Ontario
Cancer Care Ontario
Action Cancer Ontario

Recommendation Report SCT-5

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Extra-corporeal Photopheresis in the Management of Graft-Versus-Host Disease in Patients who Have Received Allogeneic Blood or Bone Marrow Transplants: Recommendations

C. Bredeson, R.B. Rumble, N.P. Varela, J. Kuruvilla, C.T. Kouroukis, and the Stem Cell Transplant Steering Committee

Report Date: August 29, 2013

An assessment conducted in February 2023 deferred the review of Recommendation Report SCT-5. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Recommendation Report SCT-5 is comprised of 2 sections. You can access the summary and full report here:

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/966

Section 1:	**Recommendations**
Section 2:	**Evidentiary Base**

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Bredeson C, Rumble RB, Varela NP, Kuruvilla J, Kouroukis CT; Stem Cell Transplant Steering Committee. Extra-corporeal photopheresis in the managemet of graft-versus-host disease in patients who have received allogeneic blood or bone marrow transplants: recommendations. Toronto (ON): Cancer Care Ontario; 2013 Aug 29. Program in Evidence-Based Care Recommendation Report No.: SCT-5.

Journal Citation (Vancouver Style): Bredeson C, Rumble RB, Varela NP, Kuruvilla J, Kouroukis CT; Stem Cell Transplant Steering Committee. Extracorporeal photopheresis in the management of graft-versus-host disease. Curr Oncol. 2014;21(2):e310-25.

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Extra-corporeal Photopheresis in the Management of Graft-Versus-Host Disease in Patients who Have Received Allogeneic Blood or Bone Marrow Transplants: Recommendations

C. Bredeson, R.B. Rumble, N.P. Varela, J. Kuruvilla, C.T. Kouroukis, and the Stem Cell Transplant Steering Committee

Report Date: August 29, 2013

RESEARCH QUESTION

Is there a benefit associated with the use of extra-corporeal photopheresis (ECP) compared with other treatment options for patients who have received an allogeneic transplant and are experiencing graft-versus-host disease (GVHD) if response rate, survival, or improvement in symptoms are the outcomes of interest?

TARGET POPULATION

Adult and paediatric patients who have received an allogeneic transplant and are experiencing graft-versus-host disease.

RECOMMENDATIONS AND JUSTIFICATION

Extra-corporeal Photopheresis (ECP) in the Management of Graft-Versus-Host Disease (GVHD)
• ECP is an acceptable therapy for the treatment of steroid-dependent / refractory acute GVHD in adult and paediatric patients
Justification: Three non-comparative studies in adult patients [one prospective single cohort (8) and two case series (1,2)], and six studies in paediatric patients [one clinical trial (3), one prospective cohort (4), and four case series (5-8)] reported response rates in favour of the ECP ranging from 32% to 100%. Only one of the paediatric studies reported comparable response rates between patients who received ECP and patients who remained on conventional treatment (6). In the opinion of the Expert Panel, although the quality of the data for steroid refractory aGVHD is limited, patients with primarily refractory skin GVHD should be considered for ECP treatment.

Recommendation Report SCT-5

- ECP is an effective therapy for the treatment of steroid-dependent / refractory chronic GVHD in adult and paediatric patients

Justification:

This recommendation is supported by the evidence obtained from two studies [an RCT (9), and a crossover RCT (10)], because in both studies, significant increase in response rates favour the ECP over conventional corticosteroid treatment. Five additional comparative studies (3,4,11-13) and six non-comparative studies (2,5,7,8,14,15) reported response rates ranging from 50% to 80%.

QUALIFYING STATEMENTS

- ECP is currently a covered therapy in Ontario for patients with steroid refractory GVHD who meet certain eligibility criteria

FUTURE RESEARCH

- Patients should be encouraged to participate in National and International trials evaluating ECP as available
- Ontario transplant centres should develop a study evaluating the effectiveness of ECP

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

Stem Cell Transplantation in Adults, K. Imrie, R.B. Rumble, M. Crump, the Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care [Report Date: January 30, 2009]. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/951

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Updating

All PEBC documents are maintained and updated
as described in the PEBC Document Assessment and Review Protocol.

Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

Recommendation Report SCT-5: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Extra-corporeal Photopheresis in the Management of Graft-Versus-Host Disease in Patients who Have Received Allogeneic Blood or Bone Marrow Transplants: Evidentiary Base

C. Bredeson, R.B. Rumble, N.P. Varela, J. Kuruvilla, C.T. Kouroukis, and the Stem Cell Transplant Steering Committee

Report Date: August 29, 2013

CLINICAL QUESTION

Is there a benefit associated with the use of extra-corporeal photopheresis compared with other treatment options for patients who have received an allogeneic transplant and are experiencing graft-versus-host disease if response rate, survival or improvement of symptoms are the outcomes of interest?

INTRODUCTION

Graft-versus-host disease (GVHD) is a common complication following allogeneic stem cell transplantation occurring in traditional terminology as either acute (aGVHD: onset ≤100 days post-transplant) or chronic (cGVHD: >100 days post-transplant) (16-18). More than half of all patients undergoing an allogeneic transplant experience GHVD. In simplest terms, GVHD is a complication of the new donor's immune system recognizing the host patient's tissues and organs as foreign and attacking them like it would an infection. This response of the donor immune system leads to tissue damage, morbidity and, for many patients either directly or indirectly, mortality.

Chronic GVHD is associated with high rates of significant morbidity and mortality (19, 20). Most patients with cGVHD require treatment with immune suppressive medications for 2 or 3 years. These medications increase the risk of infection in these patients, and over 60% of deaths in cGVHD patients are related to infections. In addition, approximately half of all cGVHD patients report significantly compromised functional status and poor quality of life (21,22). Ultimately, many patients with cGVHD die from the complications of the illness or treatment such that cGVHD is the leading cause of non-relapse mortality after transplant. Survival post-transplant is inversely related to the severity of cGVHD as determined by the NIH Consensus Criteria (23,24).

Primary therapy of aGVHD has remained unchanged over the past 30 years and consists primarily of a calcineurin inhibitor in combination with corticosteroids. Approximately half of patients will have a complete resolution of their aGVHD with this approach. Patient failing

first-line therapy have a poor prognosis with 1-year survival <50%. Second-line therapies are varied and supported mostly by small single-arm trials or cohort studies (25,26). Many randomized trials of promising therapies for GVHD have been negative or stopped early due to toxicity or futility. It is well recognized that there is no defined standard second-line therapy for aGVHD. Photopheresis in the setting of steroid-dependent and refractory aGVHD has demonstrated steroid-sparing effects and clinical responses in limited studies (1-3,6,11,27).

