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PRACTICE GUIDELINE

Extracorporeal photopheresis in the management of graft-versus-host disease

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ABSTRACT

Question

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

Perspectives

After allogeneic SCT, GVHD is a common complication historically categorized as either acute (aGVHD: onset ≤100 days post-transplantation) or chronic (cGVHD: >100 days post-transplantation). Graft-versus-host disease occurs when the donor's immune cells recognize the host patient's tissues and organs as foreign and attack them, causing a multitude of problems, often in liver, gastrointestinal system, and skin.

Photopheresis is one therapy that has emerged since the early 2000s for the management of steroid-refractory GVHD because of its steroid-sparing ability, low associated toxicity, and efficacy in some clinical settings.

The present recommendation report summarizes the available data about photopheresis for the treatment of GVHD and provides recommendations on its use.

Methodology

The MEDLINE (Ovid) database was systematically searched for January 1995 to August 2013, and the best available evidence was used to draft recommendations relevant to adult and pediatric patients in Ontario who have received allogeneic SCT and are experiencing GVHD. Draft recommendations were first reviewed by clinical and methodology experts before undergoing internal review. Final approval of this practice guideline report was obtained from both the Stem Cell Transplant Steering Committee and the Report Approval Panel of the Program in Evidence-Based Care.

Recommendations

These recommendations apply to adult and pediatric patients who have received an allogeneic SCT and are experiencing GVHD:

- ECP is an acceptable therapy for the treatment of steroid-dependent or refractory aGVHD in adult and pediatric patients.
- ECP is an effective therapy for the treatment of steroid-dependent or refractory cGVHD in adult and pediatric patients.

Qualifying Statement

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

KEY WORDS

Stem-cell transplantation, bone marrow, peripheral blood, graft-versus-host disease, photopheresis

1. RATIONALE

Graft-versus-host disease (GVHD) is a common complication after allogeneic stem-cell transplantation (SCT) occurring either acutely (aGVHD: onset ≤100 days post-transplantation) or chronically (cGVHD: >100 days post-transplantation)[1–3]. More than half of all patients undergoing allogeneic SCT experience GVHD. In the simplest terms, GVHD is a complication in which the infused donor's immune cells recognize the host patient's tissues and organs as foreign and begin causing tissue damage. The result is significant morbidity and, for many patients, mortality—either directly or indirectly.

Primary therapy for aGVHD has remained unchanged for 30 years and consists primarily of a calcineurin inhibitor in combination with corticosteroids. Approximately half the affected patients will experience complete resolution of their aGVHD with this approach. Patients failing first-line therapy have a poor prognosis, with a 1-year survival of less than 50%. Second-line therapies are varied and are supported mostly by small single-arm trials or cohort studies[4,5]. Many randomized trials of promising therapies for GVHD have been negative or were stopped early because of 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[6–11].

As already indicated, cGVHD is one of the main morbidities and causes of mortality in patients surviving the first few months after allogeneic SCT. Like aGVHD, cGVHD is treated in the first line with corticosteroids with or without a calcineurin inhibitor[12,13]. Patients with cGVHD have compromised quality of life and lesser survival and a very poor prognosis when front-line therapy for cGVHD fails. As for aGVHD, there is no standard second-line therapy for cGVHD. In practice, a variety of therapies for steroid-refractory cGVHD are applied in a trial-and-error approach[14,15]. In addition to having 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, no novel therapy currently in trials offers a foreseeable and significant advance over the current state of the art. Photopheresis is a therapy that emerged in the early 2000s for the management of steroid-refractory GVHD because of its steroid-sparing ability, low associated toxicity, and efficacy in some clinical settings[6,16–19].

Photopheresis is currently covered by the Ontario Ministry of Health and Long-Term Care for patients with steroid-refractory GVHD, but the therapy requires patients to travel to Toronto for therapy at the Princess Margaret Cancer Centre, which results in limited access for patients from other regions of the province because of travel and cost. More importantly, this patient population is medically complex, often with compromised functioning, and the travel requirement can be medically unsafe.

The present recommendation report summarizes the available data about photopheresis for the treatment of GVHD and provides recommendations on its use.

2. METHODS

2.1 Recommendation Development

This recommendation report, produced by the Program in Evidence-Based Care (PEBC) and the Stem Cell Transplantation Steering Committee of Cancer Care Ontario was developed through systematic review of the available evidence and interpretation of that evidence by clinical experts. Members of the Committee formed a working group 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 mandate of the Stem Cell Transplantation Steering Committee to provide advice to the Ontario Ministry of Health and Long-Term Care 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.

