total, data from 67 reports on 6-month survival, CR and PR of aGvHD have been reviewed. Among the five studies with outliers in the 6-month survival rate, the clinical trial by Messina *et al.* was particularly prominent. Since only children were treated (median age of 9.6 years), Martin *et al.*[148] concluded that these outliers could be the result of age differences between patient cohorts, as the benchmark study had used horse ATG and included patients with a median age of 27 years. In conclusion, no specific agent was recommended or suggested to be avoided in the second-line therapy of steroid-refractory aGvHD.

The ASBMT reported on blood loss, hypocalcaemia, mild cytopenia and catheter-associated bacteraemia due to ECP therapy but did not identify an increased risk of infections compared to other treatments. In particular, the ASBMT stated that there are no concerns about viral reactivations during ECP treatment. A typical ECP treatment schedule consists of three administrations during the first week followed by two administrations per week thereafter. According to ASBMT, the appropriate choice of second-line treatment regimens should be guided by factors such as the potential toxicity of drugs, drug interactions, the experience of the physician with the agents, tolerability, and drug costs. Due to the excellent safety profile of ECP and the lack of interactions with other agents, ECP compares favourably to alternative immunosuppressive strategies, supporting the concept of its frequent use as second-line therapy of steroid-refractory aGvHD.

The Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and the Italian Group for Bone Marrow Transplantation (GITMO) stated that ECP is a valuable option for patients with aGvHD who are unresponsive to steroids and calcineurin inhibitors.[101] GITMO and SIdEM recommend the use of ECP in both adults and children. The early start of ECP therapy, particularly in children and recipients of haploidentical or unrelated donor HCTs is suggested. In a recent survey of twenty-four Italian HCT centres, more than 85% of these GITMO accredited centres agreed with best practice recommendations including the use of ECP.[100]

Recommendations

Patient selection Patients presenting with aGvHD but not responding to first-line therapy with corticosteroids at 2 mg/kg/day (progression of aGvHD after ≥3 days or lack of response after ≥7 days of corticosteroid treatment) should receive adjunct ECP as second-line therapy.

Treatment schedule Patients should undergo ECP cycles every week, comprising 2 to 3 treatments per week. At present, there is no evidence that maintenance ECP therapy is necessary. Thus, as soon as patients achieve CR, ECP should be discontinued.

Response assessment The activity of aGvHD should be assessed at seven-day intervals with staging according to published criteria.[149,150] Clinical assessments should relate to organ involvement, and data on the quality of life should also be collected.

Summary/conclusions

The first results from an international, prospective, multicentre clinical study on the use of ECP for the treatment of CTCL were published by Edelson *et al.*[2] almost 32 years ago. Based on these data, the US FDA approved ECP as the first cellular immunotherapy for cancer. This approval triggered many investigators to test ECP in the prevention and treatment of a variety of T-cell mediated diseases as outlined in the present guideline document. Over the last two decades, a large body of data has been derived from retrospective or prospective single and multicentre clinical trials with ECP that allow for the provision of recommendations on treatment schedules for different patient populations.

Extracorporeal photopheresis is a well-tolerated therapy with an excellent safety profile. No significant side-effects have been reported in any of the conditions reviewed here except for the short-term effects of oral 8-MOP observed in the earlier studies. Unlike other immunosuppressive therapies, ECP has not been associated with an increased incidence of infections. New technical developments and advances have substantially shortened the cycle duration and qualified ECP for the use in children. Initially, ECP had only been used empirically in clinical settings. However, recent preclinical and clinical research activities are throwing more light on the complexities of its mechanisms of action. Also, promising data on the identification of potential surrogate markers that are considered predictive of clinical response to ECP therapy are emerging.

Recent technical advances and a large body of data on the usefulness, safety and efficacy of ECP have established this method as a well-recognized and accepted immunomodulatory second-line therapy in a variety of dermal and non-dermal diseases.

Acknowledgements

Thanks go to Christian Joukhadar, Christian Kunte, Pablo Luis Ortiz-Romero, Meinhard Schiller, Ulrike Just, Harald Maier and Constanze Jonak for their excellent assistance in the development of these guidelines.