As stated above, chronic GVHD is one of the main morbidities and causes of mortality in patients surviving the first few months following an allogeneic transplant. As with aGVHD, first-line therapy for patients includes corticosteroids ± a calcineurin inhibitor (28,29). As outlined above, patients with cGVHD have compromised quality of life and decreased survival. Patients who fail front-line therapy of cGVHD have a very poor prognosis. As with aGVHD, there is no standard second line therapy for cGVHD. A variety of therapies exist for steroid refractory cGVHD that in practice are applied through a "trial-and-error' approach (30,31). In addition to limited efficacy, each of these therapies is either expensive, associated with the potential of moderate-to-severe toxicities or both. Although research continues on the biology and treatment of cGVHD, there is no novel therapy currently in trials that offers a significant advance on the current state of the art for the foreseeable future. Photopheresis is one of the therapies that has emerged in the last decade in the management of steroid refractory GVHD because of its steroid-sparing ability, low associated toxicity and efficacy in some clinical settings (2, 9, 10, 12, 13).

Photopheresis is a therapy that requires special machines and vascular access. Patients are treated preferably as out patients for several hours, on 2 consecutive days, at least every other week for several months. If a response is obtained, therapy is eventually weaned, but total therapy duration often exceeds 1 year.

Photopheresis is currently a covered therapy by the MOHLTC for patients with steroid refractory GVHD. At present, the therapy requires patients to travel to Toronto for therapy at the Princess Margaret Hospital. This has limited access to patients from other regions in the province as the travel and residency requirements are difficult and expensive. More importantly, this patient population is medically complex, often with compromised function, and the travel requirements are medically unsafe. According to C. Bredeson, MD MSc FRCPC (written communication, January 2013), significant adverse medical events have occurred in patients while travelling for photopheresis.

The purpose of this recommendation report is to summarize the available data regarding photopheresis for the treatment of GVHD and to provide recommendations on its use.

METHODS

This recommendation report, produced by the Program in Evidence-Based Care (PEBC) and the Stem Cell Transplantation Steering Committee (the Committee) of CCO was developed through a systematic review of the available evidence and the interpretation of that evidence by clinical experts to develop recommendations. A working group was formed of members of the Committee to develop the report. The working group members disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

This report was developed as part of the Stem Cell Transplantation Steering Committees mandate to provide the Ontario Ministry of Health and Long Term Care advice with respect to stem cell transplantation and associated technologies and supportive care interventions. It will be assessed for currency and updated in the future at the request of the Committee.

Literature Search Strategy

The MEDLINE (Ovid) (1995 through July Week 1 2012) database was searched on July 17, 2012 and updated on August 14, 2013. The search strategy for MEDLINE is shown in Appendix 1. Search terms for stem cell transplantation, bone marrow transplantation, and peripheral blood stem cell transplantation were combined, and articles that also included graft-versus-host disease outcomes where photopheresis was administered were retained. As it was expected that there would be little indexed evidence, no restrictions were made based on publication date.

Relevant articles and abstracts were selected and reviewed by two reviewers (C.B., B.R.), and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full-report articles or published meeting abstracts of:

1. Studies that reported on outcomes of extra-corporeal photopheresis administered for either acute or chronic graft-versus-host disease for patients of all ages following allogeneic stem cell transplantation.
2. One of the following publication types or study designs: practice guidelines with systematic review, systematic reviews (with meta-analyses), systematic reviews (without meta-analyses), randomized phase III trials, randomized phase II trials, or other comparative studies.

   No specific outcomes were required, as long as the study met the two points above.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, due to financial considerations for translation.
3. Reported on fewer than five patients.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis would be conducted using the Review Manager software (RevMan 4.2) available from the Cochrane Collaboration (32). For time-to-event outcomes, hazard ratios (HRs), rather than the number of events at a certain time point, would be the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they would be derived from other information reported in the study, if possible, using the methods described by Parmar et al (33). For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in [the software used] would be used.

Statistical heterogeneity would be calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

Assessment of Study Quality

For systematic reviews that would be used as the sole evidence base for our recommendations, the AMSTAR tool would be used to assess quality. For Clinical Practice Guidelines, the AGREE II instrument would be used to assess quality. However, because of

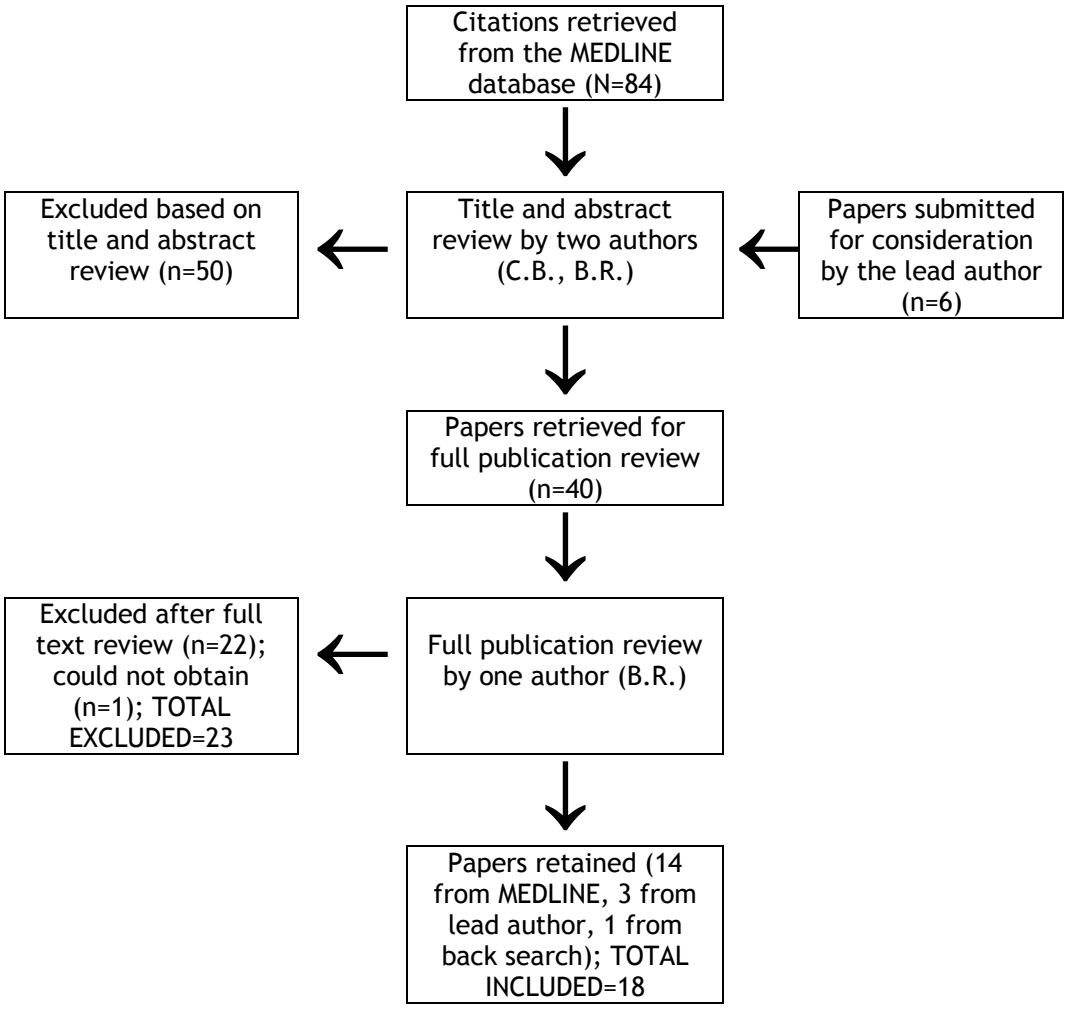
the time and effort necessary to properly implement the AGREE II instrument, it would be used only if adaptation of the recommendations was considered feasible by the working group given the nature and coverage of the guideline and an informal assessment of the guideline's methods. Where recommendations from CPGs were not adapted, the evidence base in those CPGs would be informally assessed for completeness, and any relevant evidence within would be considered as a basis for recommendations in this report. Any meta-analysis would be assessed for quality using similar criteria as used for RCTs, where appropriate. RCTs would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received, all relevant outcomes, and the source of funding.