2.2 Literature Search Strategy

The MEDLINE (Ovid) database (1995 through July Week 1, 2012) was searched on July 17, 2012, and the search was updated on August 14, 2013. The search used logic combination of terms: [graft-versus-host disease] AND [stem cell transplantation, OR bone marrow transplantation, OR peripheral blood cell transplantation] AND [photopheresis].

Relevant articles and abstracts were selected and reviewed by two reviewers (CB, RBR), and the reference lists in those sources were searched for additional trials. Personal files were also searched.

3. RESULTS

3.1 Literature Search

The eighteen papers retained[6–11,16–27] included, for adults, one consensus report based on a systematic review[22], one randomized controlled trial (RCT)[18], one crossover RCT[19], one prospective cohort study[9], three retrospective cohort studies[8,16,17], one case series with historical controls[11], and four case series[6,21,24,27]; and for pediatric patients, one clinical practice guideline[23] (which also contained case-series data), one nonrandomized controlled trial[10], one prospective cohort study[26], and four case series[7,20,23,25] (including the series from the practice guideline). Of those eighteen papers, fourteen were identified using the MEDLINE (Ovid) database, three were submitted from the files of the lead author (CB), and one was identified from the reference list in one of the papers located in the search (Figure 1).

3.2 Adult Patients

In the twelve papers on the use of photopheresis in adult patients with GVHD after SCT[6,8,9,11,16–19,21,22,24,27], the number of patients reported ranged from 9 (in the case series reported by Lucid *et al.*[24]) to 82 (in

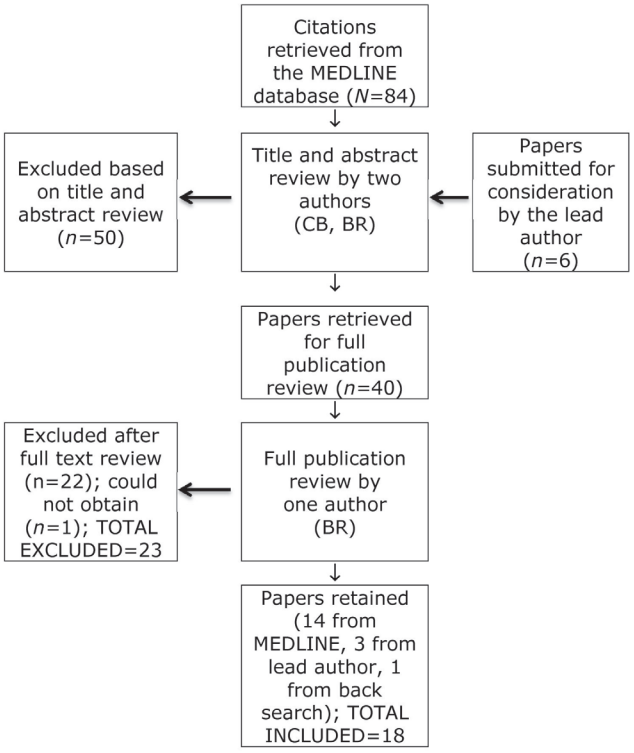

FIGURE 1 Selection of studies investigating extracorporeal photopheresis in the management of graft-versus-host disease in patients who underwent allogeneic blood or bone marrow transplantation.

the case series reported by Dignan *et al.*[21]). The patient diagnoses varied, but the typical population comprised patients with GVHD in whom either steroid treatment[6,9,21] or immunosuppressive therapy[24,27] had failed. Where an ECP device was reported, the only one described was either the UVAR or UVAR XTS system by Therakos (Raritan, NJ, U.S.A.)[6,9,16–18,21,27]. The duration for which patients received ECP treatment varied greatly, from a low of 2 weeks (median not reported) in the prospective cohort study by Greinix *et al.*[9] to a high of 528 weeks (median: 68 weeks) in the retrospective cohort study by Bisaccia *et al.*[17]. The most commonly reported outcome was the response rate, followed by survival, treatment-related mortality (TRM), safety, quality of life, and the effect of ECP on various measures of GVHD by affected site (Table I).