References

1 Knobler R, Barr ML, Couriel DR *et al*. Extracorporeal photopheresis: past, present, and future. *J Am Acad Dermatol* 2009; **61**: 652–665.
2 Edelson R, Berger C, Gasparro F *et al*. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. *N Engl J Med* 1987; **316**: 297–303.
3 Schooneman F. Extracorporeal photopheresis technical aspects. *Transfus Apher Sci* 2003; **28**: 51–61.
4 Geskin L. ECP versus PUVA for the treatment of cutaneous T-cell lymphoma. *Skin Therapy Lett* 2007; **12**: 1–4.
5 Knobler RM, Trautinger F, Graninger W, Macheiner W, Gruenwald C, Neumann R *et al*. Parenteral administration of 8-methoxypsoralen in photopheresis. *J Am Acad Dermatol* 1993; **28**: 580–584.
6 Trautinger F, Just U, Knobler R. Photopheresis (extracorporeal photochemotherapy). *Photochem Photobiol Sci* 2013; **12**: 22–28.
7 Wong ECCJD. ECP in children and adolescents. In Greinix H, R Knobler, eds. Extracorporeal Photopheresis, pp. 8–21. Berlin/Boston: Walter de Gruyter GmbH & Co. KG; 2012.
8 Regles-de-bonnes-pratiques-relatives-a-la-preparation-a-la-conservation-au transport-la-distribution-et-a-la-cession-des-tissus-des-cellules-et-des-preparations. AFSSAPS/ANSM Décembre 2010. 2010.
9 Hambsch J, Buttner S, Heck M, Nicolay JP, Felcht M, Booken N *et al*. Single-center retrospective analysis of extracorporal photopheresis in clinical practice: peripheral venous compared to central venous access. *Hautarzt* 2019; **70**: 193–203.
10 Bladon J, Taylor PC. Extracorporeal photopheresis induces apoptosis in the lymphocytes of cutaneous T-cell lymphoma and graft-versus-host disease patients. *Br J Haematol* 1999; **107**: 707–711.
11 Gerber A, Bohne M, Rasch J, Struy H, Ansorge S, Gollnick H. Investigation of annexin V binding to lymphocytes after extracorporeal photoimmunotherapy as an early marker of apoptosis. *Dermatology* 2000; **201**: 111–117.
12 Voss CY, Fry TJ, Coppes MJ, Blajchman MA. Extending the horizon for cell-based immunotherapy by understanding the mechanisms of action of photopheresis. *Transfus Med Rev* 2010; **24**: 22–32.
13 Goussetis E, Varela I, Tsirigotis P. Update on the mechanism of action and on clinical efficacy of extracorporeal photopheresis in the treatment of acute and chronic graft versus host disease in children. *Transfus Apher Sci* 2012; **46**: 203–209.
14 Wolnicka-Glubisz A, Fraczek J, Skrzeczynska-Moncznik J, Friedlein G, Mikolajczyk T, Sarna T *et al*. Effect of UVA and 8-methoxypsoralen, 4, 6, 4'-trimethylangelicin or chlorpromazine on apoptosis of lymphocytes and their recognition by monocytes. *J Physiol Pharmacol* 2010; **61**: 107–114.
15 Girardi M, Berger C, Hanlon D, Edelson RL. Efficient tumor antigen loading of dendritic antigen presenting cells by transimmunization. *Technol Cancer Res Treat* 2002; **1**: 65–69.
16 Merlin E, Hannani D, Veyrat-Masson R, Chassagne J, Gabert F, Berger M *et al*. Cryopreservation of mononuclear cells before extracorporeal photochemotherapy does not impair their anti-proliferative capabilities. *Cytotherapy* 2011; **13**: 248–255.
17 Spisek R, Gasova Z, Bartunkova J. Maturation state of dendritic cells during the extracorporeal photopheresis and its relevance for the treatment of chronic graft-versus-host disease. *Transfusion* 2006; **46**: 55–65.
18 Girardi M, Berger CL, Wilson LD, Christensen IR, Thompson KR, Glusac EJ *et al*. Transimmunization for cutaneous T cell lymphoma: a Phase I study. *Leuk Lymphoma* 2006; **47**: 1495–1503.
19 Fimiani M, Rubegni P, Pimpinelli N, Mori M, De Aloe G, Andreassi L. Extracorporeal photochemotherapy induces a significant increase in CD36+ circulating monocytes in patients with mycosis fungoides. *Dermatology* 1997; **194**: 107–110.
20 Di Renzo M, Rubegni P, De Aloe G, Paulesu L, Pasqui AL, Andreassi L *et al*. Extracorporeal photochemotherapy restores Th1/Th2 imbalance in patients with early stage cutaneous T-cell lymphoma. *Immunology* 1997; **92**: 99–103.
21 Bladon J, Taylor PC. Extracorporeal photopheresis: a focus on apoptosis and cytokines. *J Dermatol Sci* 2006; **43**: 85–94.
22 Rieber N, Wecker I, Neri D, Fuchs K, Schafer I, Brand A *et al*. Extracorporeal photopheresis increases neutrophilic myeloid-derived suppressor cells in patients with GvHD. *Bone Marrow Transplant* 2014; **49**: 545–552.
23 Merlin E, Goncalves-Mendes N, Hannani D, de la Torre A, Farges MC, Laroye H *et al*. Extracorporeal photochemotherapy induces arginase 1 in patients with graft versus host disease. *Transpl Immunol* 2011; **24**: 100–106.
24 Maeda A, Schwarz A, Kernebeck K, Gross N, Aragane Y, Peritt D *et al*. Intravenous infusion of syngeneic apoptotic cells by photopheresis induces antigen-specific regulatory T cells. *J Immunol* 2005; **174**: 5968–5976.
25 Maeda A, Beissert S, Schwarz T, Schwarz A. Phenotypic and functional characterization of ultraviolet radiation-induced regulatory T cells. *J Immunol* 2008; **180**: 3065–3071.
26 Maeda A, Schwarz A, Bullinger A, Morita A, Peritt D, Schwarz T. Experimental extracorporeal photopheresis inhibits the sensitization and effector phases of contact hypersensitivity via two mechanisms: generation of IL-10 and induction of regulatory T cells. *J Immunol* 2008; **181**: 5956–5962.
27 Whittle R, Taylor PC. Circulating B-cell activating factor level predicts clinical response of chronic graft-versus-host disease to extracorporeal photopheresis. *Blood* 2011; **118**: 6446–6449.
28 Wiese F, Reinhardt-Heller K, Volz M, Gille C, Kostlin N, Billing H *et al*. Monocytes show immunoregulatory capacity on CD4(+) T cells in a human in-vitro model of extracorporeal photopheresis. *Clin Exp Immunol* 2019; **195**: 369–380.
29 Wei YX, Sun B, Xiao L, Shi BY. Infusion of Lymphocytes treated With 8-methoxypsoralen and ultraviolet A light induces CD19(+)IL-10(+) regulatory B cells and promotes skin allograft survival. *Transplant Proc* 2018; **50**: 3906–3910.
30 Rezvani K, Mielke S, Ahmadzadeh M, Kilical Y, Savani BN, Zeilah J *et al*. High donor FOXP3-positive regulatory T-cell (Treg) content is associated with a low risk of GVHD following HLA-matched allogeneic SCT. *Blood* 2006; **108**: 1291–1297.
31 Zhai Z, Sun Z, Li Q, Zhang A, Liu H, Xu J *et al*. Correlation of the CD4+CD25high T-regulatory cells in recipients and their corresponding donors to acute GVHD. *Transpl Int* 2007; **20**: 440–446.
32 Gatza E, Rogers CE, Clouthier SG, Lowler KP, Tawara I, Liu C *et al*. Extracorporeal photopheresis reverses experimental graft-versus-host disease through regulatory T cells. *Blood* 2008; **112**: 1515–1521.
33 Quaglino P, Comessatti A, Ponti R, Peroni A, Mola F, Fierro MT *et al*. Reciprocal modulation of circulating CD4+CD25+bright T cells induced by extracorporeal photochemotherapy in cutaneous T-cell lymphoma and chronic graft-versus-host-disease patients. *Int J Immunopathol Pharmacol* 2009; **22**: 353–362.
34 Rao V, Saunes M, Jorstad S, Moen T. Cutaneous T cell lymphoma and graft-versus-host disease: a comparison of in vivo effects of extracorporeal photochemotherapy on Foxp3+ regulatory T cells. *Clin Immunol* 2009; **133**: 303–313.
35 Di Biaso I, Di Maio L, Bugarin C, Gaipa G, Dander E, Balduzzi A *et al*. Regulatory T cells and extracorporeal photochemotherapy: correlation with clinical response and decreased frequency of proinflammatory T cells. *Transplantation* 2009; **87**: 1422–1425.
36 Schmitt S, Johnson TS, Karakhanova S, Naher H, Mahnke K, Enk AH. Extracorporeal photophoresis augments function of