RESULTS

Literature search results and quality appraisal

A total of 18 papers were retained (1-15,27,34,35). *For adults:* one consensus report based on a systematic review (34), one RCT (9), one crossover RCT (10), one prospective cohort study (27), three retrospective cohort studies (11-13), one case series with historical controls (1), and four case series (2,14,15,35) were retained. *For paediatric patients:* one clinical practice guideline (8) (which also contained case-series data, and appears in that section as well), one non-randomized controlled trial (3), one prospective cohort study (4), and four case series (5-8) were retained. Fourteen of the papers retained were identified using the MEDLINE (OVID) database, three were submitted from the files of the lead author (C.B.), and one was identified from the references listing in one of the obtained papers. See Figure 1 for details. A table of the articles that were ordered for full-text review but were then excluded are provided in Appendix 3 along with the reason for exclusion.

Figure 1. Selection of studies investigating extra-corporeal photopheresis in the management of graft-versus-host disease in patients who have received allogeneic blood or bone marrow transplants search results



Study and Patient Characteristics: adult patients

Overview: adult patients

Twelve papers were obtained on the use of photopheresis in adult patients with GVHD following stem cell transplantation (1,2,9-15,27,34,35). The number of patients reported on in each paper ranged from a low of 9 in the case series reported by Lucid et al (14) to a high of 82 in the case series reported by Dignan et al (15). The patient diagnosis varied, but the typical population comprised patients that had GvHD but had failed either steroid treatment (2,15,27) or immunosuppressive therapy (14,35). Where reported, the only ECP device described was either the UVAR or UVAR XTS system by Therakos, Inc. (2,9,12,13,15,27,35). The duration that patients received ECP treatment greatly varied, from a low of 2 weeks (median: NR) in the prospective cohort study reported by Greinix et al (27) to a high of 528 weeks (median: 68) in the retrospective cohort study reported by Bisaccia et al (12). The most commonly reported outcome was response rates, followed by survival, TRM, safety,

quality of life, and the effect of ECP on various measures of GvHD by site that was affected. See Table 1 for details.

Assessment of study quality: adult patients

Quality was assessed according to the criteria described in the Methods section. See Table 1 for details on the patient selection criteria, details on the ECP treatment given, and the outcomes reported. As the recommendations in the consensus statement (34) were only indirectly related to photopheresis, and the data that the recommendations were based on was not fully described, the working group decided that adaption was not feasible, and therefore, a formal assessment of quality using the AGREE 2 instrument was not performed.

The RCT reported by Flowers et al (9) did not explicitly describe the method of randomization, but noted that a block method was used in a 1:1 ratio. It was reported as being a single-blind trial, but was not well described. There was no description of the power and sample size calculation, nor the length of follow-up. The statistical analyses used were well described, with continuous variables summarized with medians and ranges, categorical variables summarized with totals and percentages, the primary end point of Total Skin Score analysed using a Wilcoxon rank sum test, and cumulative response (CR and PR) compared using the log-rank test. Withdrawals were well described for both arms, and there were no reported losses to follow-up. Therakos, Inc. (Exton, PA) provided funding for this trial.

The crossover study reported by Greinix et al (10) included patients from the RCT reported by Flowers et al (9) that crossed over from the non-ECP arm to the ECP arm, and this sample was well described, as was the intervention each patient received. All relevant outcomes were reported on, including response rates, total skin scores, and change in steroid use. Therakos, Inc. provided funding for this study.

The prospective cohort study reported by Greinix et al (27) selected patients based on non-response to steroid treatment in a well-described population. The ECP treatment was well described, as were the outcomes of response and survival. A European Commission Grant (QLK3-CT-2002-01936 TransEurope) provided funding for this study.

Three retrospective cohort studies were obtained (11-13) in this review. All three of these studies had well-described patient samples representative of a typical patient population. The study by Couriel et al (11) did not report details on the ECP methods, and the study by Apisarnthanarax et al (13) reported on a series of patients that used various ECP regimens and, therefore, did not report the details, unlike the study by Bisaccia et al (12) that fully described the single ECP protocol used for all patients. All three studies reported response rates, two reported on survival (12,13), and one reported median TTR as well (12). Therakos, Inc. supported the study by Apisarnthanarax et al (13). Neither of the other two studies reported any source of funding.

One case-series study with historical controls, reported by Perfetti et al, was obtained (1). This study had a well-described series of patients, which were representative of the population under study. The ECP regimen given was also well reported. Outcomes reported were response rates and survival. This study reported non-industry funding (Association Italiana Ricerca contro il Cancro (AIRC), CARIGE, Fondazione Ricerca per Trapianto Midollo Osseo).

Four case-series studies were obtained for this review (2,14,15,35). All four studies had a well-defined group of patients that were representative of the population of interest, but Lucid et al (14) only included patients with bronchiolitis obliterans, and Dignan et al (15) only included patients with mucocutaneous symptoms of GvHD. All four of the studies included detailed descriptions of the ECP intervention, and all patients received the same regimen. Lucid et al (14) reported response rates, and Dignan et al (15) reported on response rates, survival, and reductions in dosages of immunosuppressant drugs or steroid use. Seaton

et al (35) and Greinix et al (2) both reported on changes in various scores associated with site afflicted by GvHD. None of the studies reported on the source of funding.

In summary, the quality assessment performed found all of the above studies of extracorporeal photopheresis in the treatment of GvHD in adult patients to be of acceptable quality given the nature of their study designs.