Quality was assessed according to the criteria described in Section 2, "Methods." See Table I for details of patient selection criteria, ECP treatment given, and outcomes reported. Because the recommendations in the consensus statement[22] are only indirectly related to photopheresis, and because the data on which the recommendations were based are not fully described, the working group decided that adapting the statement was not feasible, and a formal assessment of quality using the AGREE 2 instrument was therefore not performed.

The RCT reported by Flowers *et al.*[18] did not explicitly describe the method of randomization, but noted that a block method was used in a 1:1 ratio. The trial was reported as being single-blind, but no description of the power and sample size calculation, nor of the length of follow-up, was provided. The statistical analyses used were well described, with continuous variables summarized as medians and ranges, and categorical variables, as totals and percentages. The primary endpoint of total skin score was analyzed using a Wilcoxon rank-sum test, and cumulative response rates [complete (CR) and partial (PR)] were compared using the log-rank test. Withdrawals were well described for both arms, and no losses to follow-up were reported. Therakos provided funding for the trial.

The crossover study reported by Greinix *et al.*[19] included patients from the RCT reported by Flowers *et al.*[18] that crossed over from the non-ECP arm to the ECP arm, and the resulting sample was well described, as was the intervention that each patient received. All relevant outcomes were reported, including response rates, total skin scores, and change in steroid use. Therakos provided funding for the study.

The prospective cohort study reported by Greinix *et al.*[9] selected patients based on nonresponse 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 the study.

All three of the retrospective cohort studies[8,16,17] located for this review had well-described patient samples representative of a typical patient population. The study by Couriel *et al.*[8] did not report details of the ECP methods. The study by Apisarnthanarax *et al.*[16] reported on a series of patients in whom various ECP regimens were used, and those authors therefore did not report the details. By contrast, the study by Bisaccia *et al.*[17] fully described the single ECP protocol used for all patients. All three studies reported response rates, two reported survival[16,17], and one also reported median time to response[17]. Therakos supported the study by Apisarnthanarax *et al.*[16]. The other two studies did not report any source of funding.

The case-series study with historical controls reported by Perfetti *et al.*[11] had a well-described series of patients, which were representative of the population under study. The ECP regimen was also well reported. Outcomes reported were response rates and survival. This study reported non-industry funding (Association Italiana Ricerca contro il Cancro, CARIGE, Fondazione Ricerca per Trapianto Midollo Osseo).

The four case-series studies located for this review[6,21,24,27] had well-defined groups of patients who were representative of the population of interest; however, Lucid *et al.*[24] included only patients

TABLE I Study and patient characteristics, adult patients

Reference	*Study years*	*Patients (n)*	*Diagnosis*	*Extracorporeal photopheresis (ECP)*		*Outcomes reported*
				Details (device)	*Treatment weeks [range (median)]*	
Consensus recommendations and evidence review						
Hildebrandt *et al.,* 2011[22]		8 Studies of ECP in cGVHD	BOOP/COP/obstructive lung involvement	Varies	Varies	Response
Randomized controlled trial						
Flowers *et al.,* 2008[18]	2002–2005	ECP: 48 Control: 47	Histologically confirmed cGVHD with cutaneous symptoms at 100 days or more after transplantation	Week 1: 3 times Weeks 2–12: 2 times per week on consecutive days; responsive patients could continue with 2 treatments every 4 weeks until week 24 (UVAR XTS[a])	12–24	Skin response, steroid-sparing effects, extracutaneous response, quality of life, safety, mortality
Crossover randomized controlled trial						
Greinix *et al.,* 2011[19]	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 study						
Greinix *et al.,* 2006[9]	1996–1999	59	Grade II–IV aGVHD after first-line treatment with steroids	Patients were treated on 2 consecutive days (1 cycle) at 1- to 2-week intervals until improvement and then every 2–4 weeks until maximal response; treatment was reduced over 25 months (UVAR XTS[a])	NR	Response, treatment-related mortality, survival, long-term outcome
Retrospective cohort studies						
Apisarnthanarax *et al.,* 2003[16]	1998–2001	32	Patients had cutaneous symptoms of cGVHD after day 100 post-transplantation	ECP sessions— Total: 34 (median), 12–98 (range) Per month: 6 (median) 2–17 (range) (UVAR or UVAR XTS[a])	4–121 (23)	Response, survival

