

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

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Received 25 October 2016; accepted for
 publication 23 November 2016

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Extracorporeal photopheresis (ECP) is a cell-based immuno-
 modulatory therapy involving the separation of leucocyte-
 rich plasma followed by *ex-vivo* administration of a
 photosensitiser and ultraviolet A (UVA) radiation before

Summary

Extracorporeal photopheresis (ECP) has been used for over 35 years in the
 treatment of erythrodermic cutaneous T-cell lymphoma (CTCL) and over
 20 years for chronic and acute graft-versus-host disease (GvHD) and solid
 organ transplant rejection. ECP for CTCL and GvHD is available at spe-
 cialised centres across the UK. The lack of prospective randomised trials in
 ECP led to the development of UK Consensus Statements for patient selec-
 tion, treatment schedules, monitoring protocols and patient assessment cri-
 teria for ECP. The recent literature has been reviewed and considered when
 writing this update. Most notably, the national transition from the UVAR
 XTS[®] machine to the new CELLEX machine for ECP with dual access and
 a shorter treatment time has led to relevant changes in these schedules.
 This consensus statement updates the previous statement from 2007 on the
 treatment of CTCL and GvHD with ECP using evidence based medicine
 and best medical practise and includes guidelines for both children and
 adults.

Keywords: graft-versus-host disease, cutaneous T-cell lymphoma, rejection,
 extracorporeal photopheresis, treatment protocol.

re-infusion. The approach was first published in 1987,
 reporting the treatment of erythrodermic cutaneous T-cell
 lymphoma (CTCL) in a multicentre trial (Edelson *et al*,
 1987). The UVAR system for ECP (Therakos, Exton, PA,

USA) was approved in the US by the Food and Drug Administration in 1988. Since then, data have been published on over 1000 patients with CTCL treated with ECP from centres worldwide. Their findings have verified those reported by Edelson *et al* (1987) and have cited response rates of ~60% and complete responses (CRs) of 14–26% (Table I).

Extracorporeal photopheresis involves three stages: (i) leukapheresis; (ii) photoactivation with 8-methoxypsoralen (8-MOP)/UVA; and (iii) re-infusion of buffy coat.

Closed and open ECP systems are now available for clinical use. In a closed ECP system (i.e. a 'one-step' method), the cell separation, drug photoactivation and re-infusion stages are fully integrated and automated and the components are validated for use together, tested and approved for use with 8-MOP. There is no risk of improper reinfusion when used according to their labelling and the risk of infection and contamination associated with the medical device itself is low. Open ECP systems use separate devices for cell separation and drug photoactivation ('two-step' methods), which have not been validated for use together: the combination of a device approved for separation and one approved for photoactivation is not equivalent to a device approved for ECP. Closed systems are therefore the treatment of choice in the UK. The closed system CELLEX (Therakos) has recently replaced the UVAR XTS[®] (Therakos) and is used at all UK sites. The CELLEX has several advantages over the UVAR XTS[®]. Firstly, it allows double needle access, significantly shortening treatment times (from 3.5 to 1.5 h); secondly, it allows lower body weight patients to be treated (<40 kg), which has allowed safe expansion of paediatric uses for ECP.

The mechanism of action of ECP in CTCL is thought to result from 8-MOP binding covalently to DNA in separated leucocytes leading to cell cycle arrest and apoptosis. Apoptotic leucocytes are reintroduced into the peripheral circulation and phagocytosed by antigen presenting cells, with the production of specific tumour suppressor cells against malignant lymphocytes (Edelson *et al*, 1987). The mechanism of action of ECP in graft-versus-host disease (GvHD) remains poorly understood and may be multifactorial (Marshall, 2006; Franklin *et al*, 2015).

Extracorporeal photopheresis is recommended therapy for erythrodermic CTCL in the European Organisation for the Treatment and Research in Cancer (EORTC) mycosis fungoides/Sézary Guidelines (Trautinger *et al*, 2006) and in the Joint British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines, endorsed in the Improving Outcomes Guidance in Skin Cancer by the National Institute for Health and Care Excellence (NICE, 2006). Whilst the licensed indication in the United States is currently restricted to treatment of skin manifestations of CTCL (<http://www.therakos.com/full-prescribing-information>) ECP is used in a number of other indications, most commonly the treatment of chronic GvHD following

allogeneic haematopoietic cell transplantation (HCT). Over 600 patients are reported to have been treated with ECP for GvHD, with response of between 20% and 80%, which was highest for those with cutaneous or mucous membrane involvement. A favourable response in liver cGvHD has also been noted.

Extracorporeal photopheresis is available in 200 medical centres worldwide including the USA, Europe, South America and the Near East. ECP therapy is available at specialised centres across the UK including London, Rotherham, Nottingham, Manchester, Newcastle, Glasgow, Birmingham, Sheffield, Oxford, Cambridge, Bristol, Southampton, Liverpool and Belfast. All centres consider patients with erythrodermic CTCL and GvHD for treatment with ECP and some centres have limited experience at treating other conditions, such as scleroderma and solid organ transplant rejection.

In 2006 an Expert Photopheresis Group was formed with representative clinicians from all UK sites. Whilst ECP is a relatively mature treatment option with a substantial evidence base to support its use, guidance on the appropriate use of ECP remains scarce. Over the past 10 years there have been several larger retrospective studies published on the use of ECP in CTCL and GvHD, but no large prospective randomised controlled trials have been undertaken.

This paper reviews the existing literature on ECP with particular emphasis on a consensus statement for its use, efficacy in CTCL, GvHD and solid organ rejection. The strength of recommendations and quality of evidence assessment for the various conditions are shown in Appendix S1. This information has been utilised by the UK Photopheresis Society to update the pre-existing consensus statements (Scarlsbrick *et al*, 2008; Das-Gupta *et al*, 2014) to produce a clinically relevant consensus statement for 2016 using evidence-based medicine and best medical practise on the appropriate use of ECP in CTCL and GvHD, to include acute and chronic disease in both adults and children. The major updates in this new consensus are shown in Table II. The aim of these updates is to improve upon the existing statement to allow the most suitable patients access to ECP using a schedule most likely to derive benefit. This consensus statement provides standardised eligibility, assessment and treatment strategies across the UK, to enable more accurate comparison of treatment response between UK sites and provide foundations for multicentre UK trials.

Methods

Guidelines on the use of ECP in the management of CTCL and GvHD were identified through a literature and internet search of relevant medical databases (e.g. PUBMED, MEDLINE, CINAHL) as well as a targeted search of relevant professional bodies (e.g. British Association of Dermatologists). Key words search included extracorporeal photopheresis, ECP, treatment CTCL, treatment cGvHD, guidelines CTCL, and guidelines cGvHD. The databases held by the Centre for

Table I. Summary of studies using extracorporeal photochemotherapy for the treatment of CTCL.