Table 1. Study and patient characteristics: adult patients

Study [study years]	N	Diagnosis	ECP details (device)	Duration of ECP treatment: range in weeks (median)	Outcomes reported
Consensus Recommendations and Evidence Review					
Hildebrandt et al, 2011 (34)	Eight studies on ECP in cGvHD	Bronchiolitis obliterans organizing pneumonia (BOOP)/ cryptogenic organizing pneumonia (COP)/ obstructive lung involvement	Varies	Varies	Response
Randomized Controlled Trials (RCTs)					
Flowers et al, 2008 (9) [2002-2005]	ECP: 48 Control: 47	Histologically confirmed cGvHD with cutaneous symptoms at 100 days or more following transplantation	Week 1: 3 times per week Weeks 2-12: 2 times per week on consecutive days; responsive pts could continue with 2 tx every 4 weeks until week 24 [UVAR XTS]	12-24	Skin response, steroid-sparing effects, extracutaneous response, QoL, safety, mortality
Crossover RCT					
Greinix et al, 2011 (10) [2003-2006]	25	(Same as Flowers et al, 2008)	(Same as Flowers et al, 2008)	12-24	Skin response, steroid-sparing effects, extracutaneous response, safety
Prospective Cohort Studies (PCS)					
Greinix et al, 2006 (27) [1996-1999]	59	Grade II – IV aGvHD following first-line tx with steroids	Patients were treated on 2 consecutive days (one cycle) at 1- to 2-week intervals until improvement and then every 2 to 4 weeks until	NR	Response, TRM, survival, long-term outcome

			maximal response. Treatment was reduced down over 25 months [UVAR XTS]		
Retrospective Cohort Studies (RCS)					
Couriel et al, 2006 (11) [1998-2002]	63	Patients had steroid-resistant cGvHD and had three or fewer lines of immunosuppres-sant tx	Patients were started on 2- to 3-weekly ECP treatment, then decreased to 1 or 2 according to clinical response and the discretion of the managing physician	NR	Response, survival
Bisaccia et al, 2006 (12) [2000-2005]	14 (of 20)	Patients had cGvHD following BMT or PBSCT, but were in complete remission of primary disease and had adequate haemodynamic and cardiac status	Three times per week on alternating days, but could be decreased to twice per week, once per week, or once on alternating weeks, depending on patient response [UVAR XTS]	13-191 (74)	Response, time to response, survival
Apisarnthanarax et al, 2003 (13) [1998-2001]	32	Patients had cutaneous symptoms of cGvHD after day 100 post-transplantation	Total ECP sessions: Median: 34 Range: 12 – 98 ECP sessions per month: Median: 6 Range: 2 – 17 [UVAR or UVAR XTS]	4–121 (23)	Response, survival
Case Series with Historical Controls					
Perfetti et al, 2008 (1) [1996-2006]	23	Steroid-refractory patients with Grade II – IV aGvHD	Two treatments on 2 consecutive days every week for the first month, a cycle every 2 weeks for the following 2 months, and a cycle every month until GvHD was resolved or stabilized	0–144 (30)	Average GvHD score, average steroid dose, overall response, overall survival

Case Series					
Lucid et al, 2011 (14) [2008-2009]	9	Patients with bronchiolitis obliterans refractory to immunosuppres-sive treatment	Two sessions per week for 3 to 4 weeks and then 2 sessions every 2 to 3 weeks, with the goal of bringing patients to a once every 4-week treatment schedule	NR	Response
Dignan et al, 2012 (15) [2005-2010]	82	Patients were steroid-refractory, steroid-dependent, or steroid-intolerant with mucocutaneous cGvHD	Two consecutive days every 2 weeks until a partial response was reported, then treatment was reduced to one cycle per month [UVAR XTS]	6–141 (47)	Response, reduction in immunosuppres sive treatment, reduction in steroid treatment, overall survival
Seaton et al, 2003 (35) [1994-2001]	28	Patients with cGvHD refractory to immunosuppres-sive treatment	Given on 2 consecutive days once every 2 weeks for the first 4 months, and then on 2 consecutive days once per month. Continuing ECP treatment was re-assessed every 6 months [UVAR and UVAR XTS]	4–252 (26)	Skin score, hepatic score, pulmonary score, mucosal score, neuromuscular score, TRM
Greinix et al, 1998 (2) [1993-1998]	21	Patients with chronic extensive GVHD or with aGVHD resistant to steroid treatment	Pts treated on 2 consecutive days at 2-week intervals for the first 3 months and then every 4 weeks until resolution of GvHD [UVAR]	17-135	Response by site affected: skin, liver, joints, mouth, ocular, thrombopenia

ECP = extracorporeal photopheresis; cGvHD = chronic graft-versus-host disease; pts = patients; tx = treatment; QoL = quality of life; N = number; aGvHD = acute graft-versus-host disease; TRM = treatment-related mortality; NR = not reported; BMT = bone marrow transplantation; PBSCT = peripheral blood stem cell transplantation; GvHD = graft-versus-host disease.

Study and Patient Characteristics: paediatric patients

Overview: paediatric patients

Six papers were obtained on the use of photopheresis in paediatric patients with GVHD following stem cell transplantation (3-8). One of the papers, the CPG reported by Kanold et al (8), also reported case-series data, which is described in Table 2 and Table 4. The number

of patients included in the studies obtained ranged from a low of 9 in the prospective cohort study reported by Salvaneschi et al (4) to a high of 77 in the non-randomized controlled trial reported by Messina et al (3). As with the adult patients reported earlier, the patient diagnosis varied, but the typical population comprised patients that had GvHD but had failed either steroid treatment (4,5,7) or immunosuppressive therapy (3). The two studies that reported on the ECP system used both used the UVAR system by Therakos, Inc. (3,7). The outcomes reported varied, but responses rates were the most common, followed by survival, TRM, reductions in steroid or immunosuppression use, infection rates, mycosis, and changes in skin scores. See Table 2 for details.

Assessment of study quality: paediatric patients

Quality was assessed according to the criteria described in the Methods section. See Table 2 for details on the patient selection criteria, details on the ECP treatment given, and the outcomes reported.

One CPG was obtained, reported by Kanold et al (8). However, in this CPG, no supporting evidence was obtained, and the recommendations are based solely on expert opinion and a single case series reported by the same authors. Therefore, the working group decided that it would be more appropriate to review the evidence directly and develop new recommendations than attempt to adapt this guideline, and a formal assessment of quality using the AGREE 2 instrument was not performed.

One non-randomized controlled study, reported by Messina et al (3), was obtained. In this study, the patient selection criteria were well described, and were representative of the population of interest, as was the ECP regimen. The reported outcomes were response, survival and adverse effects. This study was funded through non-industry sources [grants from AIRC (Associazione Italiana Ricerca sul Cancro), CNR (Consiglio Nazionale delle Ricerche), MURST (Ministero dell'Universita e della Ricerca Scientifica e Tecnologica), IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico].

One prospective cohort study (4) was obtained. In this study, the patients were well described, and were representative of the population of interest, as was the ECP regimen. The reported outcomes were response and survival. This study was funded through non-industry sources [grants from AIRC (Associazione Italiana Ricerca sul Cancro), CNR (Consiglio Nazionale delle Ricerche), MURST (Ministero dell'Universita e della Ricerca Scientifica e Tecnologica), IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico].

Four case-series were obtained (5-8). Three of the studies (5-7) included full descriptions of the included patients and the ECP regimen used, while the study by Kanold et al (8) did not describe the patients included nor the ECP regimen at all. Outcomes reported in these four studies were response rates (5-8), survival (5-7), TRM (6,7), PFS (6), infection (6), and mycosis (6). Two of the studies reported non-industry funding (5,6): the study reported by Perotti et al (5) reported hospital funding, while the study reported by Calore et al (6) reported funding from the Fondazione Citta della Speranza, Associazione Italiana Leucemie e Linfomi.

In summary, the quality assessment performed found all of the above studies of extracorporeal photopheresis in the treatment of GvHD in paediatric patients to be of acceptable quality given the nature of their study designs.