TABLE I Continued

Reference	*Study years*	*Patients (n)*	*Diagnosis*	*Extracorporeal photopheresis (ECP)*		*Outcomes reported*
				Details (device)	*Treatment weeks [range (median)]*	
Retrospective cohort studies (continued)						
Bisaccia *et al.,* 2006[17]	2000–2005	14 (of 20)	Patients had cGVHD after BMT or PBSCT, but were in complete remission of primary disease and had adequate hemodynamic 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[a])	13–191 (74)	Response, time to response, survival
Couriel *et al.,* 2006[8]	1998–2002	63	Patients had steroid-resistant cGVHD and 3 or fewer lines of immunosuppressant treatment	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
Case series with historical controls						
Perfetti *et al.,* 2008[11]	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						
Greinix *et al.,* 1998[6]	1993–1998	21	Patients with chronic extensive GVHD or with aGVHD resistant to steroid treatment	Patients treated on 2 consecutive days at 2-week intervals for the first 3 months and then every 4 weeks until resolution of GVHD (UVAR[a])	17–135	Response by site affected: skin, liver, joints, mouth, ocular, thrombopenia

TABLE I Continued

Reference	*Study years*	*Patients (n)*	*Diagnosis*	*Extracorporeal photopheresis (ECP)*		*Outcomes reported*
				Details (device)	*Treatment weeks [range (median)]*	
Case series (continued)						
Seaton *et al.*, 2003[27]	1994–2001	28	Patients with cGVHD refractory to immunosuppressive 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 reassessed every 6 months (UVAR and UVAR XTS[a])	4–252 (26)	Skin score, hepatic score, pulmonary score, mucosal score, neuromuscular score, treatment-related mortality
Lucid *et al.*, 2011[24]	2008–2009	9	Patients with bronchiolitis obliterans refractory to immunosuppressive treatment	Two sessions per week for 3–4 weeks and then 2 sessions every 2–3 weeks, with the goal of bringing patients to a once-every-4-weeks treatment schedule	NR	Response
Dignan *et al.*, 2012[21]	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 1 cycle per month (UVAR XTS[a])	6–141 (47)	Response, reduction in immunosuppressive treatment, reduction in steroid treatment, overall survival

[a] Johnson and Johnson, West Chester, PA, U.S.A.

GVHD = graft-versus-host disease (cGVHD: chronic GVHD; aGVHD = acute GVHD); BOOP = bronchiolitis obliterans organizing pneumonia; COP = cryptogenic organizing pneumonia; NR = not reported; BMT = bone marrow transplantation; PBSCT = peripheral blood stem-cell transplantation.

with bronchiolitis obliterans, and Dignan *et al.*[21] included only 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.*[24] reported response rates, and Dignan *et al.*[21] reported response rates, survival, and reductions in the dose of immunosuppressant drugs or in use of steroids. Seaton *et al.*[27] and Greinix *et al.*[6] both reported on the change in various scores associated with the sites affected by GVHD. No study reported the source of funding.

In summary, the quality assessment found that all studies of ECP in the treatment of GVHD in adult patients were of acceptable quality given the nature of their study designs. Table II presents results for all adult patients.

3.3 Pediatric Patients

Among the six papers on the use of photopheresis in pediatric patients with GVHD after SCT[7,10,20,23,25,26], the clinical practice guideline by Kanold *et al.*[23] also reported case-series data (described in Tables III and IV). The number of patients included in the studies ranged from 9 in the prospective cohort study reported by Salvaneschi *et al.*[26] to 77 in the nonrandomized controlled trial reported by Messina *et al.*[10]. As in the adult patients, the diagnoses in the pediatric patients varied, but the typical population comprised patients with GVHD for whom either steroid treatment[20,25,26] or immunosuppressive therapy[10] had failed. The two studies that reported specifics of the ECP system both used the UVAR system by Therakos[10,20]. The reported outcomes varied, but response rate was the most common, followed by survival, TRM, reductions in the use of steroids or immunosuppression, infection rates, mycosis, and changes in skin scores (Table III).

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

One clinical practice guideline, reported by Kanold *et al.*[23], was obtained. However, this guideline located no supporting evidence, and its recommendations are based solely on expert opinion and a single case series reported by the same authors. Our working group therefore decided that a direct review of the evidence and development of new recommendations would be more appropriate than an attempt to adapt the guideline, and so a formal assessment of quality using the AGREE 2 instrument was not performed.