Study reference	Total CTCL patients (n)	Overall response	CR	PR	Median duration of response (months)	Median or mean (range) Tx duration (months)	Median or mean (range) number of cycles	Median survival from diagnosis
Edelson <i>et al</i> (1987)	37 (erythrodermic 29)	73% (27/37)	24% (9/37)	35% (13/37)				
Heald <i>et al</i> (1989)	32 (erythrodermic 22)	86% (19/22)	23% (5/22)	45% (10/22)				
Nagatani <i>et al</i> (1990)	7	43% (3/7)	NK	NK				
Zic <i>et al</i> (1992)	20	55% (11/20)	25% (5/20)	30% (6/20)				
Koh <i>et al</i> (1994)	34 (erythrodermic 31)	53% (18/34)	15% (5/34)	38% (13/34)				
Prinz <i>et al</i> (1995)	17 (erythrodermic 3)	70% (12/17)	0% (0/17)	41% (7/17)				
Stevens <i>et al</i> (1996)	17 (erythrodermic)	53% (9/17)	29% (5/17)	24% (4/17)				
Gottlieb <i>et al</i> (1996)	28 (erythrodermic NK)	71% (20/28)	25% (7/28)	46% (13/28)				
Duvic <i>et al</i> (1996)	34 (erythrodermic 28)	50% (17/34)	18% (6/34)	32% (11/34)				
Zic <i>et al</i> (1996)	20 (erythrodermic 3)	50% (10/20)	25% (5/20)	25% (5/20)	53			
Russell-Jones <i>et al</i> (1997)	19 (erythrodermic)	53% (10/19)	16% (3/19)	37% (7/19)				
Konstantinow and Balda (1997)	12 (erythrodermic 6)	67% (8/12)	8% (1/12)	42% (5/12)				
Miracco <i>et al</i> (1997)	7	86% (6/7)	14% (1/7)	71% (5/7)				
Vonderheid <i>et al</i> (1998)	36 (erythrodermic 29)	33% (12/36)	14% (5/36)	19% (7/36)				
Zouboulis <i>et al</i> (1998)	20	65% (13/20)	NK	NK				
Fritz <i>et al</i> (1999)	17	70% (12/17)	0 (0/17)	41% (7/17)				
Jiang <i>et al</i> (1999)	25 (erythrodermic)	80% (20/25)	20% (5/25)	60% (15/25)				
Bisaccia <i>et al</i> (2000)	37	54% (20/37)	14% (5/37)	41% (15/37)				
Crovetti <i>et al</i> (2000)	30 (erythrodermic 9)	73% (22/30)	33% (10/30)	40% (12/30)				
		66% (6/9)	33% (3/9)	33% (3/9)				
Wollina <i>et al</i> (2000)	20	65% (13/20)	50% (10/20)	15% (3/20)				
Wollina <i>et al</i> (2001)	14	50% (7/14)	29% (4/14)	21% (3/14)				
Bouwhuis <i>et al</i> (2002)	55 SS	80% (44/55)	62% (34/55)	18% (10/55)				
Knobler <i>et al</i> (2002)	20 (erythrodermic 13)	50% (10/20)	15% (3/20)	54% (7/13)				
		85% (11/13)	15% (2/13)					
Stevens <i>et al</i> (2002)	17 (SS 15)				60			
Suchin <i>et al</i> (2002)	47	79% (37/47)	26% (12/47)	53% (25/47)				
Quaglino <i>et al</i> (2004)	19	63% (12/19)	NK	NK				
de Misa <i>et al</i> (2005)	10 (advanced SS)	60% (6/10)	10% (1/10)					
Wain <i>et al</i> (2005)	14 (erythrodermic)							
Rao <i>et al</i> (2006)	16	44% (7/16)	NK	NK				
Gasova <i>et al</i> (2007)	8 (2 with CTCL)	100% (2/2)	NK	NK			34	
Tsirigotis <i>et al</i> (2007)	5 (SS 2)	80% (4/5)	20% (1/5)	60% (4/5)				
Arulogun <i>et al</i> (2008)	13 (all SS; 12 erythrodermic)	62% (8/13)	15% (2/13)	46% (6/13)				
Booken <i>et al</i> (2010)	12 (all SS)	42% (4/12)	0% (0/12)	42% (4/12)		30 (8–64)	37 (10–75)	42 months
McGirt <i>et al</i> (2010)	19 (all early stage MF)	63% (12/19)	11% (2/19)	53% (10/19)	6-5	12	12 (2–32)	
Raphael <i>et al</i> (2011)	21 (18 erythrodermic)	57% (12/21)	14% (3/21)	43%				64 months
Siakantaris <i>et al</i> (2012)	98 (all erythrodermic)	75% (73/98)	30% (29/98)	45% (44/98)	21			65 months
Knobler <i>et al</i> (2012)	18 patients'	61%	28% (5/18)		29	NK	NK	NK

Table I. (Continued)

Study reference	Total CTCL patients (<i>n</i>)	Overall response	CR	PR	Median duration of response (months)	Median or mean (range) Tx duration (months)	Median or mean (range) number of cycles	Median survival from diagnosis
Quaglino <i>et al</i> (2013)	39 (31 erythrodermic) 14 SS	74% SS RR 91%	41%	33%	14		63.5 (mean)	From Dx: 9.2 years, from ECP: 6.6 years
Weber <i>et al</i> (2015)	51 (all erythrodermic)	63% 32/51	16%	37%	22			
Edelson <i>et al</i> (1987)	11 patients	64%	NR	NR	NR	5 (1–27)	32 (3–134)	

CR, complete response; CTCL, cutaneous T-cell lymphoma; Dx, diagnosis; MF, mycosis fungoides; MR, minor response (>25% improvement in skin scores); NK, not known; NR, no response; PR, partial response (>50% improvement in skin scores); SS: Sézary syndrome; Tx, treatment.

Table II. Changes in the updated consensus statement.

Section	Update in 2016 statement
CTCL	It is recommended that the treatment schedule may be continued in patients with a complete, partial or minimal response as opposed to treatment taper. This is in keeping with other treatments for advanced MF/SS, which should be continued whilst a clinical benefit is derived and cessation of therapy is not recommended whilst a response is durable. This is because there are no curative therapies for CTCL and, in some patients, durable responses >5 years are shown with ECP, which is markedly improved compared to the median survival of advanced stage patients around 3 years (Appendix S2)
Acute GvHD	New section, with recommendations on patient selection, treatment schedule, assessment criteria and steroid taper (Appendix S3). Literature review updated to include adults and paediatrics
Chronic GvHD	Update to assessment of response using National Institutes of Health criteria (Lee <i>et al</i> , 2015) – Appendix S4
Solid organ transplantation	New section on the use of ECP in solid organ transplantation
Technical considerations	New section with the use of closed system CELLEX (Therakos, Exton, PA USA), significantly shortening treatment times, allowing double needle access and treatment of lower body weight patients (<40 kg) low body weight is no longer an exclusion criteria Update on technical aspects of administration of ECP, including complications and their management (Appendix S5)
Quality management	New section setting out a modular Quality Assurance programme (Appendix S6)

CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; GvHD, graft-versus-host disease; MF, mycosis fungoides; SS, Sézary syndrome.

Reviews and Dissemination at the University of York, which collate information on existing clinical and economic guidelines, were also trawled along with targeted searches of bodies responsible for producing evidence based guidelines (e.g., NICE, the Agency for Healthcare Research and Quality, the National Institutes of Health).

The UK Photopheresis Society developed the updated consensus statement during two meetings over a 1-year period. This updated consensus statement builds on previously published consensus statements (Scarlsbrick *et al*, 2008; Das-Gupta *et al*, 2014), evidence-based reports and the expert opinion of the group on the appropriate use of ECP. Each centre delivering ECP was invited to comment on previously published guidelines for patient selection criteria, treatment schedule, monitoring protocol and patient assessment criteria

to determine efficacy of ECP. Where differences in opinion were identified, the group were asked to agree on an appropriate consensus position using evidence-based medicine to aid these decisions. A review of the safety and tolerability of ECP was previously undertaken with no new publications so this section has not been updated (Scarlsbrick *et al*, 2008).

Cutaneous T-cell lymphoma

Review of literature on the use of ECP in CTCL

Review of the literature on the use of ECP in CTCL continues to indicate benefit in erythrodermic CTCL, both mycosis fungoides (MF) and Sézary syndrome (SS). The schedule is agreed at one cycle consisting of two consecutive treatments

every 2–4 weeks, with response rates consistently around 60%, up to 30% CRs and a median survival of 6–8 years (Zic *et al*, 1996; Knobler *et al*, 2002). This is favourable compared to median survival of 29–62 months in stage III-IV MF/SS (Scarlsbrick *et al*, 2015). However there may be a bias towards selecting patients with a lower tumour burden who have a better prognosis as these patients respond better to ECP (Evans *et al*, 2001; Scarlsbrick *et al*, 2001).

The British Association of Dermatologists and the UK Cutaneous Lymphoma Group produced guidelines on the management of primary CTCLs in 2003 (Whittaker *et al*, 2003). There has been no further update for these guidelines nor the 2006 EORTC guidelines (Trautinger *et al*, 2006). Both guidelines advise on the treatment of all stages of CTCL from diagnosis to initial assessment and treatment according to the stage of the disease. Both recommend ECP as a first-line therapy for erythrodermic MF and SS along with other forms of immunotherapy. ECP is well tolerated with minimal side effects and is usually performed on two consecutive days every 2–4 weeks – this schedule is continued for up to 6 months to assess response. Maintenance therapy may be tailored according to disease response and severity. The response rate to ECP may be increased with the addition of immuno-modulatory therapy, such as interferon-alpha (IFN α) or bexarotene. The UK guidelines were endorsed by NICE Improving Outcomes Guidance (NICE, 2006).

The National Comprehensive Cancer Network guidelines, updated annually and published online (www.nccn.org) recommend ECP in MF/SS therapy ahead of chemotherapy in patients unresponsive to skin-directed therapy or requiring systemic therapies due to high response rates and infrequent toxicities. Improved responses without further toxicities are seen in combinations with other biological agents. A preferred selection due to better responses is for treatment in erythrodermic patients.

A comprehensive guideline produced by the European Dermatology Forum (EDF; Knobler *et al*, 2014) reports on the use of ECP for all indications. In CTCL most ECP studies have primarily included patients with advanced stages of the disease. The following prognostic factors identified include; a short duration of disease prior to ECP commencing, preferably <2 years; absence of bulky lymphadenopathy or major internal organ involvement; leucocyte count <20 $\times 10^9/l$, presence of a discrete number of Sézary cells (10–20% of mononuclear cells); natural killer cell activity close to normal; cytotoxic T-lymphocytes close to normal (CD8+ >15%); absence of prior intensive chemotherapy; and plaque stage disease not covering more than 10–15% of total skin surface.