Table 2. Study and patient characteristics: paediatric patients

Study [study years]	N	Diagnosis	ECP details	Duration of ECP treatment (median)	Outcomes reported
Clinical Practice Guideline					
Kanold et al, 2007 (8) [1996 - 2006]	27	aGvHD or cGvHD	Pts treated three times per week (with a 1-day rest between two sessions) for the first 3 weeks, then gradually reduced for patients that stabilized or showed improvement	NR	ECP should be considered as first-line therapy in Grade IV aGvHD (in association with conventional pharmacologic approaches) and limited cGVHD ECP should be considered as second-line therapy in steroid-resistant Grades II-III aGvHD and extensive cGvHD
Non-Randomized Controlled Trial					
Messina et al, 2003 (3) [1992-2000]	77	Patients refractory to immunosup-pressive therapy with aGvHD or cGvHD	Pts were treated on 2 consecutive days at 1-week intervals for the first month, then every 2 weeks for the second and third month, and then monthly for at least 3 months [UVAR]	1–66 (10.5)	Response, survival
Prospective Cohort Study					
Salvaneschi et al, 2001 (4) [1998-NR]	9	Patients with steroid-resistant, grade II-IV aGVHD and cGVHD, all whom had been refractory to at least one line of treatment	aGvHD: three times week on alternate days until improvement, then on 2 consecutive days at 2-week intervals for 3 months until discontinued cGvHD: 2 consecutive days at 2-week intervals for 3 months. If improvements were shown, then ECP was given on 2 consecutive days at 3-week intervals for another 3 months Discontinuation was dependent on individual assessment of response	NR	Response, survival, reduction in immunosuppres-sive therapy
Case Series					
Perotti et al, 2010 (5)	73	Steroid-refractory	aGvHD: 2 or 3 per week (on alternate days) until clinical	NR	Response, survival

[NR]		patients with aGvHD or cGvHD	improvement cGvHD: two procedures per week for two times, two procedures every other week for three times, then two procedures per month until clinical improvement and/or immunosuppressive therapy reduction		
Calore et al, 2008 (6) [1999-2005]	31	Patients with Grade II – IV aGvHD	Two consecutive days every week for the first month, then every 2 weeks for the second and third month, then monthly for another 3 months (6 months total tx) Immunosuppressive tx was maintained and then reduced or discontinued, depending on clinical response	5–44 (24)	Response, survival, progression-free survival, TRM, infection, mycosis
Berger et al, 2007 (7) [2001-2005]	25	Steroid-refractory patients with aGvHD or cGvHD	Two consecutive days at weekly intervals for the first month, 2 consecutive days every other week for the second and third month, and then 2 consecutive days once a month for 3 months [UVAR]	NR	Response, survival, TRM
Kanold et al, 2007 (8) [1996-2006]	27	aGvHD or cGvHD	Pts treated three times per week (with a 1-day rest between two sessions) for the first 3 weeks, then gradually reduced for patients that stabilized or showed improvement	NR	Response, survival, change in skin scores

ECP = extracorporeal photopheresis; aGvHD = acute graft-versus-host disease; cGvHD = chronic graft-versus-host disease; pts = patients; NR = not reported; TRM = treatment-related mortality.

RESULTS: Adult patients

See Table 3 for all adult patient results.

Response

The RCT by Flowers et al (9) detected a statistically significant difference in response rates in favour of ECP over conventional corticosteroid treatment (40% vs. 10%; p=0.002). Similarly, the crossover RCT reported a significant increase in the overall response rate associated with EPC when compared to conventional treatment (26% vs. 8%; p=0.04) (10). None of the other comparative studies reported a difference between groups (11-13,27). Non-comparative studies reported response rates ranging from 50% (1,12) to 100% (in liver manifesting aGvHD only) (2). The RCT reported by Flowers et al (9), which did detect a benefit in favour of ECP, remains the best evidence due to the study design.

Treatment-related mortality

Only the RCT by Flowers et al (9) reported on TRM, with no difference being detected.

Overall survival

Only one study, the case series with historical controls reported by Perfetti et al (1), compared overall survival between ECP and a control group, with no difference being detected (ECP: 45% vs. control: 44%). Survival for the remaining studies ranged from a low of 41% in the study reported by Couriel et al (11) to a high of 85% in the study reported by Bisaccia et al (12) (both were retrospective cohort studies).

Quality of life

Only the RCT by Flowers et al (9) reported on quality-of-life outcomes, with a significant benefit being detected with ECP treatment compared with conventional treatment (ECP: 19% vs. control: 2.5%; p=0.01).

Other outcomes

The RCT by Flowers et al (9) reported on Total Skin Scores, eye, oral, and joint changes associated with GvHD, and adverse events. Significant differences were only detected in eye GvHD, which showed an improvement associated with ECP compared with conventional treatment (ECP: 30% vs. control: 7%; p=0.04).

The case series by Seaton et al (35) reported on changes from baseline scores after 6 months for cutaneous, hepatic, pulmonary, mucosal, and neuromuscular cGvHD, and significant improvements were detected for cutaneous cGvHD scores only [baseline: 89% (skin median score: 131, 132) versus 6 months: 52% (skin median score: 61); p=0.003].

Table 3. Results: adult patients

Study [studyyears]	N	Response (CR/PR)	Treatment-related mortality	Overall survival	Quality of life
Randomized Controlled Trials (RCTs)					
Flowers et al, 2008 (9) [2002-2005]	48 (ECP) 47 (Con)	40% 10% p=0.002	98% 94% p=NR	NR	19% 2.5% p=0.01
Crossover RCT					
Greinix et al, 2011 (10) [2003-2006]	@12 wks @24wks N=25	26% [EPC] 8% [Con] (p=0.04) 31% [EPH]*	NR	NR	NR
Prospective Cohort Studies (PCS)					
Greinix et al, 2006 (27) [1996-1999]	59	82% [cutaneous] 61% [liver] 61% [gut] p=NR	NR	47% [4-year] 47% [with CR] 11% [without CR] p<0.0001	NR
Retrospective Cohort Studies (RCS)					
Couriel et al, 2006 (11) [1998-2002]	63	59% [overall] 21% [CR only] p=NR	NR	41% [5-year] Primary cause of death: GvHD: 68% Relapse: 26% Infection: 3%	NR

Bisaccia et al, 2006 (12) [2000-2005]	14	50% [cutaneous] 21% [CR only] p=NR	NR	85%	NR
Apisarnthanarax et al, 2003 (13) [1998-2001]	32	56% 22% [CR only] p=NR	NR	66% 100% of all deaths under study were related to cGvHD	NR
Case Series with Historical Controls					
Perfetti et al, 2008 (1) [1996-2006]	23 [ECP] 307 [ctl]	52% [CR]	NR	48% 45% [ECP] 44% [ctl] p=ns	NR
Case Series					
Lucid et al, 2011 (14) [2008-2009]	9	67%	NR	NR	NR
Dignan et al, 2012 (15) [2005-2010]	82	79% 94% [@6 months]	NR	69% [3 years]	NR
Seaton et al, 2003 (35) [1994-2001]	28	NR	14%	NR	NR
Greinix et al, 1998 (2) [1993-1998]	21	aGvHD: (6/21) Skin: CR: 67% (4/6) PR: 33% (2/6) Liver: CR: 100% (2/2) PR: - cGvHD: (15/21) Skin: CR: 80% (12/15) PR: 20% (3/15) Joints: CR: - PR: 100% (4/4) Mouth: CR: 100% (11/11) PR: - Liver: CR: 70% (7/10) PR: 20% (2/10) NC: 10% (1/10) Ocular: CR: 16% (1/6) PR: 67% (4/6) NC: 17% (1/6) Thrombopenia: CR: 67% (2/3)	NR	NR	NR