CD4+CD25+FoxP3+ regulatory T cells by triggering adenosine production. *Transplantation* 2009; **88**: 411–416.
37 Tsirigotis P, Kapsimalli V, Baltadakis I, Kaloyannidis P, Karakasis D, Papalexandri A *et al*. Extracorporeal photopheresis in refractory chronic graft-versus-host disease: the influence on peripheral blood T cell subpopulations. A study by the Hellenic Association of Hematology. *Transfus Apher Sci* 2012; **46**: 181–188.
38 Biagi E, Di Biaso I, Leoni V, Gaipa G, Rossi V, Bugarin C *et al*. Extracorporeal photochemotherapy is accompanied by increasing levels of circulating CD4+CD25+GITR+Foxp3+CD62L+ functional regulatory T-cells in patients with graft-versus-host disease. *Transplantation* 2007; **84**: 31–39.
39 Klemke CD, Fritzsching B, Franz B, Kleinmann EV, Oberle N, Poenitz N *et al*. Paucity of FOXP3+ cells in skin and peripheral blood distinguishes Sezary syndrome from other cutaneous T-cell lymphomas. *Leukemia* 2006; **20**: 1123–1129.
40 Tiemessen MM, Mitchell TJ, Hendry L, Whittaker SJ, Taams LS, John S. Lack of suppressive CD4+CD25+FOXP3+ T cells in advanced stages of primary cutaneous T-cell lymphoma. *J Invest Dermatol* 2006; **126**: 2217–2223.
41 George JF, Gooden CW, Guo L, Kirklin JK. Role for CD4(+)CD25(+) T cells in inhibition of graft rejection by extracorporeal photopheresis. *J Heart Lung Transplant* 2008; **27**: 616–622.
42 Reinisch W, Nahavandi H, Santella R, Zhang Y, Gasche C, Moser G *et al*. Extracorporeal photochemotherapy in patients with steroid-dependent Crohn's disease: a prospective pilot study. *Aliment Pharmacol Ther* 2001; **15**: 1313–1322.
43 Garrett WS, Gordon JI, Glimcher LH. Homeostasis and inflammation in the intestine. *Cell* 2010; **140**: 859–870.
44 Ludvigsson J, Samuelsson U, Ernerudh J, Johansson C, Stenhammar L, Berlin G. Photopheresis at onset of type 1 diabetes: a randomised, double blind, placebo controlled trial. *Arch Dis Child* 2001; **85**: 149–154.
45 Ernerudh J, Ludvigsson J, Berlin G, Samuelsson U. Effect of photopheresis on lymphocyte population in children with newly diagnosed type 1 diabetes. *Clin Diagn Lab Immunol* 2004; **11**: 856–861.
46 Faresjo MK, Ernerudh J, Berlin G, Garcia J, Ludvigsson J. The immunological effect of photopheresis in children with newly diagnosed type 1 diabetes. *Pediatr Res* 2005; **58**: 459–466.
47 Jonson CO, Pihl M, Nyholm C, Cilio CM, Ludvigsson J, Faresjo M. Regulatory T cell-associated activity in photopheresis-induced immune tolerance in recent onset type 1 diabetes children. *Clin Exp Immunol* 2008; **153**: 174–181.
48 Dummer R, Assaf C, Bagot M, Gniadecki R, Hauschild A, Knobler R *et al*. Maintenance therapy in cutaneous T-cell lymphoma: who, when, what? *Eur J Cancer* 2007; **43**: 2321–2329.
49 Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R *et al*. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 1713–1722.
50 Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH *et al*. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019; **133**: 1703–1714.
51 Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R *et al*. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome – update 2017. *Eur J Cancer* 2017; **77**: 57–74.
52 Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M, Committee EG. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018;**29**(Suppl 4):iv30–iv40.
53 Knobler R, Duvic M, Querfeld C, Straus D, Horwitz S, Zain J *et al*. Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. *Photodermatol Photoimmunol Photomed* 2012; **28**: 250–257.
54 Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. *Dermatol Ther* 2003; **16**: 337–346.
55 Scarisbrick JJ, Taylor P, Holtick U, Makar Y, Douglas K, Berlin G *et al*. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158**: 659–678.
56 Tsirigotis P, Pappa V, Papageorgiou S, Kapsimali V, Giannopoulou V, Kaitsa I *et al*. Extracorporeal photopheresis in combination with bexarotene in the treatment of mycosis fungoides and Sezary syndrome. *Br J Dermatol* 2007; **156**: 1379–1381.
57 Arulogun S, Prince HM, Gambell P, Lade S, Ryan G, Eaton E *et al*. Extracorporeal photopheresis for the treatment of Sezary syndrome using a novel treatment protocol. *J Am Acad Dermatol* 2008; **59**: 589–595.
58 Booken N, Weiss C, Utikal J, Felcht M, Goerdt S, Klemke CD. Combination therapy with extracorporeal photopheresis, interferon-alpha, PUVA and topical corticosteroids in the management of Sezary syndrome. *J Dtsch Dermatol Ges* 2010; **8**: 428–438.
59 McGirt LY, Thoburn C, Hess A, Vonderheid EC. Predictors of response to extracorporeal photopheresis in advanced mycosis fungoides and Sezary syndrome. *Photodermatol Photoimmunol Photomed* 2010; **26**: 182–191.
60 Talpur R, Demierre MF, Geskin L, Baron E, Pugliese S, Eubank K *et al*. Multicenter photopheresis intervention trial in early-stage mycosis fungoides. *Clin Lymphoma Myeloma Leuk* 2011; **11**: 219–227.
61 Raphael BA, Shin DB, Suchin KR, Morrissey KA, Vittorio CC, Kim EJ *et al*. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. *Arch Dermatol* 2011; **147**: 1410–1415.
62 Quaglino P, Knobler R, Fierro MT, Savoia P, Marra E, Fava P *et al*. Extracorporeal photopheresis for the treatment of erythrodermic cutaneous T-cell lymphoma: a single center clinical experience with long-term follow-up data and a brief overview of the literature. *Int J Dermatol* 2013; **52**: 1308–1318.
63 Kim YH, Bishop K, Varghese A, Hoppe RT. Prognostic factors in erythrodermic mycosis fungoides and the Sezary syndrome. *Arch Dermatol* 1995; **131**: 1003–1008.
64 Heald PW, Perez MI, Christensen I, Dobbs N, McKiernan G, Edelson R. Photopheresis therapy of cutaneous T-cell lymphoma: the Yale-New Haven Hospital experience. *Yale J Biol Med* 1989; **62**: 629–638.
65 Gottlieb SL, Wolfe JT, Fox FE, DeNardo BJ, Macey WH, Bromley PG *et al*. Treatment of cutaneous T-cell lymphoma with extracorporeal photopheresis monotherapy and in combination with recombinant interferon alfa: a 10-year experience at a single institution. *J Am Acad Dermatol* 1996; **35**: 946–957.
66 Zic JA, Stricklin GP, Greer JP, Kinney MC, Shyr Y, Wilson DC *et al*. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1996; **35**: 935–945.
67 Suchin KR, Cucchiara AJ, Gottleib 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. *Arch Dermatol* 2002; **138**: 1054–1060.
68 Duvic M, Chiao N, Talpur R. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma. *J Cutan Med Surg* 2003; **7**(4 Suppl): 3–7.
69 Bisaccia E, Gonzalez J, Palangio M, Schwartz J, Klainer AS. Extracorporeal photochemotherapy alone or with adjuvant therapy in the treatment of cutaneous T-cell lymphoma: a 9-year retrospective study at a single institution. *J Am Acad Dermatol* 2000; **43**(2 Pt 1): 263–271.
70 Olsen EA, Rook AH, Zic J, Kim Y, Porcu P, Querfeld C *et al*. Sezary syndrome: immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma Consortium (USCLC). *J Am Acad Dermatol* 2011; **64**: 352–404.