In the nonrandomized controlled study reported by Messina *et al.*[10], the patient selection criteria were well described, and the resulting cohort was representative of the population of interest, as was the ECP regimen. The reported outcomes were response, survival, and adverse effects. This study was funded by non-industry sources (grants from the Associazione Italiana Ricerca sul Cancro, the Consiglio Nazionale delle Ricerche, the Ministero dell'Universita e della Ricerca Scientifica e Tecnologica, and the Istituto di Ricovero e Cura a Carattere Scientifico).

In the prospective cohort study[26] that was located, 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 the Associazione Italiana Ricerca sul Cancro, the Consiglio Nazionale delle Ricerche, the Ministero dell'Universita e della Ricerca Scientifica e Tecnologica, and the Istituto di Ricovero e Cura a Carattere Scientifico).

Of the four case series[7,20,23,25] located, three[7,20,25] included full descriptions of the patients included and the ECP regimen used; the study by Kanold *et al.*[23] had no description at all of the patients included or the ECP regimen. Outcomes reported in these studies were response rate[7,20,23,25], survival[7,20,25], TRM[7,20], progression-free survival[7], infection[7], and mycosis[7]. Two studies reported non-industry funding: the study by Perotti *et al.*[25] reported hospital funding, and the study by Calore *et al.*[7] reported funding from the Fondazione Citta della Speranza, Associazione Italiana Leucemie e Linfomi.

In summary, the quality assessment found that all the studies of ECP in the treatment of GVHD in pediatric patients were of acceptable quality given the nature of the study designs.

4. OUTCOMES

4.1 Adult Population

4.1.1 Response

The RCT by Flowers *et al.*[18] detected a statistically significant difference in response rate in favour of ECP over conventional corticosteroid treatment (40% vs. 10%, $p = 0.002$). Comparing ECP with conventional treatment, the crossover RCT reported a similarly significant increase in the overall response rate (26% vs. 8%, $p = 0.04$)[19]. None of the other comparative studies reported a difference between groups[8,9,16,17]. Noncomparative studies reported response rates ranging from 50%[11,17] to 100% (in liver manifesting aGVHD only)[6]. The RCT reported by Flowers *et al.*[18], which detected a benefit in favour of ECP, remains the best evidence because of the study design.

4.1.2 Treatment-Related Mortality

Only the RCT by Flowers *et al.*[18] reported on TRM, with no difference being detected.

4.1.3 Overall Survival

Only one study, the case series with historical controls reported by Perfetti *et al.*[11], compared overall survival between ECP and a control group, with no

TABLE II Results, adult patients

Reference	*Study years*	*Patients (n)*	*Response (%)*	*Treatment-related mortality (%)*	*Overall survival (%)*	*Quality of life (%)*
Randomized controlled trial						
Flowers *et al.,* 2008[18]	2002–2005	ECP: 48 Cnvl: 47	CR, 40; PR, 10 p=0.002	ECP, 98; Cnvl, 94 p=NR	NR	ECP, 19; Cnvl, 2.5 p=0.01
Crossover randomized controlled trial						
Greinix *et al.,* 2011[19]	2003– 2006	25	At 12 weeks: EPC, 26; Cnvl, 8 p=0.04 At 24 weeks: EPC, 31[a]	NR	NR	NR
Prospective cohort study						
Greinix *et al.,* 2006[9]	1996–1999	59	Cutaneous, 82; liver, 61; gut, 61 p=NR	NR	4-Year: 47 With CR: 47 Without CR: 11 p<0.0001	NR
Retrospective cohort studies						
Bisaccia *et al.,* 2006[17]	2000–2005	14	Cutaneous, 50; CR only, 21 p=NR	NR	85	NR
Couriel *et al.,* 2006[8]	1998–2002	63	Overall, 59; CR only, 21 p=NR	NR	5-Year: 41 Primary causes of death: GVHD, 68%; relapse, 26%; infection, 3%	NR
Apisarnthanarax *et al.,* 2003[16]	1998–2001	32	Overall, 56; CR only, 22 p=NR	NR	66 (Of all deaths under study, 100% were related to cGVHD)	NR
Case series with historical controls						
Perfetti *et al.,* 2008[11]	1996–2006	ECP: 23 Ctrl: 307	CR, 52	NR	48 ECP, 45; Ctrl, 44 p=NS	NR