		PR: - NC: 33% (1/3)			

* No data reported for the non-ECP arm at 24 weeks due to large number of patients from this arm that discontinued the study. CR = complete response; PR = partial response; ECP = extracorporeal photopheresis; Con = conventional treatment; NR = not reported; wks = weeks; Ctl = control; aGvHD = acute graft-versus-host disease; cGvHD = chronic graft-versus-host disease; NC = no change.

RESULTS: Paediatric patients

See Table 4 for all paediatric patient results.

Response

Only one of the paediatric studies reported comparable response outcomes between ECP and another treatment option, and this was the case-series by Calore et al (6). This study reported response rates between patients that received ECP and patients that remained on steroid treatment and complete response rates (CR) were higher in the ECP group (73% versus 56%; p=NR) but partial response rates (PR) were higher in the group that received steroid treatment (44% vs. 27%; p=NR).

For the remaining studies, CR rates ranged from a low of 32% (5) to a high of 100% (Grade II only) (7) and PR rates ranged from a low of 21% (3) to a high of 29% (3,4) in patients with acute GvHD. For patients with chronic GvHD, CR rates ranged from a low of 21.7% (5) to highs of 44% (3,4), and for PR, rates ranged from a low of 29% (3) to a high of 56% (4).

Treatment-related mortality

Two of the studies reported on TRM outcomes, the two case-series by Calore et al (6) and Berger et al (7). The study by Calore et al found a TRM of 6% in the group that had a good response to steroid treatment compared with zero mortality in the ECP group (p=NR). The study by Berger et al found an increase in TRM in patients according to worse acute GvHD symptoms (Grade II: 0 vs. Grade III-IV: 42%; p=0.05) and in non-responders to both steroid treatment and ECP treatment (ECP responders: 0 vs. non-responders: 50%; p=0.022).

Overall survival

Six of the studies reported on overall survival outcomes (3-8). Only the study by Calore et al (6) reported comparable survival rates for ECP and another treatment, and patients that received ECP showed a survival rate of 85%, whereas patients that received steroid-based treatment showed a survival rate of 57% (p=0.2).

For acute GvHD, the study by Messina et al (3) detected a significant survival benefit in ECP responders compared with non-responders (69% vs. 12%; p=0.001). The study by Perotti et al (5) reported a 62% survival rate compared with 6.3% in non-responders (p=NR). The study by Berger et al reported a 100% survival rate in patients with Grade II acute disease compared with 30% in patients with Grade III/IV disease (p=0.006).

In patients with chronic GvHD, the study by Messina et al (3) reported survival rates of 96% in ECP responders compared with 58% in non-responders (p=0.04), and the study by Salvaneschi et al (4) reported survival rates of 79% in ECP responders compared with none in the non-responders (p=NR). The study by Berger et al (7) reported survival rates of 100% in patients with limited symptoms, but this fell to 28% in patients with extensive symptoms (p=0.03).

Quality of life

None of the studies obtained reported on quality of life.

Other outcomes

The case series by Calore et al (6) reported on 2-year PFS, but no difference was reported (ECP: 87% vs. steroid responders: 67%; p=NR).

Table 4. Results: paediatric patients

Study [study years]	N	Response (CR/PR)	Treatment-related mortality	Overall survival	Quality of life
Non-Randomized Controlled Trials (RCTs)					
Messina et al, 2003 (3) [1992-2000]	77 aGVHD: 33 cGvHD: 44	aGvHD: n=33 CR: 54% (18/33) PR: 21% (7/33) No response: 24% (8/33) cGvHD: n=44 CR: 44% (15/34) PR: 29% (10/34) No response: 26% (9/34)	NR	aGvHD: 5-year OS 69% (responders) vs. 12%(non-responders) p=0.001 cGvHD: 5-year OS 96% (responders) vs. 58%(non-responders) p=0.04	NR
Prospective Cohort Studies (PCS)					
Salvaneschi et al, 2001 (4) [1998-NR]	23 aGVHD: 9 cGvHD: 14	aGvHD: n=9 Response rate: 78% (7/9) CR: 71% (5/7) PR: 29% (2/7, both evolved into cGvHD) cGvHD: n=14 Response rate: 64% (9/14) CR: 44% (4/9) PR: 56% (5/9) No Response: 36% (5/14, SD=2, worsened=3)	NR	aGvHD: OS: 78% (7/9) cGvHD: OS: 79% (11/14) (All three of the non-responders died)	NR
Case Series					
Perotti et al, 2010 (5) [NR]	73 aGvHD: 50 cGvHD: 23	aGvHD: OR: 68% (34/50) CR: 32% (16/50) cGvHD: OR: 69.5% (16/23) CR: 21.7% (5/23)	NR	aGvHD: 44% (22/50) Responders: 62% (21/34) Non-responders: 6.3% (1/16) cGvHD: 78.3% (18/23) Responders: 87.5% (14/16) Non-responders: 57% (4/7)	NR
Calore et al, 2008 (6) [1999-2005]	15 [ECP] 16 [GR]	CR:73% (11/15) PR:27% (4/15) CR:56% (9/16) PR:44% (7/16)	ECP: 0 GR: 6% (1/16)	2-year: ECP: 85% (13/15) GR: 57% (9/16)	NR
Berger et al, 2007 (7)	25	CR: 100% (7/7) [aGvHD II]	0 [aGvHD II]	100% [aGvHD II] 30% [aGvHD III/IV]	

[2001-2005]		50% (2/4) [aGvHD III] PR: 25% (1/4) [aGvHD III] No response: 25% (1/4) [aGvHD III] 100% (4/4) [aGvHD IV] CR, limited vs. extensive, cGvHD: 100% (3/3) limited vs. 14% (1/7) extensive PR, extensive, cGvHD: 14% (1/7) No response, extensive, cGvHD: 71% (5/7)	42% [aGvHD III/IV] p=0.05 0: [cGvHD ECP responder] 50% [cGvHD ECP non-responder] p=0.022	p=0.006 100% [cGvHD limited] 28% [cGvHD extensive] p=0.03	
Kanold et al, 2007 (8) [1996-2006]	27 12 [aGvHD] 15 [cGvHD]	aGvHD: 58% (7/12) [CR] 25% (3/12) [PR] cGvHD: 27% (4/15) [CR] 47% (7/15) [PR]	NR	aGvHD: 75% (8/12) cGvHD: 67% (10/15)	NR

N = number; CR = complete response; PR = partial response; OR = overall response; aGvHD = acute graft-versus-host disease; cGvHD = chronic graft-versus-host disease; OS = overall survival; NR = not reported; SD = stable disease; ECP = extracorporeal photopheresis; GR = good response to steroid-based treatment.