The United States Cutaneous Lymphoma Consortium (USCLC) Review of therapeutic options, and recommendations for treatment of SS (Olsen *et al*, 2011) reports on many trials using ECP as monotherapy and in combination, with response rates varying from 40% to 80%. Excellent response to combination therapy of IFN α and ECP are reported in

those with SS. ECP is recommended as a first-line single agent in SS and treatment option with IFN α , bexarotene and methotrexate as alternatives. ECP is also recommended as combination therapy with total skin electron therapy, bexarotene, IFN α or IFN γ and methotrexate. This wide range of combinations available is representative of ECP's relative safety and tolerability.

A comprehensive review of ECP in MF and SS (Zic, 2015) reports on the benefit of ECP as a safe and effective therapy either as first-line systemic therapy in erythrodermic MF/SS or combined with IFN or bexarotene. Response rates of 50–70% with 15–25% CRs are achieved. Responses were highest with combinations reaching >80% with ECP, IFN α and bexarotene. A median overall survival of 6–8 years has been reported but needs to be proven in a trial setting. This paper also reports on predictors of response to ECP and states an improved response with relatively lower burden of malignant cells in blood as designated by the percentage of Sézary cells (32% vs. 54%), higher eosinophil count, lower CD4:CD8 ratio (13.2 vs. 44.2) or CD4+CD26– (27.4% vs. 57.2%).

UK consensus statement on ECP in CTCL

Patient selection for ECP in CTCL patients. All patients with erythrodermic CTCL stage III or IVA (Major Criteria) may be considered for ECP therapy as first-line therapy. Patients should be selected with proven peripheral blood involvement either by molecular analysis demonstrating a peripheral blood T-cell clone and/or circulating Sézary cells more than 10% of peripheral circulating lymphocytes and/or CD4:CD8 ratio >10 (Minor Criteria). Patients with major criteria and one or more minor criteria are considered suitable for ECP. This is in line with reports showing that ECP has efficacy in erythrodermic CTCL but not those with patches and plaques even with a peripheral blood clone (Child *et al*, 2004). This criterion allows treatment of patients with a peripheral blood clone who may not have a high peripheral blood burden, as these patients may benefit from ECP (Zouboulis *et al*, 1998; Stevens *et al*, 2002).

There is limited literature in early stage disease MF to determine if this group of patients may benefit from ECP although some centres have noted a response in these patients (Talpur *et al*, 2011).

Failure or intolerance of methotrexate is not considered a prerequisite prior to ECP therapy as efficacy is similar (Wain *et al*, 2005) but may be considered as an alternative first-line therapy in erythrodermic MF before ECP is initiated, particularly because it is a relatively inexpensive therapy with a once weekly oral dose. However, in SS, ECP is preferred over methotrexate due to improved responses in blood for those with leukaemic disease. Bone marrow and/or liver toxicity may occur with methotrexate and patients require regular follow-up. The National Patient Safety Agency have recently made changes to the prescribing of methotrexate including

the compulsory holding of a methotrexate record, which may alter prescribing patterns.

Patients should be excluded from ECP therapy if they are photosensitive, have a sensitivity to psoralen compounds such as 8-MOP or suffer aphakia, because of the significantly increased risk of retinal damage due to the absence of lenses. Unlike UVAR XTS[®], the CELLEX machine may be safely used in low body-weight patients. We recommend children should be considered for treatment in specialist paediatric centres.

A history of heparin-induced thrombocytopenia is a relative contraindication as heparin is used to flush the ECP machine but citrate may be used as an alternative. Treatment during pregnancy is not recommended.

Treatment schedule for CTCL. One cycle every 2–4 weeks remains the gold standard of treatment for CTCL. Despite the benefits of more frequent cycles for aGvHD patients, this benefit is not seen in CTCL. To document response in skin, blood and lymph nodes a 3-monthly assessment is required (Appendix S2). The modified Severity-Weighted Assessment Tool (mSWAT) assessment should be performed to skin score erythrodermic patients (Stevens *et al*, 2002; Appendix S7).

Peripheral blood involvement and lymph node disease must be assessed, as they are important indicators of response to treatment and stage of disease. Disease progression in blood or lymph nodes should result in a similar change to treatment protocol as disease progression in the skin. Peripheral blood tumour burden should be measured using lymphocyte count, CD4:CD8 ratio and Sézary cell count. Lymph nodes may be assessed by physical examination or imaging (computed tomography or positron emission tomography scans). Palpable lymph nodes ≥ 15 mm are considered clinically significant and should be investigated by imaging and excisional lymph node biopsy for histology to determine the 'N' stage and T cell receptor gene analysis.

Psychosocial disability is important in this group of patients and can be documented using a quality of life questionnaire, such as Skindex 29 or EORTC 30. Pruritus is a frequent and disabling symptom of erythrodermic CTCL and may be monitored using a visual analogue score. A full list of assessments to be performed is shown in Appendix S2.

Three-monthly assessments are required to monitor patient response and detect those with disease progression so combination or alternative therapies could be offered. The median time for a response to ECP is 5–6 months (Edelson *et al*, 1987; Duvic *et al*, 1996) and an early response after 6–8 cycles may be associated with an improved long-term outcome (Zic *et al*, 1996). Late responses to ECP up to 10 months after treatment has commenced have been reported (Duvic *et al*, 1996).

The 3-monthly patient assessment is aimed to highlight those with an early response and to identify those with progressive disease for combination or alternative therapy. All

patients tolerating ECP without disease progression should receive a minimum of 6 months therapy before combination or alternative therapy is considered.

Patient assessment criteria for CTCL. Patient assessments should be used to determine response to treatment. A global response assessment, as defined in the Clinical End Points Paper (Olsen *et al*, 2011), should be performed every 3 months. All responses should be determined by the percentage change in the skin score from baseline using mSWAT analysis. Patients with significant peripheral blood involvement, as defined by a raised CD4:CD8 ratio or Sézary cell count should have a blood response measured as a percentage change since baseline. (Olsen *et al*, 2011). New palpable nodes ≥ 15 mm should be considered disease progression; resolution of palpable nodes should be considered a partial (some palpable nodes ≥ 15 mm still present) or CR (no palpable nodes ≥ 15 mm). The first assessment at 3 months should be used to determine which patients may require combination therapy or offered an alternative therapy. All patients commencing ECP should receive a minimum of 6 months therapy to allow time for responses.

Combination therapy with IFN α and/or bexarotene may be considered in patients with stable or possibly progressive disease. In progressive disease, the physician should consider other treatment options (Whittaker *et al*, 2003; Trautinger *et al*, 2006) and the decision to continue treatment should only be made if the alternative treatment options are inferior. Increased response rates with both IFN α and/or bexarotene have been proven. These combinations are highly efficacious, with response rates up to 80% particularly in those with a high tumour burden (Gottlieb *et al*, 1996; Suchin *et al*, 2002). However, no prospective randomised trials have been performed.

Patients with a complete, partial or minimal response to ECP therapy should continue on the same frequency of ECP. The mean time to maximal response in CTCL has been reported as 10 months (Duvic *et al*, 1996). As with other treatments for advanced MF/SS, ECP should be continued whilst a clinical benefit is derived and cessation of therapy is not recommended whilst a response is durable. This is because there are no curative therapies for CTCL and in some patients, durable responses >5 years are shown with ECP, which is markedly improved compared to the median survival of advanced stage patients (around 3 years). Relapses of $>25\%$ in skin and blood from best response should be treated with an increased number of treatment cycles or consideration of adjuvant therapy. The median time to treatment failure is 18 months (Duvic *et al*, 2003).

Patients without response or progressive disease despite having received 6 months ECP plus combination therapy for 3 months should be considered for cessation of therapy or adjuvant therapy; only where no other treatment options exist should treatment be continued.

ECP in GvHD

Acute GvHD (aGvHD)

Review of current guidelines for use of ECP in aGvHD. The American Society of Blood and Marrow Transplantation has developed recommendations for treatment of aGvHD based on results of 29 studies evaluating products that are commercially available for secondary therapy of aGvHD (Martin *et al*, 2012). The review was limited to published studies that enrolled at least 10 patients. The evaluation of 6-month survival estimates did not support the superior choice of any specific agent for secondary therapy of aGvHD. Two studies with ECP were included, which reported different rates of 6-month survival (Messina *et al*, 2003; Perferetti *et al*, 2008). Furthermore it was concluded that even considering the evaluation of 6-month survival estimates, CR rates and overall response rates, the available data could not support the choice of any specific agent for secondary therapy of aGvHD above another (Martin *et al*, 2012). The choice of agent for second-line therapy should be based on the potential toxicity, physician familiarity and experience with the agent, convenience, availability and expense. The timing of initiation of second-line treatment should be based on severity of GvHD and rate of progression. With regard to ECP, overall infection risks do not appear to be increased beyond standard therapy; no significant interactions or increased viral reactivations are noted. They also comment on the catheter-related issues, travel inconvenience and cost. The ECP treatment schedule recommended is 3 per week (Week 1), 2 per week (Weeks 2–12) and 2 per 4 weeks thereafter.

A joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Bone Marrow Transplantation (BSBMT) has made recommendations for the diagnosis and management of aGvHD (Dignan *et al*, 2012a). The goal of treatment is effective control of GvHD while minimizing risk of toxicity and relapse. With regards to second-line treatment of aGvHD, ECP along with anti-tumour necrosis factor α (TNF α) antibodies, mammalian/mechanistic target of rapamycin (mTOR) inhibitors, mycophenolate mofetil (MMF) or interleukin-2 receptor (IL2R) antibodies are suggested (Grade 2c recommendation). ECP is noted to have an excellent safety profile with no reports of increased infection risk or disease relapse. At the time of publication, ECP for this indication was limited to centres in the UK with ECP, as patients were too unwell to travel. However outreach models have been developed for clinically unwell patients who are unable to travel to ECP centres (Maher *et al*, 2014).

The Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and the Italian Group for Bone Marrow Transplantation (GITMO) developed consensus best practice

recommendation for the use of ECP in aGvHD and cGvHD in adults and children (Pierelli *et al*, 2013). ECP is recommended for aGvHD not responding to steroid and calcineurin inhibitors. Better results are expected in patients with isolated skin involvement, while the efficacy of the procedure in visceral aGvHD is less well defined.

The EDF recommend the use of ECP in patients with aGvHD not responding to first-line therapy with corticosteroids at 2 mg/kg/day, defined as progression of aGvHD after ≥ 3 days of corticosteroid treatment or lack of response after ≥ 7 days of corticosteroids (Knobler *et al*, 2014). Patients should be treated on a weekly basis, with two to three treatments per week with cessation on achieving CR.

Review of current literature for use of ECP in aGvHD. Greinix *et al* (2006) reported a phase II study on 59 patients with acute steroid-refractory GvHD grades II to IV given extracorporeal photochemotherapy (ECP) weekly and analysed response and long-term survival. ECP was given on two consecutive days at weekly intervals and stopped immediately after achieving maximal response. Complete resolution of GvHD was achieved in 82% of patients with cutaneous involvement, 61% with liver involvement, and 61% with gut involvement. Probability of survival was 59% among complete responders compared to 11% in patients with incomplete response. Response to ECP, a shorter interval from day 0 of HSCT until the start of ECP and a shorter duration of ECP all had significantly favourable impacts on TRM. Overall survival at 4 years was significantly better in complete responders compared to those not achieving a CR (59% vs. 11%, $P < 0.0001$). Despite abrupt discontinuation of ECP after maximal response in the phase II study, the durability of response was not compromised. Intensification of ECP to 2–3 treatments per week on a weekly basis resulted in significantly improved CR rates in patients with gastrointestinal (GI) involvement (73% vs. 25%) and patients with grade IV aGvHD (60% vs. 12%). Garban *et al* (2005) reported a single-centre study of 27 patients treated with ECP for corticosteroid-resistant GvHD. Six courses were given during the first 3 weeks, then, after clinical evaluation, ECP was stopped if there was CR; in cases of partial response (PR), maintenance therapy was one course per week until CR. Nine of 12 patients with aGvHD responded to treatment. The response rates for skin, gut and liver were 10/12 (83%), 2/5 (40%) and 0/2 (0%). The authors suggest that ECP is better if performed as soon as possible after the diagnosis of aGvHD when there is minimal skin or gut involvement (Garban *et al*, 2005).

Perfetti *et al* (2008) published data on 23 patients treated with ECP for steroid-refractory aGvHD. Twelve (52%) achieved CR: 70%, 42% and 0% of patients, with grades II, III and IV aGvHD, respectively; CRs in the skin, liver and gut were 66%, 27% and 40%. Patients treated within 35 days from onset of aGvHD had higher responses (83% vs. 47%;

$P = 0.1$) suggesting ECP should be initiated early in the course of aGvHD.

Jagasia *et al* (2013) reported a multicentre comparative analysis of ECP *versus* anticytokine therapy as a second-line treatment for steroid-refractory aGvHD. Anticytokine therapy consisted of inolimumab or etanercept. Both overall response (CR+PR) and CR were significantly higher in the ECP group compared with the anti-cytokine group (66% vs. 32%, $P = 0.001$; 54% vs. 20%, $P = 0.001$). There was a significantly higher efficacy of ECP compared with anti-cytokine treatment directed at either the IL2R or TNF α pathway in patients with steroid-refractory grade II aGvHD, along with a significant survival advantage for patients receiving ECP. The study was limited by the fact that the proportions of grade III-IV aGvHD and those receiving 2 mg/kg steroids at onset of aGvHD were higher in the anti-cytokine therapy group compared with the ECP group. Further, there was no standardisation of ECP schedules and taper of immune suppression.

In a systematic review of studies for ECP in the treatment of acute and chronic GvHD, aGvHD overall response rates (ORRs) were 69% (95% confidence interval [CI], 34–95%) (Abu-Dalle *et al*, 2014). The highest ORRs were for cutaneous GvHD, at 84% (95% CI, 75–92%), followed by GI with 65% (95% CI, 52–78%). Rates of immunosuppression discontinuation were 55% (95% CI, 40–70%).

Alousi *et al* (2015) presented data from a Phase II, randomized, adaptive Bayesian design-based study. Eighty-one patients were randomized to ECP + methylprednisolone (MP) (51 patients) or MP alone (30 patients). Most patients had GvHD grade II (90%) with only 10% having grade III/IV involvement. Skin (86%) was the most commonly involved organ followed by upper GI (22%), lower GI (22%) and liver (10%). The ECP arm was more beneficial in

patients with skin-only aGvHD (72% vs. 57% response rate) whereas visceral-organ involvement response rates were similar (47% vs. 43%). Patients in the ECP arm were on lower doses of steroids by day 56 (43% vs. 30%). The ECP arm also showed better immune recovery and higher regulatory T-cells.

A summary of published data on the treatment regimens and response rates using ECP in the treatment of aGvHD is provided in Table III with data on paediatric patients given in Table IV.

ECP in chronic GvHD

Chronic GvHD (cGvHD) remains a significant barrier to long-term outcomes in patients undergoing allogeneic HCT and is a leading cause of long-term mortality and morbidity (Wingard *et al*, 2011; Socié & Ritz, 2014). There is an increased incidence of cGvHD – a trend confirmed despite controlling for factors related to donor, graft and conditioning regimen (Arai *et al*, 2015). ECP is widely used in the second-line treatment of cGvHD. In a review of both prospective and retrospective studies in the secondary treatment of cGvHD published between 1990 and 2011, ECP was the most frequently studied therapy (Martin *et al*, 2011).

Review of guidelines. A joint working group established by the BCSH and the BSBMT (Dignan *et al*, 2012b) recommended that ECP may be considered as a second-line treatment in skin, oral or liver cGvHD. The ECP schedule should be fortnightly-paired treatments for a minimum assessment period of 3 months. The strength of recommendation is Grade 1, indicating that there is confidence of the benefits and no other immunosuppressive therapeutic modality received a stronger recommendation for second-line therapy

Table III. Studies regarding use of extracorporeal photopheresis in acute graft-versus-host disease (adults).

Study reference	Patients (<i>n</i>)	Schedule	Age (years)	CR skin	CR gut	CR hepatic	ORR	Other
Ussowicz <i>et al</i> (2013)	8		Median: 20.5				Complete or partial symptom remission in 3	
Hautmann <i>et al</i> (2013)	30						30% CR, 50% PR ORR 80%	Steroids >50% in 83%
Perfetti <i>et al</i> (2008)	23			15/23 (66%)	8/20 (40%)	3/11 (27%)	12/23 (52%)	CR
Greinix <i>et al</i> (2006)	59			47/57 (82%)	9/15 (60%)	14/23 (61%)		
Garban <i>et al</i> (2005)	12	Six treatments over 3 weeks followed by consolidation		10/12 (83%)	2/5 (40%)	0/2 (0%)		
Smith <i>et al</i> (1998)	6						0%	
Dall'Amico and Messina (2002)	14			10/14 (71%)	6/10 (60%)	4/7 (57%)		
Jagasia <i>et al</i> (2013)							38 (66%)	

CR, complete response; ORR, overall response rate; PR, partial response.

of cGvHD. ECP may be considered as a third-line option for cGvHD involving other organs, a Grade 2 recommendation (Grade 2 recommendations require judicious application to individual patients).