71 Sanyal S, Child F, Alfred A, Callaghan T, Alband N, Whittaker S *et al*. U.K. national audit of extracorporeal photopheresis in cutaneous T-cell lymphoma. *Br J Dermatol* 2018; **178**: 569–570.

72 Wilson LD, Jones GW, Kim D, Rosenthal D, Christensen IR, Edelson RL *et al*. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. *J Am Acad Dermatol* 2000; **43**(1 Pt 1): 54–60.

73 Trautinger F, Knobler R, Willemze R, Peris K, Stadler R, Laroche L *et al*. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer* 2006; **42**: 1014–1030.

74 Whittaker SJ, Marsden JR, Spittle M, Russell Jones R, British Association of D, Group UKCL. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003; **149**: 1095–1107.

75 NCI. USNIoH. Mycosis Fungoides (Including Sézary Syndrome) Treatment (PDQ®)–Health Professional Version. 2018. URL https://www.cancer.gov/types/lymphoma/hp/mycosis-fungoides-treatment-pdq/#section/_50. Accessed September 2019.

76 U.S. NCCN. Mycosis fungoides. version 1 2016. URL https://wwwnccnorg/patients/guidelines/nhl-mycosis/files/assets/common/downloads/files/mycosispdf.2016.

77 Miller JD, Kirkland EB, Domingo DS, Scull H, Jekutis B, Dallas M *et al*. Review of extracorporeal photopheresis in early-stage (IA, IB, and IIA) cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed* 2007; **23**: 163–171.

78 Zic JA. Extracorporeal photopheresis in the treatment of mycosis fungoides and Sezary syndrome. *Dermatol Clin* 2015; **33**: 765–776.

79 Knobler R, Jantschitsch C. Extracorporeal photochemoimmunotherapy in cutaneous T-cell lymphoma. *Transfus Apher Sci* 2003; **28**: 81–89.

80 Berger C, Hoffmann K, Vasquez JG, Mane S, Lewis J, Filler R *et al*. Rapid generation of maturationally synchronized human dendritic cells: contribution to the clinical efficacy of extracorporeal photochemotherapy. *Blood* 2010; **116**: 4838–4847.

81 Evans AV, Wood BP, Scarisbrick JJ, Fraser-Andrews EA, Chinn S, Dean A *et al*. Extracorporeal photopheresis in Sezary syndrome: hematologic parameters as predictors of response. *Blood* 2001; **98**: 1298–1301.

82 Alfred A, Taylor PC, Dignan F, El-Ghariani K, Griffin J, Gennery AR *et al*. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. *Br J Haematol* 2017; **177**: 287–310.

83 McKenna KE, Whittaker S, Rhodes LE, Taylor P, Lloyd J, Ibbotson S *et al*. Evidence-based practice of photopheresis 1987–2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; **154**: 7–20.

84 Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ *et al*. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. *Br J Dermatol* 2019; **180**: 496–526.

85 Dippel E, Assaf C, Becker JC, von Bergwelt-Baildon M, Beyer M, Cozzio A *et al*. S2k guidelines – cutaneous lymphomas update 2016 – part 1: classification and diagnosis (ICD10 C82–C86). *J Dtsch Dermatol Ges* 2017; **15**: 1266–1273.

86 Dippel E, Assaf C, Becker JC, von Bergwelt-Baildon M, Beyer M, Cozzio A *et al*. S2k guidelines – cutaneous lymphomas update 2016 – part 2: treatment and follow-up (ICD10 C82–C86). *J Dtsch Dermatol Ges* 2018; **16**: 112–122.

87 Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A *et al*. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 479–484.