DISCUSSION

GVHD remains the main complication and main cause of non-relapse mortality following allogeneic transplant (16-18). Primary therapy results in complete remission of GVHD in, at best, half of patients (18). For patients with either acute or chronic GVHD who fail front-line therapy, the prognosis is poor (18,21,25,26,31). The majority of these patients will remain on some type of immune suppression for at least 1 year and a third or more for at least 2 years. GVHD is associated with both decreased quality of life and increased mortality (22-24). Contributing to the morbidity and mortality of GVHD therapy are the immunosuppressive therapies and the varied toxicities of the therapies themselves. Current options for patients who fail front-line GVHD treatment are inadequate (25,26,31).

The pathophysiology of cGVHD is poorly understood, and most therapies are directed at interfering with the immune response in some way, either by overall suppression or modulation of some aspect of the immune response.

There are several theories, each with some data that attempt to explain the effect of ECP on GVHD, including apoptosis of activated lymphocytes, shifts in function of cell populations to a more tolerant type (e.g., monocytes), potential selective enhancement of other cell populations such as T-regulatory cells (Foxp3+CD4+CD25+) (1,11,16,18). Likely, there are several aspects of the effect of ECP on various cell populations that result in the clinical effects noted in individual patients, case series and trials.

While the proof of efficacy of ECP is of mixed quality, the weight of evidence supports that it works in certain patients, and that when it works, can provide clinical improvement.

The best data as summarized above, supports the use of ECP for steroid refractory cGVHD that is primarily affecting skin/subcutaneous tissues, lung or liver (9-11,14,15,18,27,34). The data for steroid refractory aGVHD is more limited, but patients with primarily refractory skin GVHD should also be considered (8,11,27). Additional factors that favour the use of photopheresis include its steroid-sparing effect and its lack of toxicity. Steroid sparing is of particular importance, because many patients with cGVHD are older patients who tolerate corticosteroids poorly. Definitive randomized trial data defining second-line therapy for either aGVHD or cGVHD is many years away for a variety of reasons (no good candidates, complexity of trials, cost to conduct trials, limited peer funding for such trials, small market discourages industry form pursuing the indication). In the interim, the transplant community has, based on practice patterns, identified photopheresis as a valuable component of GVHD management for some patients who fail front-line therapy (11,25,26,31). Appropriate application of photopheresis combined with data collection and reporting will enable ongoing evaluation of this therapy versus other emerging options for GVHD patients in Ontario.

ONGOING TRIALS

The clinical trials registry (located at http://www.clinicaltrials.gov) was searched for information on relevant studies using the terms "photopheresis" and "graft-versus-host disease" on November 14, 2012. A total of 14 studies were identified, but only four would have potentially met the inclusion criteria for this review and their details are given in Appendix 2.

CONFLICT OF INTEREST

The authors of this recommendation report disclosed potential conflicts of interest relating to the topic. The lead author reported a potential conflict because if photopheresis were to become a widely funded procedure, his income could potentially increase by more than $10,000. The remaining authors (B.R., N.V., J.K., T.K.) reported no conflicts of interest.

ACKNOWLEDGEMENTS AND AUTHORSHIP

The Stem Cell Transplant Steering Committee, the Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the working group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Sheila McNair and Hans Messersmith for providing feedback on draft versions
- Mark Gichuru for conducting a data audit
- Bruce Histed for copyediting

The PEBC would like to thank Dr. Chris Bredeson and Mr. R. Bryan Rumble for taking the lead in drafting this recommendation report.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Updating

All PEBC documents are maintained and updated
as described in the PEBC Document Assessment and Review Protocol.

Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. 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 Nov;42(9):609-17.
2. 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 Nov 1;92(9):3098-104.
3. 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 Jul;122(1):118-27.
4. 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 Oct;41(10):1299-305.
5. 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 Jun;50(6):1359-69.
6. 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 Sep;42(6):421-5.
7. 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 Oct;29(10):678-87.
8. 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 Dec;47(12):2276-89.
9. 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 Oct 1;112(7):2667-74.
10. 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 Dec;17(12):1775-82.
11. Couriel D, Hosing C, Saliba R, Shpall EJ, Andelini P, Popat U, et al. Extracorporeal photopheresis for acute and chronic graft-versus-host disease: does it work? Biol Blood Marrow Transplant. 2006 Jan;12(1 Suppl 2):37-40.
12. Bisaccia E, Palangio M, Gonzalez J, Adler KR, Scarborough R, Goldberg SL, et al. Treatment of extensive chronic graft-versus-host disease with extracorporeal photochemotherapy. J Clin Apher. 2006 Oct;21(3):181-7.
13. 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 Mar;31(6):459-65.
14. Lucid CE, Savani BN, Engelhardt BG, Shah P, Clifton C, Greenhut SL, et al. Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT. Bone Marrow Transplant. 2011 Mar;46(3):426-9.

15. 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 Jun;47(6):824-30.
16. Ferrara JLM, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550-61.
17. 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 Mar 17;117(11):3214-9.
18. Pavletic SZ, Fowler DH. Are we making progress in GVHD prophylaxis and treatment? Hematology / the Education Program of the American Society of Hematology. 2012; American Society of Hematology. Education Program. 2012:251-64.
19. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005 Dec;11(12):945-56.
20. Przepiorka D, Anderlini P, Saliba R, Cleary K, Mehra R, Khouri I, et al. Chronic graft-versus-host disease after allogeneic blood stem cell transplantation. Blood. 2001 Sep 15;98(6):1695-700.
21. Arora M, Klein JP, Weisdorf DJ, Hassebroek A, Flowers ME, Cutler CS, et al. Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis. Blood. 2011 Jun 16;117(24):6714-20.
22. 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 Apr 28;117(17):4651-7.
23. Jacobsohn DA, Kurland BF, Pidala J, Inamoto Y, Chai X, Palmer JM, et al. Correlation between NIH composite skin score, patient-reported skin score, and outcome: results from the Chronic GVHD Consortium. Blood. 2012 Sep 27;120(13):2545-52; quiz 774.
24. 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 Apr;26(4):746-56.
25. Martin PJ, Inamoto Y, Flowers ME, Carpenter PA. Secondary treatment of acute graft-versus-host disease: a critical review. Biol Blood Marrow Transplant. 2012 Jul;18(7):982-8.
26. 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 Aug;18(8):1150-63.
27. 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 Mar;91(3):405-8.
28. Couriel D, Carpenter PA, Cutler C, Bolanos-Meade J, Treister NS, Gea-Banacloche J, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transplant. 2006 Apr;12(4):375-96.
29. 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 Dec;16(12):1611-28.
30. Inamoto Y, Flowers ME. Treatment of chronic graft-versus-host disease in 2011. Curr Opin Hematol. 2011 Nov;18(6):414-20.
31. 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 Jan;17(1):1-17.
32. Review Manager (RevMan) [Computer proram]. Version 4.2 for Windows. Copenhagen: The Noordic Cochrane Centre TCC.
33. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998 Dec 30;17(24):2815-34.
34. Hildebrandt GC, Fazekas T, Lawitschka A, Bertz H, Greinix H, Halter J, et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. Bone Marrow Transplant. 2011 Oct;46(10):1283-95.
35. 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 Aug 15;102(4):1217-23.