The German/Austrian/Swiss consensus conference on second-line treatment of cGvHD reviewed published evidence and conducted a survey on current clinical practice in transplant centres from Germany, Austria and Switzerland (Wolff *et al*, 2011). ECP was recommended with C-1 grading, indicating that use in second-line treatment was justified. Particular note was made of the steroid-sparing effect and excellent safety profile. Two Italian scientific societies, SIdEM and GITMO, joined to develop and disseminate recommendations on appropriate application of ECP treatment in patients with GvHD (Pierelli *et al*, 2013). ECP is recommended in both adults and paediatric patients with cGvHD, either steroid-resistant or steroid-dependent, irrespective of disease extent and severity. ECP could potentially allow for steroid sparing in responding patients and is anticipated to improve quality of life in responding patients.

Review of literature. Since the publication of the last consensus statement there have been further publications regarding the use of ECP in cGvHD (Martin *et al*, 2011). However there remains a lack of high quality data due to the continuing difficulty of conducting trials in cGvHD. In addition, comparison between different studies is complicated by the different ECP regimens used, different immune suppressive regimens adopted and lack of consistent application of diagnostic and response criteria. Despite these limitations, studies have shown consistently high ORR and a good safety profile. There is also a suggestion that, in addition to clinical responses, ECP may also lead to an improvement in quality of life in cGvHD (Pierelli *et al*, 2013; Dignan *et al*, 2014).

Our literature search identified a total of 27 studies, including 725 adult patients treated with ECP with steroid-resistant, -intolerant, or -dependent cGvHD with at least five patients in each study (Table V). Response rates for cutaneous cGvHD were available from 23 studies with a mean response rate of 74%. Response rates for hepatic cGvHD were reported in 15 studies with a mean response of 62%. The mean response rate reported in four studies for ocular GvHD was 60%. Twelve studies reported on mucosal GvHD with a mean response rate of 62% and five studies reported a mean response rate of 46% in relation to GI involvement. The response rate was 46% for pulmonary cGvHD in nine studies reported. ORRs were available from 14 studies with a mean ORR of 68%. Pierelli *et al* (2013) reviewed 23 studies reporting on 735 patients treated with ECP for steroid-resistant, -intolerant, or -dependent cGvHD. Overall and CRs were observed in 64% and 35% of cases with cutaneous involvement and in 56% and 27% with hepatic cGvHD, respectively. The ORR was 47–57% in oral mucosa and GI cGvHD. High response rates, i.e. near 50%, were also reported in children with ocular involvement.

Scarlsbrick *et al* (2008) reported on 23 individual studies published responses to ECP in 521 patients. The response rate in cutaneous cGvHD was reported in 18 studies with a mean response of 68% and CR being achieved in some patients; response rates in the liver were reported in 10 studies with a mean response of 63% and response rates in the mucosa were reported in nine studies with a mean response of 63%. A multicentre prospective phase 2 randomized study of ECP for treatment of cGvHD compared ECP plus standard *versus* standard therapy alone in patients with cutaneous manifestations of cGvHD that could not be adequately controlled by corticosteroid treatment (Flowers *et al*, 2008). The primary efficacy end point was a blinded quantitative

Table IV. Studies regarding use of extracorporeal photopheresis in acute and chronic graft-versus-host disease (paediatrics)

Study reference	Patients (n)	CR acute skin, n (%)	CR acute liver, n (%)	CR acute gut, n (%)	cGvHD	OR (%)
Calore <i>et al</i> (2015)	72	50 (78%)	10 (84%)	42 (76%)	52 (72%)	Acute: 83%
Uygun <i>et al</i> (2015)	6 acute 4 overlap 2 chronic	3/6 (50%)	0/2 (0%)	2/4 (50%)		66% Acute: 50% Chronic: 100% Overlap: 75%
Bykova <i>et al</i> (2013)	37 chronic				26/37 (70%)	Acute: 70%
Salvaneschi <i>et al</i> (2001)	9 acute 14 chronic	7/9 (78%)	1/3 (33%)	3/5 (60%)	9/14 (64%)	Acute: 78% Chronic: 64%
Messina <i>et al</i> (2003)	33 acute 44 chronic	27/33 (82%)	9/15 (60%)	15/20 (75%)	26/44 (59%)	Acute: 76% Chronic: 59%
Berger <i>et al</i> (2007)	15	8/12 (67)	3/4 (75)	5/7 (71)		
Gonzalez Vicent <i>et al</i> (2010)	8	8/8 (100)	2/2 (100)	4/7 (57)		
Kanold <i>et al</i> (2007)	12 acute 15 chronic	10/10 (100%)	6/9 (67%)	5/6 (83%)	11/15 (73%)	Acute: 83% Chronic: 70%
Perotti <i>et al</i> (2010)	50 acute 23 chronic	39/47 (83%)	16/24 (67%)	8/11 (73%)	16/23 (70%)	Acute: 68% Chronic: 70%

cGvHD, chronic graft-versus-host disease; CR, complete response; OR, overall response.

Table V. Studies regarding use of ECP in cGvHD.

Study reference	Patients (n)	Study type	Treatment schedule	cGvHD							Prior to ECP	During ECP	Catheter-related		
				Skin	Mucosa	Liver	GI	Ocular	Lung	ORR				CR%	PR
Ussowicz <i>et al</i> (2013)	13									4-year OS 67.7%					
Bykova <i>et al</i> (2013)	49	Retrospective		74%	76%	82%				OS 70%					
Hautmann <i>et al</i> (2013)	32	Retrospective, COBE Spectra	One cycle/week until improvement followed by one cycle every other week for 3–4 weeks and subsequent treatment one cycle every month	59%	60%	100%			44%	2 (6%)	12 (38%)	TRM deaths 11 (34%); Relapse deaths 3 (9%)	Steroids <50% in 29% patients after 3 months. 16% discontinued steroids	3	Catheter infection: AF: 1
Del Fante <i>et al</i> (2012)	102	64 (62.7%) had classic cGvHD, 24 (23.5%) had overlap cGvHD	3 rounds of 2/week, 3 of 2 every other week, and finally 2/ month until clinical improvement and/or IST tapering						80%	16 (15.7%)	38 (37.3%)		Complete withdrawal of ECP in 56.25%		
Dignan <i>et al</i> (2012c)	82	Retrospective	Bimonthly for two consecutive days tapered to a monthly regimen depending on response	91%	91%				65/69 (94%) had ≥50% improvement in symptoms and signs of cGvHD		69% at 3 years	None (12), one (10), two (40), three (14), ≥four (6)	80% had decreased their steroid dose (27.5% stopped, 30% had ≥75% reduction, 17.5% had ≥50% reduction and 25% had <50% reduction)	Skin with CR 7/62 (11%), PR 50/62 (81%); mucosa with CR 1/32 (3%), PR 28/32 (88%)	

Table V. (Continued)

Study reference	Patients (n)	Study type	Treatment schedule	cGvHD							ORR	CR%	PR	Prior to ECP	During ECP	Catheter-related
				Skin	Mucosa	Liver	GI	Ocular	Lung							
Greenix <i>et al</i> (2011)	29	Open-label crossover ECP study	3 times during week 1, then twice weekly until week 12, followed by 2 treatments monthly until week 24	31%	70%	50%	60%	57%	57%	31%			<25% reduction in corticosteroid dose at week 12 of the initial study	4 (17%) and 8 (33%) patients, a >50% reduction in corticosteroid dose at weeks 12 and 24 was observed		
Flowers <i>et al</i> (2008)	48	Prospective phase 2 randomized study		40%	53%	29%	30%							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 ($P = 0.04$)		
Jagasia <i>et al</i> (2009)	Overlap 12; cGvHD 31	Classic and overlap	Paired weekly for 3-4 weeks and then decreased to an every 2- to 3-week interval							88%	3 (10%) 10 (32%) 1 (3%)	17 (55%) 36% at 3 years				
Perseghin <i>et al</i> (2007)	25	19 treatments		80%											NK	
Gasova <i>et al</i> (2007)	6			87%												
Motolese <i>et al</i> (2007)		Prospective, ocular	12 months ECP								10/21 (48%)					
Bisaccia <i>et al</i> (2006)	14	'3 treatments over 17 months'		100%	42%	60%	42%	20%	100%					4/13 (31%) discontinued steroids		

Table V. (Continued)