88 Flowers ME, Inamoto Y, Carpenter PA, Lee SJ, Kiem HP, Petersdorf EW *et al*. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood* 2011; **117**: 3214–3219.

89 Arai S, Arora M, Wang T, Spellman SR, He W, Couriel DR *et al*. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant* 2015; **21**: 266–274.

90 Kuzmina Z, Eder S, Bohm A, Pernicka E, Vormittag L, Kalhs P *et al*. Significantly worse survival of patients with NIH-defined chronic graft-versus-host disease and thrombocytopenia or progressive onset type: results of a prospective study. *Leukemia* 2012; **26**: 746–756.

91 Owsianowski M, Gollnick H, Siegert W, Schwerdtfeger R, Orfanos CE. Successful treatment of chronic graft-versus-host disease with extracorporeal photopheresis. *Bone Marrow Transplant* 1994; **14**: 845–848.

92 Arora M, Cutler CS, Jagasia MH, Pidala J, Chai X, Martin PJ *et al*. Late acute and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2016; **22**: 449–455.

93 Socie G, Ritz J. Current issues in chronic graft-versus-host disease. *Blood* 2014; **124**: 374–384.

94 MacDonald KP, Blazar BR, Hill GR. Cytokine mediators of chronic graft-versus-host disease. *J Clin Invest* 2017; **127**: 2452–2463.

95 Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW *et al*. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 2015; **21**:389–401 e1.

96 Wolff D, Gerbitz A, Ayuk F, Kiani A, Hildebrandt GC, Vogelsang GB *et al*. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. *Biol Blood Marrow Transplant* 2010; **16**: 1611–1628.

97 Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M *et al*. Consensus conference on clinical practice in chronic GVHD: second-line treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2011;**17**:1–17.

98 Jagasia M, Scheid C, Socie G, Ayuk FA, Tischer J, Donato ML *et al*. Randomized controlled study of ECP with methoxsalen as first-line treatment of patients with moderate to severe cGVHD. *Blood Adv* 2019; **3**: 2218–2229.

99 Pidala J, Kurland B, Chai X, Majhail N, Weisdorf DJ, Pavletic S *et al*. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood* 2011; **117**: 4651–4657.

100 Pierelli L, Bosi A, Olivieri A. "Best practice" for extracorporeal photopheresis in acute and chronic graft-versus-host disease by Societa' Italiana di Emaferesi and Manipolazione Cellulare and Gruppo Italiano Trapianto Midollo Osseo: a national survey to ascertain its degree of application in Italian transplant centers. *Transfusion* 2018; **58**: 217–222.

101 Pierelli L, Perseghin P, Marchetti M, Messina C, Perotti C, Mazzoni A *et al*. Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process. *Transfusion* 2013; **53**: 2340–2352.

102 Dignan FL, Aguilar S, Scarisbrick JJ, Shaw BE, Potter MN, Cavenagh J *et al*. Impact of extracorporeal photopheresis on skin scores and quality of life in patients with steroid-refractory chronic GVHD. *Bone Marrow Transplant* 2014; **49**: 704–708.

103 Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V *et al*. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood* 2008; **112**: 2667–2674.

104 Ni M, Wang L, Yang M, Neuber B, Sellner L, Huckelhoven-Krauss A *et al*. Shaping of CD56(bri) natural killer cells in patients with steroid-