TABLE II Continued

Reference	*Study years*	*Patients (n)*	*Response (%)*	*Treatment-related mortality (%)*	*Overall survival (%)*	*Quality of life (%)*
Case series						
Greinix *et al.,* 1998[6]	1993–1998	21	aGVHD (*n*=6) Skin (*n*=6): CR, 67; PR, 33 Liver (*n*=2): CR, 100; PR, — cGVHD (*n*=15) Skin (*n*=15): CR, 80; PR, 20 Joints (*n*=4): CR, —; PR, 100 Mouth (*n*=11): CR, 100; PR, — Liver (*n*=10): CR, 70; PR, 20; NC: 10 Ocular (*n*=6): CR, 17; PR, 67; NC, **17** Thrombopenia (*n*=3): CR, 67; PR, —; NC, 33	NR	NR	NR
Seaton *et al.,* 2003[27]	1994–2001	28	NR	14	NR	NR
Lucid *et al.,* 2011[24]	2008–2009	9	67	NR	NR	NR
Dignan *et al.,* 2012[21]	2005–2010	82	79; at 6 months, 94	NR	3-Year: 69	NR

[a] No data reported for the non-ECP arm at 24 weeks because of the large number of patients in that arm who discontinued the study.
ECP = extracorporeal photopheresis; Cnvl = conventional treatment; CR = complete response; PR = partial response; NR = not reported; GVHD = graft-versus-host disease (cGVHD: chronic GVHD; aGVHD = acute GVHD); Ctrl = control group; NC = no change.

TABLE III Study and patient characteristics, pediatric patients

Reference	*Study years*	*Patients (n)*	*Diagnosis*	*Extracorporeal photopheresis (ECP)*		*Outcomes reported*
				Details (device)	*Treatment weeks [range (median)]*	
Clinical practice guideline						
Kanold *et al.,* 2007[23]	1996–2006	27	aGVHD or cGVHD	Patients treated 3 times weekly (with a 1-day rest between 2 sessions) for the first 3 weeks, and then gradually reduced for patients who stabilized or showed improvement	NR	ECP should be considered first-line therapy in grade IV aGVHD (in association with conventional pharmacologic approaches) and in limited cGVHD; ECP should be considered second-line therapy in steroid-resistant grades II–III aGVHD and extensive cGVHD
Nonrandomized controlled trial						
Messina *et al.,* 2003[10]	1992–2000	77	Patients refractory to immunosuppressive therapy with aGVHD or cGVHD	Patients were treated on 2 consecutive days at 1-week intervals for the 1st month, and then every 2 weeks for the 2nd and 3rd months, and then monthly for at least 3 months (UVAR[a])	1–66 (10.5)	Response, survival
Prospective cohort study						
Salvaneschi *et al.,* 2001[26]	1998–NR	9	Patients with steroid-resistant, grade II–IV aGVHD and cGVHD, all of whom had been refractory to at least 1 line of treatment	aGVHD: 3 times weekly on alternate days until improvement, and 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 depended on individual assessment of response	NR	Response, survival, reduction in immunosuppressive therapy

TABLE III Continued

Reference	*Study years*	*Patients (n)*	*Diagnosis*	*Extracorporeal photopheresis (ECP)*		*Outcomes reported*
				Details (device)	*Treatment weeks [range (median)]*	
Case series						
Berger *et al.,* 2007[20]	2001–2005	25	Steroid-refractory patients with aGVHD or cGVHD	2 Consecutive days at weekly intervals for the 1st month, 2 consecutive days every other week for the 2nd and 3rd months, and then 2 consecutive days once monthly for 3 months (UVAR[a])	NR	Response, survival, treatment-related mortality
Kanold *et al.,* 2007[23]	1996–2006	27	aGVHD or cGVHD	Treatments 3 times weekly (with a 1-day rest between 2 sessions) for the first 3 weeks, and then gradually reduced for patients who stabilized or showed improvement	NR	Response, survival, change in skin scores
Calore *et al.,* 2008[7]	1999–2005	31	Patients with grades II–IV aGVHD	2 Consecutive days weeklyfor the 1st month, then every 2 weeks for the 2nd and 3rd months, then monthly for another 3 months (6 months' total treatment); immunosuppressive treatment was maintained and then reduced or discontinued, depending on clinical response	5–44 (24)	Response, survival, progression-free survival, treatment-related mortality, infection, mycosis
Perotti *et al.,* 2010[25]	NR	73	Steroid-refractory patients with aGVHD or cGVHD	aGVHD: 2 or 3 treatments per week (on alternate days) until clinical improvement; cGVHD: 2 procedures weekly 2 times, 2 procedures every other week 3 times, then 2 procedures monthly until clinical improvement or reduction in immunosuppressive therapy (or both)	NR	Response, survival

[a] Johnson and Johnson, West Chester, PA, U.S.A.