Study reference (n)	Patients (n)	Study type	Treatment schedule	cG×HD							PR	During ECP	Catheter-related	
				Skin	Mucosa	Liver	GI	Ocular	Lung	ORR				CR%
Couriel <i>et al</i> (2006)	71			57%	78%	71%		67%	54%	61%	20% (14/71)	53% at 1 year	Overall response 61%. Best responses were observed in skin, liver, oral mucosa and eye	
Rubegni <i>et al</i> (2005)	32			100%		90%		100%	60%	78%				
Garban <i>et al</i> (2005)	15		6 courses over 3 weeks followed by consolidation	100%		33%	77%			87%	11/15 (73%)	2/11 (18%)		
Foss <i>et al</i> (2005)	25	Prospective	2 consecutive days every 2 weeks or one per week	80%	24%		46%			64%	ORR 64%			
Ilhan <i>et al</i> (2004)	8	2 consecutive days every 2–4 weeks		75%						75%				
Seaton <i>et al</i> (2003)	28		Fortnightly for 4 months and then monthly	53%	50%									
Messina <i>et al</i> (2003)	44			84%		60%	47%		44%	73%		5-year overall survival was 96% for responders versus 58% for non-responders (<i>P</i> = 0.04).		
Bisaccia <i>et al</i> (2003)	6		Thrice weekly for mean 7.2 months	100%		100%				81%				
Apisarnhanarax <i>et al</i> (2003)	32		A median of 6 sessions per month	56%						56%			All 21 surviving patients remain on some therapy	
Child <i>et al</i> (1999)	11		2 treatments/ 2 weeks for 4 months then taper	90%	75%	20%			40%				PSE (9), CSA (7), Az (6), Th (3), PUVA (3)	PSE (7), CSA (5), Az (4)

Table V. (Continued)

Study reference	Patients (n)	Study type	Treatment schedule	cGvHD							PR	Prior to ECP	During ECP	Catheter-related
				Skin	Mucosa	Liver	GI	Ocular	Lung	ORR				
Greinix <i>et al</i> (1998)	15		2 treatments/ 2 weeks for 3 months then 2 treatments/ 4 weeks	80%	100%	70%						MP (13), CSA (11), Az (1), Th (2), PUVA (2)	MP (8), CSA (8), Th (1), none (2)	
Smith <i>et al</i> (1998)	18		2-3 treatments/ 3 weeks	36%		30%			0%	33%		PSE (18), CSA (18), Th (8), PUVA (5)	PSE + CSA (all)	
Besnier <i>et al</i> (1997)	5		3 treatments/week for 3 weeks then taper	100%		100%			100%			PSE (2), MP (1), Th (1), none (2), CSA (1), Az (1) (1)	PSE/MP (3), CSA (1), Az (1), Th (1)	
Rossetti <i>et al</i> (1996)	8		2 treatments/ 3 weeks for 6 months then taper	43%	20%	33%	0%		40%			PSE (5), CSA (5), Az (3), Th (3), MTX (2), Ab (1), NK (2)	PSE (3), CSA (3), NK (4)	
Aubin <i>et al</i> (1995)	7		NK	70%								NK	NK	

Ab, OKT3 monoclonal antibody; AF, atrial fibrillation; Az, azathioprine; cGvHD, chronic graft-versus-host disease; CR, complete response; CSA, ciclosporin; ECP, extracorporeal photopheresis; GI, gastrointestinal; IST, immunosuppressive therapy; MP, methylprednisolone; MTX, methotrexate; NK, not known; OR, overall response; PR, partial response; PSE, prednisolone; PUVA, psoralen-ultraviolet A, Th, thalidomide; TRM, treatment-related mortality; TSS, total skin score.

comparison of per cent change from baseline in Total Skin Score (TSS) of 10 body regions at week 12. 48/95 patients were randomized to ECP and standard therapy and 47/95 to standard therapy alone. The proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease from baseline in TSS was 8.3% in the ECP arm at week 12 and 0% in the control arm. The non-blinded investigator assessment of skin CR or PR revealed a significant improvement in favour of ECP, which was generally well tolerated. These results suggest that ECP may have a steroid-sparing effect in the treatment of cGvHD. In this study, however, only the skin score was used to assess primary efficacy end point and the physicians changing the immunosuppression were aware of the study assignment. A follow-up crossover randomized study showed progressive improvement in cutaneous and extra-cutaneous cGvHD after a 24-week course of ECP with a steroid-sparing effect, suggesting that prolonged ECP is necessary for optimal therapeutic effects in corticosteroid-refractory cGvHD patients (Greinix *et al*, 2011). Complete or partial skin response at week 24 was noted in 31%. In 17% and 33% patients, a >50% reduction in corticosteroid dose at weeks 12 and 24 was observed. Extra cutaneous cGvHD response was highest in oral mucosa with 70% complete and partial resolution after week 24.

Twenty-five patients with extensive, steroid-refractory cGvHD were enrolled in a prospective trial evaluating the efficacy of ECP in skin and visceral cGvHD (Foss *et al*, 2005). Twenty had improvement in cutaneous GvHD and six had healing of oral ulcerations. Steroid-sparing or discontinuation of immunosuppressive medications was possible in 80% of patients. Response rates were similar between patients receiving treatment weekly *versus* fortnightly and in patients commencing ECP less than *versus* greater than 18 months from transplant (70% *vs.* 66%). Del Fante *et al* (2012) reported on a 14-year experience of ECP in 102 patients with cGvHD according to the National Institutes of Health (NIH) classification. Sixty-four had classic cGvHD, 24 had overlap cGvHD. Response was complete in 15.7%, partial in 37.3%, minimal in 27.5% and absent in 19.6%. ECP represented a third-line treatment for the majority of patients and in many patients, the duration of cGvHD and the interval between GvHD diagnosis and ECP start were very long, suggesting that ECP can be proposed at any disease stage. No correlation was identified between response and NIH clinical subtype, number or degree of organ involvement. In particular, no response was seen in 13 patients with lung involvement. Couriel *et al* (2006) retrospectively evaluated 71 patients with severe cGvHD treated with ECP. Response rate was 61% and 14 patients achieved CR. The best responses were observed in skin, liver, oral mucosa and eye. There was a cumulative incidence of discontinuation of corticosteroids at 1 year of 22% (Couriel *et al*, 2006).

In a systematic analysis of prospective interventional trials – randomised controlled trials or observational trials

– evaluating the efficacy of ECP for treatment of steroid-refractory or steroid-dependent acute or cGvHD (Abu-Dalle *et al*, 2014), the pooled ORR for cutaneous disease was 71% (95% CI, 57–84%), GI was 62% (95% CI, 21–94%), hepatic 58% (95% CI, 27–86%), oral mucosa 63% (95% CI, 43–81%), 45% (95% CI, 18–74%), and pulmonary in 15% (95% CI, 0–50%). This analysis suggests organ-specific response appears to be higher in cutaneous, GI, hepatic and oral mucosa, with suggestion of a very limited role of ECP on pulmonary cGvHD. The pooled incidence of any grade 3- or 4 adverse events from two studies (53 patients) was 38% (95% CI, 6–78%). The pooled rate of discontinuation of immunosuppressive therapies, including corticosteroids, from three studies (54 patients) was 23% (95% CI, 7–44%). A systemic review looking at cGvHD showed pooled response rate for skin, liver, ocular, oral, lung, GI and musculoskeletal. Steroid-refractory cGvHD was 74%, 68%, 60%, 72%, 48%, 53% and 64%, respectively (Malik *et al*, 2014).

Steroid-sparing or reduction of other medications has been identified as an important beneficial effect of ECP therapy in patients with cGvHD, who suffer substantial immunosuppression-related morbidity and mortality (Apisarnthanarax *et al*, 2003; Foss *et al*, 2005; Dignan *et al*, 2012c; Ussowicz *et al*, 2013; Ruutu *et al*, 2014).

Response to ECP predicts survival (Couriel *et al*, 2006; Del Fante *et al*, 2012). In 2005, the NIH cGvHD Consensus Response Criteria Working Group recommended several measures to document serial evaluation of cGvHD organ involvement (Filipovich *et al*, 2005). Although meant primarily for standardizing clinical trials there is evidence for use in routine clinical practice (Palmer *et al*, 2014).

In 2014, the working group updated its recommendations for measures and interpretation of organ and overall responses (Lee *et al*, 2015). The recommendations for assessment are based on clinician-assessed and patient-reported signs and symptoms, the Lee cGvHD Symptom Scale, and clinician-assessed or patient-reported global rating scales. Collaboration with sub-specialists is encouraged for organ-specific measurements. Age-appropriate modifications of existing measures are to be used in children with cGvHD. The 2014 NIH response measures and clinician-reported response at 3 and 6 months correlated with subsequent failure-free survival in a prospective cGvHD observational trial of 575 patients, suggesting the 2014 NIH response measures as reflective of disease activity though not predictive of overall survival and a smaller study showed the lung function score is sensitive to change and is useful as a response measure (Olivieri *et al*, 2013; Palmer *et al*, 2015). In a prospective, multicentre, observational study, worsening of the NIH symptom-based lung score was associated with increased mortality (Palmer *et al*, 2014). Another study suggests that NIH classification can predict outcome after ECP for steroid-refractory/dependent GvHD (Jagasia *et al*, 2009).