Appendix 1. Literature search strategy.

Database: Ovid MEDLINE(R)

---

1 exp Stem Cell Transplantation/ (45133)
2 exp Bone Marrow Transplantation/ (39870)
3 exp Peripheral Blood Stem Cell Transplantation/ (2542)
4 1 or 2 or 3 (80904)
5 exp Graft vs Host Disease/ (16115)
6 exp Photopheresis/ (615)
7 5 and 6 (172)
8 4 and 7 (84)

Appendix 2. Ongoing trials.

A Randomized Phase II Study for the Evaluation of Extracorporeal Photopheresis (ECP) in Combination With Corticosteroids for the Initial Treatment of Acute Graft-Versus-Host Disease (GVHD)

Protocol ID:	NCT00609609
Last date modified:	September 6, 2012
Trial type:	Interventional, randomized Phase II
Accrual:	80
Primary outcome:	Treatment Failure
Sponsorship:	M.D. Anderson Cancer Center
Status:	Recruiting

Extracorporeal Photopheresis for Steroid-refractory Acute GVHD in Children and Young Adults: a Safety and Feasibility Study.

Protocol ID:	NCT00179855
Last date modified:	October 7, 2010
Trial type:	Interventional, non-randomized Phase II/III
Accrual:	50
Primary outcome:	Safety, response
Sponsorship:	Ann & Robert H Lurie Children's Hospital of Chicago
Status:	Recruiting

A Randomized Controlled Study of Extracorporeal Photopheresis (ECP) Therapy With UVADEX for the Treatment of Patients With Moderate to Severe Chronic Graft-versus-Host Disease (cGvHD)

Protocol ID:	NCT01380535
Last date modified:	September 27, 2012
Trial type:	Interventional, randomized Phase II
Accrual:	60
Primary outcome:	Response (CR, PR)
Sponsorship:	Therakos
Status:	Recruiting

Evaluation of Extracorporeal Photochemotherapy in Children and Young Adults With Refractory Acute Graft Versus Host Disease After Allogeneic Stem Cell Transplantation

Protocol ID:	NCT00824954
Last date modified:	January 18, 2011
Trial type:	Interventional, non-randomized Phase II
Accrual:	30
Primary outcome:	GVHD grading
Sponsorship:	University Hospital, Clermont-Ferrand
Status:	Recruiting

Appendix 3. Excluded articles.

	Lead author	Title	Reason for exclusion
1	Hannani et al	Photochemotherapy induces a faster apoptosis of alloreactive activated T cells than of nonalloreactive resting T cells in graft versus host disease. Transplantation. 2010;90(11):1232-8	No outcomes of interest reported on
2	Shaughnessy 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(6):1068-76	ECP given pre-treatment
3	Schneiderman et al	The use of fluid boluses to safely perform extracorporeal photopheresis (ECP) in low-weight children: a novel procedure. J Clin Apher. 2010;25(2):63-9	No outcomes of interest reported on
4	Greinix et al	Assessing the potential role of photopheresis in hematopoietic stem cell transplant. Bone Marrow Transplant. 2006;38(4):265-73	Evidence not gathered using systematic methods
5	Couriel et al	Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood. 2006;107(8):3074-80	Duplicate publication
6	Spisek et al	Maturation state of dendritic cells during the extracorporeal photopheresis and its relevance for the treatment of chronic graft-versus-host disease. Transfusion. 2006;46(1):55-65	Used cells not patients
7	Bladon et al	Lymphocytes treated by extracorporeal photopheresis can down-regulate cytokine production in untreated monocytes. Photodermatol Photoimmunol Photomed. 2005;21(6):293-302	No outcomes of interest reported on
8	Rubegni et al	Role of extracorporeal photochemotherapy in patients with refractory chronic graft-versus-host disease. Br J Haematol. 2005;130(2):271-5	Data not extractable
9	Darvay et al	The effect of extracorporeal photopheresis on intracellular cytokine expression in chronic cutaneous graft-versus-host disease. J Eur Acad Dermatol Venereol. 2004;18(3):279-84	No outcomes of interest reported on
10	Chan et al	Reduced-intensity transplantation for patients with myelodysplastic syndrome achieves durable remission with less graft-versus-host disease. Biol Blood Marrow Transplant. 2003;9(12):753-9	Focus of paper was reduced intensity transplantation
11	Di Renzo et al	ECP-treated lymphocytes of chronic graft-versus-host disease patients undergo apoptosis which involves both the Fas/FasL system and the Bcl-2 protein family. Arch Dermatol Res 2003;295(5):175-82	No outcomes of interest reported on
12	Perseghin et al	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(2):65-71	Study was on collection methods, not therapeutic outcomes
13	Gorgun et al	Immunologic mechanisms of extracorporeal photochemotherapy in chronic graft-versus-host disease. Blood. 2002;100(3):941-7	No outcomes of interest reported on
14	Perutelli et al	ATP downregulation in mononuclear cells from children with graft-versus-host disease following extracorporeal photochemotherapy. Haematologica. 2002;87(3):335-6	Letter to the Editor
15	Tambur et al	Extracorporeal photopheresis induces lymphocyte but not monocyte apoptosis. Transplant Proc. 2000;32(4):747-8	No outcomes of interest reported on
16	D'incan et al	[Extracorporeal photopheresis as an alternative therapy for drug-resistant graft versus host disease: three cases]. Annales	Not English, fewer than five

		de Dermatologie et de Venereologie. 2000;127(2):166-70	subjects
17	Child et al	Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus-host disease (GVHD). Bone Marrow Transplant. 1999;23(9):881-7	No outcomes of interest reported on; data not extractable
18	Dall'Amico et al	Photopheresis in paediatric patients with drug-resistant chronic graft-versus-host disease. Br J Haematol. 1997;97(4):848-54	No outcomes of interest reported on
19	Schooneman et al	Treatment of graft versus host disease (GVHD) by photopheresis? Transfus Sci. 1996;17(4):527-36	Fewer than five patients
20	Goussetis et al	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(2):203-9.	Review retained for discussion, excluded from Results
21	Inamoto et al	Treatment of chronic graft-versus-host disease in 2011. Curr Opin Hematol. 18:414–420	Review retained for discussion, excluded from Results
22	Kaloyannidis et al	The role of the extracorporeal photopheresis in the management of the graft-versus-host disease. Transfus Apher Sci. 2012;46(2):211-9	Review retained for discussion, excluded from Results

Unable to obtain			
23	Halle et al	Successful extracorporeal photochemotherapy for chronic graft-versus-host disease in pediatric patients. J Hematother Stem Cell Res. 2002;11(3):501-12	Unable to obtain