refractory/resistant acute graft-vs.-host disease via extracorporeal photopheresis. *Front Immunol* 2019; **10**: 547.
105 Wang L, Ni M, Huckelhoven-Krauss A, Sellner L, Hoffmann JM, Neuber B *et al*. Modulation of B cells and homing marker on NK cells through extracorporeal photopheresis in patients with steroid-refractory/resistant graft-vs.-host disease without hampering anti-viral/anti-leukemic effects. *Front Immunol* 2018; **9**: 2207.
106 Wolff D, Bertz H, Greinix H, Lawitschka A, Halter J, Holler E. The treatment of chronic graft-versus-host disease: consensus recommendations of experts from Germany, Austria, and Switzerland. *Dtsch Arztebl Int* 2011; **108**: 732–740.
107 Howell C, Douglas K, Cho G, El-Ghariani K, Taylor P, Potok D *et al*. Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products. British Committee for Standards in Haematology. *Transfus Med* 2015; **25**: 57–78.
108 Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M *et al*. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant* 2015; **21**: 984–999.
109 Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M *et al*. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the seventh special issue. *J Clin Apher* 2016; **31**: 149–162.
110 Martin PJ, Rizzo JD, Wingard JR, Ballen K, Curtin PT, Cutler C *et al*. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 2012; **18**: 1150–1163.
111 Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR *et al*. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood* 1990; **76**: 1464–1472.
112 Pidala J, Anasetti C. Glucocorticoid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2010; **16**: 1504–1518.
113 Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P *et al*. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol* 2012; **158**: 30–45.
114 Salvaneschi L, Perotti C, Zecca M, Bernuzzi S, Viarengo G, Giorgiani G *et al*. Extracorporeal photochemotherapy for treatment of acute and chronic GVHD in childhood. *Transfusion* 2001; **41**: 1299–1305.
115 Messina C, Locatelli F, Lanino E, Uderzo C, Zacchello G, Cesaro S *et al*. Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. *Br J Haematol* 2003; **122**: 118–127.
116 Kanold J, Merlin E, Halle P, Paillard C, Marabelle A, Rapatel C *et al*. Photopheresis in pediatric graft-versus-host disease after allogeneic marrow transplantation: clinical practice guidelines based on field experience and review of the literature. *Transfusion* 2007; **47**: 2276–2289.
117 Gonzalez-Vicent M, Ramirez M, Perez A, Lassaletta A, Sevilla J, Diaz MA. Extracorporeal photochemotherapy for steroid-refractory graft-versus-host disease in low-weight pediatric patients. Immunomodulatory effects and clinical outcome. *Haematologica* 2008; **93**: 1278–1280.
118 Perotti C, Del Fante C, Tinelli C, Viarengo G, Scudeller L, Zecca M *et al*. Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. *Transfusion* 2010; **50**: 1359–1369.
119 Greinix HT, Volc-Platzer B, Rabitsch W, Gmeinhart B, Guevara-Pineda C, Kalhs P *et al*. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood* 1998; **92**: 3098–3104.
120 Smith EP, Sniecinski I, Dagis AC, Parker PM, Snyder DS, Stein AS *et al*. Extracorporeal photochemotherapy for treatment of drug-resistant graft-vs.-host disease. *Biol Blood Marrow Transplant* 1998; **4**: 27–37.
121 Kanold J, Paillard C, Halle P, D'Incan M, Bordigoni P, Demeocq F. Extracorporeal photochemotherapy for graft versus host disease in pediatric patients. *Transfus Apher Sci* 2003; **28**: 71–80.
122 Dall'Amico R, Messina C. Extracorporeal photochemotherapy for the treatment of graft-versus-host disease. *Ther Apher* 2002; **6**: 296–304.
123 Greinix HT, Volc-Platzer B, Knobler RM. Extracorporeal photochemotherapy in the treatment of severe graft-versus-host disease. *Leuk Lymphoma* 2000; **36**: 425–434.
124 Perseghin P. Extracorporeal photochemotherapy as a challenging treatment for cutaneous T-cell lymphoma, acute and chronic graft-versus-host disease, organ rejection and T-lymphocyte-mediated autoimmune diseases. *Transfus Med Hemother* 2008; **35**: 8–17.
125 Greinix HT, Worel N, Knobler R. Role of extracorporeal photopheresis (ECP) in treatment of steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2010; **16**: 1747–1748. author reply 9.
126 Greinix HT, Knobler RM, Worel N, Schneider B, Schneeberger A, Hoecker P *et al*. The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica* 2006; **91**: 405–408.
127 Garban F, Drillat P, Makowski C, Jacob MC, Richard MJ, Favrot M *et al*. Extracorporeal chemophototherapy for the treatment of graft-versus-host disease: hematologic consequences of short-term, intensive courses. *Haematologica* 2005; **90**: 1096–1101.
128 Perfetti P, Carlier P, Strada P, Gualandi F, Occhini D, Van Lint MT *et al*. Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. *Bone Marrow Transplant* 2008; **42**: 609–617.
129 Delmo Walter EM, Stiller B, Hetzer R, Alexi-Meskishvili V, Hubler M, Bottcher W *et al*. Extracorporeal membrane oxygenation for perioperative cardiac support in children I: experience at the Deutsches Herzzentrum Berlin (1987–2005). *ASAIO J* 2007; **53**: 246–254.
130 Calore E, Calo A, Tridello G, Cesaro S, Pillon M, Varotto S *et al*. Extracorporeal photochemotherapy may improve outcome in children with acute GVHD. *Bone Marrow Transplant* 2008; **42**: 421–425.
131 Schneiderman J, Jacobsohn DA, Collins J, Thormann K, Kletzel M. The use of fluid boluses to safely perform extracorporeal photopheresis (ECP) in low-weight children: a novel procedure. *J Clin Apher* 2010; **25**: 63–69.
132 Berger M, Albiani R, Sini B, Fagioli F. Extracorporeal photopheresis for graft-versus-host disease: the role of patient, transplant, and classification criteria and hematologic values on outcome-results from a large single-center study. *Transfusion* 2015; **55**: 736–747.
133 Calore E, Marson P, Pillon M, Tumino M, Tison T, Mainardi C *et al*. Treatment of acute graft-versus-host disease in childhood with extracorporeal photochemotherapy/photopheresis: the padova experience. *Biol Blood Marrow Transplant* 2015; **21**: 1963–1972.
134 Hautmann AH, Wolff D, Hahn J, Edinger M, Schirmer N, Ammer J *et al*. Extracorporeal photopheresis in 62 patients with acute and chronic GVHD: results of treatment with the COBE Spectra System. *Bone Marrow Transplant* 2013; **48**: 439–445.
135 Malagola M, Cancelli V, Skert C, Leali PF, Ferrari E, Tiburzi A *et al*. Extracorporeal photopheresis for treatment of acute and chronic graft versus host disease: an Italian multicentric retrospective analysis on 94 patients on behalf of the Gruppo Italiano Trapianto di Midollo Osseo. *Transplantation* 2016; **100**: e147–e155.
136 Greinix HT, Volc-Platzer B, Kalhs P, Fischer G, Rosenmayr A, Keil F *et al*. Extracorporeal photochemotherapy in the treatment of severe steroid-refractory acute graft-versus-host disease: a pilot study. *Blood* 2000; **96**: 2426–2431.
137 Berger M, Pessolano R, Albiani R, Asaftei S, Barat V, Carraro F *et al*. Extracorporeal photopheresis for steroid resistant graft versus host disease in pediatric patients: a pilot single institution report. *J Pediatr Hematol Oncol* 2007; **29**: 678–687.
138 Das-Gupta E, Greinix H, Jacobs R, Zhou L, Savani BN, Engelhardt BG *et al*. Extracorporeal photopheresis as second-line treatment for acute