Use of ECP in thoracic organ transplantation

Heart transplantation

Although a number of case reports had suggested benefits of using ECP in heart transplant recipients, the first major study to evaluate ECP in this population was a multi-centre randomised controlled study published in 1998, evaluating ECP as an adjunct to standard triple drug immunosuppression with acute rejection episodes as the primary outcome measure (Barr *et al*, 1998). This study randomised 60 patients who had undergone heart transplant in a 1:1 ratio and the ECP group received 24 treatments in their first 6 months. The number of acute rejection episodes was significantly reduced in the ECP arm, with 0.91 ± 1.0 rejection episodes per recipient compared with 1.44 ± 1.0 in the standard treatment arm, $P = 0.04$. There was no effect on survival between the two groups at either 6 or 12 months. This pioneering study set a standard for ECP studies that has not been reached since and gave clear evidence that addition of ECP to standard immunosuppression can reduce the number of acute rejection episodes after heart transplantation.

As the use of ECP on all recipients is resource intensive and may be unnecessary, a series of small cases series were published to explore the role of ECP in the treatment of either severe or recurrent rejection in heart transplant recipients. Dall'Amico *et al* (2000) targeted 11 patients with recurrent acute rejection and gave 3 months of ECP therapy with a tapering frequency of treatment. They showed a significant reduction in the frequency of acute rejection episodes and lowering of rejection grade. Six rejection relapses were observed in a total follow-up of 60 months. This observational study was not randomised and so its findings, although encouraging, should be treated with caution. Lehrer *et al* (2001), treated four patients with refractory rejection of International Society for Heart and Lung Transplantation grades 3A to 4 with ECP on 2 consecutive days and showed complete histological resolution of rejection in 3 of 4 recipients. The other patient's rejection resolved with 2 further days of ECP treatments. The authors suggest that photopheresis is a safe and effective treatment for severe refractory heart transplant rejection. In the most severe manifestation of cardiac rejection, the recipient suffers from haemodynamic compromise and an observational study targeted ECP to this cohort of recipients (Kirklin *et al*, 2006). From a cohort of 36 patients treated with ECP for heart rejection at their centre, 12 were treated for rejection causing haemodynamic compromise. After 3 months of ECP the risk of rejection causing haemodynamic compromise was dramatically reduced to that of the standard heart transplant population. To assess the benefits of ECP in paediatric heart transplant recipients, Carlo *et al* (2014) reported outcomes from 20 heart transplant recipients, all <18 years of age with a median age of 15.3 years, at the start of ECP. The main indication was for recurrent or severe acute rejection. The survival

after ECP was 84% at 1 year and 53% at 3 years, suggesting poor outcomes. The authors suggest that 11 of these 20 recipients had issues with compliance and these are the ones with the poorest outcomes. This is important as it suggests that use of ECP without good compliance with maintenance immunosuppression may not be protective in the paediatric group.

Lung transplantation

Initial experience treating lung transplant recipients was reported in 1999, when Salerno and colleagues treated eight recipients with progressive loss of lung function after lung transplantation (Salerno *et al*, 1999). Seven of these patients had advanced bronchiolitis obliterans syndrome (BOS) stage 3. After a median of six treatments there was a stabilisation of lung function loss in 5 of 8 recipients and no significant complications were reported. Due to the lack of randomisation or monitoring of a control group with advanced BOS, whether this was a true treatment effect or represented the natural history of BOS cannot be ascertained. Villanueva *et al* (2000) treated 14 BOS patients with ECP and suggested that those ($n = 8$) with earlier stage disease BOS, 0-p or 1, experienced more benefit than those with more advanced disease in terms of stabilisation of lung function. Again, the retrospective observational nature and small sample size limits the reliability of these findings.

In 2008, a group from Zurich published a single centre experience with ECP for BOS and recurrent acute rejection after lung transplantation over a 10-year period (Benden *et al*, 2008). Twenty-four recipients were treated; 12 for BOS and 12 for acute rejection. The rate of loss of forced expiratory volume in 1 s (FEV1) and overall graft survival were used as primary and secondary endpoints respectively in BOS patients. In this group, FEV1 declined at 112 ml/month before ECP and at 12 ml/month after 12 cycles of ECP ($P = 0.011$). Median patient survival post-ECP was 4.9 (range, 0.5–8.4) years. Patients with recurrent rejection experienced stabilisation. Neither group reported any ECP-related complications.

Morrell *et al* (2010) reported the effects of ECP therapy on 60 lung transplant recipients with progressive BOS treated between 2000 and 2007. In the 6 months prior to ECP, their rate of FEV1 loss was 116 ml/month. In the 6 months after ECP was commenced, this had fallen to 28.9 ml/month, $P < 0.0001$. The authors concluded that ECP is an effective way to significantly reduce the rate of decline of FEV1 in recipients with BOS.

More recently, Greer *et al* (2013) reported their large single centre experience of 65 patients with Chronic Lung Allograft Dysfunction (CLAD) treated with ECP between 2007 and 2011. In the study, patients were retrospectively allocated to a CLAD phenotype according to the proposed new classification system as either classical BOS, restrictive allograft syndrome (RAS) or neutrophilic CLAD. The vast majority of those

receiving ECP had previously failed to respond to azithromycin therapy. After ECP, 35 (54%) patients either stabilised or increased their lung function by >10% while the remaining patients lost >10% of FEV1. In this responder group, median survival was 401 days compared to 133 days in the non-responders. Factors associated with being a non-responder were rapid decline in lung function prior to ECP, the RAS phenotype and absence of neutrophilic inflammation.

Jaksch and colleagues from Vienna, have reported a prospective study of ECP therapy in recipients with BOS (Jaksch *et al*, 2012). It was a single centre observational study with ECP added as a therapy to those with progressive BOS despite full conventional therapy. In a cohort of 194 recipients who developed BOS, 51 received ECP. Thirty-one patients (61%) from the ECP group responded to treatment and showed sustained stabilisation of lung function, improved survival and less need for re-transplantation. Factors associated with non-responders were a diagnosis of cystic fibrosis and late-onset BOS. The mechanism of action of ECP in lung transplant recipients remains poorly understood. Baskaran *et al* (2014) investigated the immunomodulatory actions of ECP when used in recipients with BOS. In their study, sera were collected from recipients with BOS immediately before and 6 months after ECP commenced. Changes in titres of donor-specific antibodies, antibodies against self-antigens (K α 1-tubulin, collagen I and V) and circulating levels of pro-inflammatory and anti-inflammatory cytokines were quantified. The study showed ECP was associated with a fall in antibody titres, a reduction in pro-inflammatory cytokine levels and increase in anti-inflammatory levels. There was a 63% reduction in the rate of decline of lung function after ECP in recipients with BOS.

Further evidence about the impact of CLAD phenotypes on the effectiveness of ECP was recently reported (Del Fante *et al*, 2015). In this single centre experience of 48 recipients with CLAD, they concluded that although ECP reduced the rate of decline in FEV1 overall it was least effective in those with the RAS phenotype but that rapid loss of lung function in BOS was not associated with a poor response rate.

Consensus statement for ECP in heart and lung transplantation.

- ECP has been used safely in both heart and lung transplant recipients with very few complications and appears to be well tolerated.
- ECP can be used as an adjunct to standard immunosuppression in heart transplantation and reduces the risk of acute rejection. Evidence of clinical and cost effectiveness of routine ECP use in improving long-term outcomes in heart transplantation is absent.
- ECP can be used to rescue both adult and paediatric heart transplant recipients with recurrent acute rejection or severe rejection associated with haemodynamic compromise with a rapid response to therapy.

- ECP has been used effectively to slow the rate of lung function loss in patients with Chronic Lung Allograft Dysfunction (CLAD). It appears that its effectiveness is limited to the BOS phenotype rather than the RAS phenotype.
- ECP has been used successfully to reduce the risk of acute rejection in those with a history of recurrent acute rejection episodes after lung transplantation.
- Only a proportion of recipients with BOS respond to ECP therapy and the responders show benefits in protection of lung function and improved survival.
- More randomised controlled studies of ECP in thoracic organ transplantation are needed before clear guidance on when and in which patients ECP has a clinical and cost-effective role.

Other solid organs

Graft-versus-host disease is a rare complication of solid organ transplantation with an incidence varying between 5-6% and 10% following small bowel (Mazariegos *et al*, 2004; Andres *et al*, 2010) and 0.1-1% after liver transplant (Kohler *et al*, 2008). The mortality remains high in the setting of small bowel transplantation (Andres *et al*, 2010). ECP has been reported to treat GvHD following solid organ transplantation (Rossi *et al*, 2014; Houston *et al*, 2016). Houston *et al* reported the use of ECP in patients with GvHD post-multivisceral transplant (stomach, pancreas, liver, small bowel and colon) as late-stage salvage therapy (Houston *et al*, 2016). ECP was delivered on days 62 and 67 post-transplant, with reduction in chimerism from 78% to 67% over 9 days but the patient succumbed to sepsis on Day 73. Rossi *et al* (2014) treated GvHD following simultaneous pancreas-kidney (SPK) transplant, providing seven treatments, associated with chimerism reduction (52-13%) and survival (Rossi *et al*, 2014). ECP has also been used in transplant rejection following face (Dubernard *et al*, 2007), kidney (Kusztal *et al*, 2011) and liver transplantation (Urbani *et al*, 2004). Kusztal *et al* (2011) incorporated ECP prophylaxis along with immunosuppressive treatment in 10 patients undergoing kidney transplantation. Addition of ECP to standard immunosuppression was associated with a significantly higher glomerular filtration rate at 6 months and with a significant increase in natural regulatory T cells among CD3 cells. Urbani *et al* (2007) reported a prospective study to evaluate a strategy to use ECP to delay calcineurin inhibitor therapy in patients at high risk of renal or neurological complications. In the 36 patients evaluated there were 18 ECP patients and 18 controls. There was no statistical significance between the groups regarding acute rejection, renal or neurological toxicities. However, 1-, 6-, and 12-month survival rates were significantly higher in the ECP arm compared to control.