graft-versus-host disease: impact on six-month freedom from treatment failure. *Haematologica* 2014; **99**: 1746–1752.
139 Jagasia M, Greinix H, Robin M, Das-Gupta E, Jacobs R, Savani BN *et al*. Extracorporeal photopheresis versus anticytokine therapy as a second-line treatment for steroid-refractory acute GVHD: a multicenter comparative analysis. *Biol Blood Marrow Transplant* 2013; **19**: 1129–1133.
140 Abu-Dalle I, Reljic T, Nishihori T, Antar A, Bazarbachi A, Djulbegovic B *et al*. Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies. *Biol Blood Marrow Transplant* 2014; **20**: 1677–1686.
141 Zhang H, Chen R, Cheng J, Jin N, Chen B. Systematic review and meta-analysis of prospective studies for ECP treatment in patients with steroid-refractory acute GVHD. *Patient Prefer Adherence* 2015; **9**: 105–111.
142 Miller KB, Roberts TF, Chan G, Schenkein DP, Lawrence D, Sprague K *et al*. A novel reduced intensity regimen for allogeneic hematopoietic stem cell transplantation associated with a reduced incidence of graft-versus-host disease. *Bone Marrow Transplant* 2004; **33**: 881–889.
143 Shaughnessy PJ, Bolwell BJ, van Besien K, Mistrik M, Grigg A, Dodds A *et al*. Extracorporeal photopheresis for the prevention of acute GVHD in patients undergoing standard myeloablative conditioning and allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2010; **45**: 1068–1076.
144 Michallet M, Sobh M, Garban F, Bulabois CE, Yakoub-Agha I, Coiteux V *et al*. Extracorporeal photopheresis for GVHD prophylaxis after reduced intensity conditioning allogeneic hematopoietic stem cell transplantation: a prospective multicenter phase 2 study. *Leuk Lymphoma* 2018; **59**: 372–380.
145 Kitko CL, Braun T, Couriel DR, Choi SW, Connelly J, Hoffmann S *et al*. Combination therapy for graft-versus-host disease prophylaxis with etanercept and extracorporeal photopheresis: results of a phase II clinical trial. *Biol Blood Marrow Transplant* 2016; **22**: 862–868.
146 Szczepiorkowski ZM, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R *et al*. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. *J Clin Apher* 2007; **22**: 106–175.
147 Das-Gupta E, Dignan F, Shaw B, Raj K, Malladi R, Gennery A *et al*. Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature. *Bone Marrow Transplant* 2014; **49**: 1251–1258.
148 MacMillan ML, Weisdorf DJ, Davies SM, DeFor TE, Burns LJ, Ramsay NK *et al*. Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2002; **8**: 40–46.
149 Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J *et al*. 1994 consensus conference on acute GVHD grading. *Bone Marrow Transplant* 1995; **15**: 825–828.
150 Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA *et al*. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation* 1974; **18**: 295–304.
151 Nagatani T, Matsuzaki T, Kim S, Baba N, Osawa J, Sugiyama A *et al*. Treatment of cutaneous T-cell lymphomas (CTCL) with extracorporeal photochemotherapy–preliminary report. *J Dermatol* 1990; **17**: 737–745.
152 Zic J, Arzubiaga C, Salhany KE, Parker RA, Wilson D, Stricklin GP *et al*. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1992; **27**(5 Pt 1): 729–736.
153 Koh HDB, Meola T, Lim H. Extracorporeal photopheresis for the treatment of 34 patients with cutaneous T-cell lymphoma. *J Invest Dermatol* 1994; **102**: 567 (abstract).
154 Prinz B, Behrens W, Holzle E, Plewig G. Extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma–the Dusseldorf and Munich experience. *Arch Dermatol Res* 1995; **287**: 621–626.
155 Duvic M, Hester JP, Lemak NA. Photopheresis therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996; **35**: 573–579.
156 Stevens SR, Baron ED, Masten S, Cooper KD. Circulating CD4+CD7- lymphocyte burden and rapidity of response: predictors of outcome in the treatment of Sezary syndrome and erythrodermic mycosis fungoides with extracorporeal photopheresis. *Arch Dermatol* 2002; **138**: 1347–1350.
157 Konstantinow ABB. Treatment of cutaneous T-cell lymphoma with extracorporeal photochemotherapy. *J Eur Acad Dermatol Venereol* 1997; **9**: 111–117.
158 Miracco C, Rubegni P, De Aloe G, D'Ascenzo G, Mazzatenta C, De Santi MM *et al*. Extracorporeal photochemotherapy induces apoptosis of infiltrating lymphoid cells in patients with mycosis fungoides in early stages. A quantitative histological study. *Br J Dermatol* 1997; **137**: 549–557.
159 Russell-Jones R, Fraser-Andrews E, Spittle M, Whittaker S. Extracorporeal photopheresis in Sezary syndrome. *Lancet* 1997; **350**: 886.
160 Vonderheid EC, Zhang Q, Lessin SR, Polansky M, Abrams JT, Bigler RD *et al*. Use of serum soluble interleukin-2 receptor levels to monitor the progression of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1998; **38**(2 Pt 1): 207–220.
161 Zouboulis CC, Schmuth M, Doepfmer S, Dippel E, Orfanos CE. Extracorporeal photopheresis of cutaneous T-cell lymphoma is associated with reduction of peripheral CD4+ T lymphocytes. *Dermatology* 1998; **196**: 305–308.
162 Jiang SB, Dietz SB, Kim M, Lim HW. Extracorporeal photochemotherapy for cutaneous T-cell lymphoma: a 9.7-year experience. *Photodermatol Photoimmunol Photomed* 1999; **15**: 161–165.
163 Crovetti G, Carabelli A, Berti E, Guizzardi M, Fossati S, De Filippo C *et al*. Photopheresis in cutaneous T-cell lymphoma: five-year experience. *Int J Artif Organs* 2000; **23**: 55–62.
164 Wollina U, Liebold K, Kaatz M, Looks A, Stuhlert A, Lange D. Survival of patients with cutaneous T-cell lymphoma after treatment with extracorporeal photochemotherapy. *Oncol Rep* 2000; **7**: 1197–1201.
165 Wollina U, Looks A, Meyer J, Knopf B, Koch HJ, Liebold K *et al*. Treatment of stage II cutaneous T-cell lymphoma with interferon alfa-2a and extracorporeal photochemotherapy: a prospective controlled trial. *J Am Acad Dermatol* 2001; **44**: 253–260.
166 Bouwhuis SA, el-Azhary RA, McEvoy MT, Gibson LE, Habermann TM, Witzig TE *et al*. Treatment of late-stage Sezary syndrome with 2-Chlorodeoxyadenosine. *Int J Dermatol* 2002; **41**: 352–356.
167 Knobler E, Warmuth I, Cocco C, Miller B, Mackay J. Extracorporeal photochemotherapy–the Columbia Presbyterian experience. *Photodermatol Photoimmunol Photomed* 2002; **18**: 232–237.
168 Quaglino P, Fierro MT, Rossotto GL, Savoia P, Bernengo MG. Treatment of advanced mycosis fungoides/Sezary syndrome with fludarabine and potential adjunctive benefit to subsequent extracorporeal photochemotherapy. *Br J Dermatol* 2004; **150**: 327–336.
169 de Misa RF, Harto A, Azana JM, Belmar P, Diez E, Ledo A. Photopheresis does not improve survival in Sezary syndrome patients with bone marrow involvement. *J Am Acad Dermatol* 2005; **53**: 171–172.
170 Rao V, Ryggen K, Aarhaug M, Dai HY, Jorstad S, Moen T. Extracorporeal photochemotherapy in patients with cutaneous T-cell lymphoma: is clinical response predictable? *J Eur Acad Dermatol Venereol* 2006; **20**: 1100–1107.
171 Gasova Z, Spisek R, Dolezalova L, Marinov I, Vitek A. Extracorporeal photochemotherapy (ECP) in treatment of patients with c-GVHD and CTCL. *Transfus Apher Sci* 2007; **36**: 149–158.
172 Knobler R, Berlin G, Calzavara-Pinton P, Greinix H, Jaksch P, Laroche L *et al*. Guidelines on the use of extracorporeal photopheresis. *J Eur Acad Dermatol Venereol* 2014; **28**(Suppl 1): 1–37.
173 Atta M, Papanicolaou N, Tsirigotis P. The role of extracorporeal photopheresis in the treatment of cutaneous T-cell lymphomas. *Transfus Apher Sci* 2012; **46**: 195–202.
174 Heald P, Rook A, Perez M, Wintroub B, Knobler R, Jegasothy B *et al*. Treatment of erythrodermic cutaneous T-cell lymphoma with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1992; **27**: 427–433.
175 Knobler E, Warmuth I. Extracorporeal photochemotherapy: a case report and update. *Cutis* 2002; **69**: 119–123.

176 Zic JA. Photopheresis in the treatment of cutaneous T-cell lymphoma: current status. *Curr Opin Oncol* 2012; **24**(Suppl 1): S1–S10.
177 Shiue LH, Couturier J, Lewis DE, Wei C, Ni X, Duvic M. The effect of extracorporeal photopheresis alone or in combination therapy on circulating CD4(+) Foxp3(+) CD25(-) T cells in patients with leukemic cutaneous T-cell lymphoma. *Photodermatol Photoimmunol Photomed* 2015; **31**: 184–194.
178 McGirt LY, Baerenwald DA, Vonderheid EC, Eischen CM. Early changes in miRNA expression are predictive of response to extracorporeal photopheresis in cutaneous T-cell lymphoma. *J Eur Acad Dermatol Venereol* 2015; **29**: 2269–2271.
179 Apisarnthanarax N, Donato M, Korbling M, Couriel D, Gajewski J, Giralt S *et al*. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone Marrow Transplant* 2003; **31**: 459–465.
180 Seaton ED, Szydlo RM, Kanfer E, Apperley JF, Russell-Jones R. Influence of extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response. *Blood* 2003; **102**: 1217–1223.
181 Foss FM, DiVenuti GM, Chin K, Sprague K, Grodman H, Klein A *et al*. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplant* 2005; **35**: 1187–1193.
182 Rubegni P, Cuccia A, Sbano P, Cevenini G, Carcagni MR, D'Ascenzo G *et al*. Role of extracorporeal photochemotherapy in patients with refractory chronic graft-versus-host disease. *Br J Haematol* 2005; **130**: 271–275.
183 Couriel DR, Hosing C, Saliba R, Shpall EJ, Anderlini P, Rhodes B *et al*. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. *Blood* 2006; **107**: 3074–3080.
184 Greinix HT, Socie G, Bacigalupo A, Holler E, Edinger MG, Apperley JF *et al*. Assessing the potential role of photopheresis in hematopoietic stem cell transplant. *Bone Marrow Transplant* 2006; **38**: 265–273.
185 Dignan FL, Greenblatt D, Cox M, Cavenagh J, Oakervee H, Apperley JF *et al*. Efficacy of bimonthly extracorporeal photopheresis in refractory chronic mucocutaneous GVHD. *Bone Marrow Transplant* 2012; **47**: 824–830.
186 Greinix HT, van Besien K, Elmaagacli AH, Hillen U, Grigg A, Knobler R *et al*. Progressive improvement in cutaneous and extracutaneous chronic graft-versus-host disease after a 24-week course of extracorporeal photopheresis–results of a crossover randomized study. *Biol Blood Marrow Transplant* 2011; **17**: 1775–1782.
187 Rossetti F, Zulian F, Dall'Amico R, Messina C, Montini G, Zacchello F. Extracorporeal photochemotherapy as single therapy for extensive, cutaneous, chronic graft-versus-host disease. *Transplantation* 1995; **59**: 149–151.
188 Dall'Amico R, Rossetti F, Zulian F, Montini G, Murer L, Andreetta B *et al*. Photopheresis in paediatric patients with drug-resistant chronic graft-versus-host disease. *Br J Haematol* 1997; **97**: 848–854.
189 Halle P, Paillard C, D'Incan M, Bordigoni P, Piguet C, De Lumley L *et al*. Successful extracorporeal photochemotherapy for chronic graft-versus-host disease in pediatric patients. *J Hematother Stem Cell Res* 2002; **11**: 501–512.
190 Perseghin P, Dassi M, Balduzzi A, Rovelli A, Bonanomi S, Uderzo C. Mononuclear cell collection in patients undergoing extra-corporeal photo-chemotherapy for acute and chronic graft-vs.-host-disease (GvHD): comparison between COBE Spectra version 4.7 and 6.0 (AutoPBSC). *J Clin Apher* 2002; **17**: 65–71.
191 Perutelli P, Rivabella L, Lanino E, Pistoia V, Dini G. ATP downregulation in mononuclear cells from children with graft-versus-host disease following extracorporeal photochemotherapy. *Haematologica* 2002; **87**: 335–336.
192 Duzovali O, Chan KW. Intensive extracorporeal photochemotherapy in pediatric patients with chronic graft-versus-host disease (cGVHD). *Pediatr Blood Cancer* 2007; **48**: 218–221.
193 Perseghin P, Galimberti S, Balduzzi A, Bonanomi S, Baldini V, Rovelli A *et al*. Extracorporeal photochemotherapy for the treatment of chronic graft-versus-host disease: trend for a possible cell dose-related effect? *Ther Apher Dial* 2007; **11**: 85–93.