Consensus statement for ECP in other solid organ transplantation.

- The use of ECP in the above transplant settings appears undefined. Further studies are needed to base recommendations regarding the role of ECP and where it fits in the overall management of the patient.

Biomarkers in GvHD

Significant efforts have been made to identify biomarkers for use in the diagnosis, risk stratification and prediction of response to treatment in GvHD. Most are limited, generated in single institutions, and are yet to be validated. The NIH 2014 Biomarker Working Group developed a consensus statement for trials in cGvHD (Paczesny *et al*, 2015). The tests for biomarkers must be cost-effective, reproducible and accurate.

Much of the initial work has been hypothesis-driven, with understanding of the pathophysiology of GvHD leading to focus on certain cells, mediators and genetic polymorphisms. More recently with the introduction of 'omics', screening of samples for large numbers of proteins (Devic *et al*, 2014), DNA (Petersdorf, 2013) and RNA transcripts (Ranganathan *et al*, 2012) has suggested more candidates. The most promising candidates include the numbers and activity of different cells, particularly B cells, natural killer (NK) cells and T regulatory cells (Tregs). Many cytokines, cytokine receptors and chemokines involved in lymphoid homeostasis, trafficking and activation have been proposed, including the common gamma chain cytokines, TNF α , B-cell activating factor (BAFF, also termed TNFSF13B), CXCL10, CXCR3 and CXCR7. Genetic polymorphisms associated with increased or reduced cytokine production have also been studied. Biomarkers have been reviewed in acute (Paczesny, 2013) and chronic GvHD (Pidala *et al*, 2014; Karimnia *et al*, 2016).

Diagnosis

Some of the most promising diagnostic biomarkers are lymphocytes. Patients with extensive chronic GvHD tend to have low B cell and NK cell counts and high T cell counts in blood (Abrahamsen *et al*, 2005). GvHD has been associated with lower IgM memory B cell counts (D'Orsogna *et al*, 2009) and CD27-positive B cells (Greinix *et al*, 2008). High BAFF levels (Sarantopoulos *et al*, 2009) and alterations in the B cell response to Toll-like receptor 9 (She *et al*, 2007) have also been seen. Tregs are also implicated, with expression of FOXP3, a transcriptional repressor uniquely expressed in Tregs, reduced in patients with GvHD (Miura *et al*, 2004). Possible mediators for the diagnosis of GvHD include BAFF, CXCL9, elafin, aminopeptidase N, soluble CD13, soluble IL2Ra, IL6 and TNF α (Tanaka *et al*, 1996; Rozmus *et al*, 2011; Kitko *et al*, 2014).

Risk stratification

The expression of FOXP3 and number of Tregs are negatively correlated with the severity of GvHD (Li *et al*, 2010). Patients with high suppression of tumorigenicity 2 (ST2) levels at initiation of therapy are more likely to fail therapy and die within 6 months (Vander Lugt *et al*, 2013). ST2 levels taken on day 28 following cord blood transplant predict the occurrence of severe GvHD (Ponce *et al*, 2015). Polymorphism of the *IL10* promoter gene have been associated, in a dose-dependent fashion, with both the likelihood of developing GvHD and the length of immunosuppression therapy required (Kim *et al*, 2005). Absence of TNF α -238 A allele is associated with chronic extensive GvHD (Bertinetto *et al*, 2006).

Prediction of response

Tregs numbers in patients with GvHD who received IL2 was associated with resolution of GvHD (Koreth *et al*, 2011). The frequency and number of recent thymic emigrants in Tregs normalise in resolved GvHD but remain decreased in active disease (Mahadeo *et al*, 2014). Lower levels of soluble IL2Ra are associated with therapeutic response (Fujii *et al*, 2008).

Consensus statement for biomarkers in ECP and GvHD.

- Despite the number of proposed biomarkers there is currently insufficient evidence to recommend the routine use of biomarkers for the diagnosis, risk stratification or assessment of therapy response of GvHD. Further investigation, including biobanking of samples, is recommended.

Safety report on ECP

Several papers have reported on the safety profile of ECP in the treatment of CTCL and GvHD and of more than 500 000 treatments performed worldwide since 1987, the incidence of reported adverse events is less than 0.003%. The most common side effects are sporadic and mild, such as nausea, fever or headache. The constant feature in all these papers is that ECP is noted to be an extremely safe form of therapy and significant reactions, such as vasovagal syncope, or infections secondary to indwelling catheters are infrequent (Perotti *et al*, 1999; Perotti *et al*, 2010; Dignan *et al*, 2012b). Safety was reported in our 2007 guidelines and no relevant additional information was identified to include here. This is beneficial in a group of patients where alternative therapies are highly immunosuppressive either as chemotherapy agents in CTCL, such as methotrexate, deoxycoformycin and CHOP (cyclophosphamide, doxorubicin, vincristine prednisone) or immunosuppressive therapies such as prednisolone, ciclosporin or MMF in GvHD.

- In summary, ECP is a safe form of therapy with serious side effects, such as sepsis, occurring infrequently, which is

extremely valuable in patients where alternative treatments are highly toxic.

Quality management

The governance arrangements for apheresis procedures including ECP have been the subject of recent National and European guidance publications (Società Italiana di Emaferesi e Manipolazione Cellulare & International Foundation for Hemapheresis and Innovative Therapies and Diagnostics, 2014; Howell *et al*, 2015). There are approximately 10 000 ECP treatments per year in the UK, performed in a variety of clinical settings and specialty departments. Whilst the majority of therapeutic apheresis is performed in large units, ECP may be sited in units that are not routinely performing other therapeutic apheresis. As a consequence it is important that the general principles of safe and effective apheresis are followed.

The predominant indication for ECP is the second-line management of GvHD and, as such, the delivery of an ECP service has been included in the FACT (Foundation for the Accreditation of Cellular Therapy)-JACIE (Joint Accreditation Committee for the ISCT [International Society for Cellular Therapy] and EBMT [European Group for Blood and Marrow Transplantation]) quality standard recommendations for HCT units, and therefore any ECP unit treating this patient group would be expected to meet these standards (FACT-Jacie, 2014). An ECP service should have a Quality Assurance programme, with regular documented oversight (Appendix S6).

Conclusions

The literature supports ECP as an effective therapy in CTCL and acute and chronic GvHD in the adult and paediatric setting. Most countries only provide ECP in specialised centres allowing expertise to develop, in keeping with NICE guidelines. We have used evidence-based medicine and best medical practise of our UK Photopheresis Society (UKPS) group to update the 2007 Consensus Statement for patient selection, treatment schedule, monitoring and assessment of ECP therapy in CTCL and GvHD and solid organ rejection. This will enable ECP to be delivered safely to the 'right' patients to obtain maximum efficacy. These recommendations are

intended to act as a guide for healthcare professionals who are currently involved in providing ECP therapy or considering developing a service. This updated consensus statement has benefited from further trials and expert knowledge from the UKPS to deliver a statement that encourages a regime which provides best response with minimal adverse events.

The recommendations are intended to act as a consensus statement on best practice based on the current evidence base on ECP and the opinions of the expert group. However, it is recognised that any recommendations may need to be revised in light of any new clinical findings on ECP.

Acknowledgements

The UK Photopheresis Society is supported by an unrestricted educational grant by Mallinckrodt Ltd.

Author contributions

All authors contributed to the sections and reviewed the manuscript.

Competing interests

No competing interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Strength of recommendations and quality of evidence assessment of ECP for various conditions.

Appendix S2. Consensus statement on the use of extracorporeal photopheresis for cutaneous T-cell lymphoma.

Appendix S3. UK consensus statement for ECP in acute graft-versus-host disease.

Appendix S4. UK consensus statement for use of ECP in cGvHD, including assessments.

Appendix S5. Technical aspects of administration of ECP including complications and their management.

Appendix S6. Quality management in ECP.

Appendix S7. Severity weighted assessment tool (mSWAT) in erythrodermic CTCL (Olsen *et al*, 2011).

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