GVHD = graft-versus-host disease (cGVHD: chronic GVHD; aGVHD = acute GVHD); NR = not reported.

TABLE IV Results, pediatric patients

Reference	*Study years*	*Patients (n)*	*Response (%)*	*Treatment-related mortality (%)*	*Overall survival (%)*	*Quality of life (%)*
Nonrandomized controlled trial						
Messina *et al.,* 2003[10]	1992–2000	77 aGVHD: 33 cGVHD: 44	aGVHD (*n*=33): CR, 54; PR, 21; no response, 24 cGVHD (*n*=34 survived treatment): CR, 44; PR, 29; no response, 26	NR	5-Year, aGVHD: responders, 69; non-responders, 12 *p*=0.001 5-Year, cGVHD: responders, 96; non-responders, 58 *p*=0.04	NR
Prospective cohort study						
Salvaneschi *et al.,* 2001[26]	1998–NR	23 aGVHD: 9 cGVHD: 14	aGVHD (*n*=9): response rate, 78; CR, 71; PR, 29 (both evolving into cGVHD) cGVHD (*n*=14): response rate, 64; CR, 44; PR, 56; no response, 36 (2 with stable disease, 3 worsening)	NR	aGVHD (*n*=9): 78 cGVHD (*n*=14): 79 (of the 3 nonresponders, all died)	NR
Case series						
Berger *et al.,* 2007[20]	2001–2005	25	CR: aGVHD II (*n*=7), 100; aGVHD III (*n*=4), 50 PR: aGVHD III, 25 No response: aGVHD III, 25; aGVHD IV (*n*=4), 100 CR: limited (*n*=3) vs. extensive (*n*=7) cGVHD, 100 vs. 14 PR: extensive cGVHD, 14 Nonresponse: extensive cGVHD, 71	aGVHD: II, 0; III/IV, 42 *p*=0.05 cGVHD: ECP responder, 0; ECP nonresponder, 50 *p*=0.022	aGVHD: II, 100; III/IV, 30 *p*=0.006 cGVHD: Limited, 100; extensive, 28 *p*=0.03	
Kanold *et al.,* 2007[23]	1996–2006	27 aGVHD 12 cGVHD 15	aGVHD (*n*=12): CR, 58; PR, 25 cGVHD (*n*=15): CR, 27; PR, 47	NR	aGVHD (*n*=12): 75 cGVHD (*n*=15): 67	NR
Calore *et al.,* 200[8]7	1999–2005	ECP: 15 GR: 16	ECP (*n*=15): CR, 73; PR, 27 GR (*n*=16): CR, 56; PR, 44	ECP, 0 GR, 6	2-Year: ECP, 85; GR, 57	NR

Perotti *et al.,* 2010[25]	NR	73
		aGVHD: 50
		cGVHD: 23
			aGVHD (*n*=50):
			overall response, 68; CR, 32
			cGVHD (*n*=23):
			overall response, 69.5; CR, 21.7
				NR	aGVHD (*n*=50): 44;
					responders, 62 (21 of 34);
					nonresponders, 6.3 (1 of 16)
					cGVHD (*n*=23): 78.3;
					responders, 87.5 (14 of 16);
					nonresponders, 57 (4 of 7)
						NR

GVHD = graft-versus-host disease (cGVHD: chronic GVHD; aGVHD = acute GVHD); CR = complete response; PR = partial response); NR = not reported; ECP = extracorporeal photopheresis; GR = good response to steroid-based treatment.

difference being detected (45% for ECP vs. 44% for control). In the remaining studies, survival ranged from a low of 41% in the study reported by Couriel *et al.*[8] to a high of 85% in the study reported by Bisaccia *et al.*[17] (both retrospective cohort studies).

4.1.4 Quality of Life

Only the RCT by Flowers *et al.*[18] reported on quality-of-life outcomes, with a significant benefit being detected for ECP treatment compared with conventional treatment (19% for ECP vs. 2.5% for control, $p = 0.01$).

4.1.5 Other Outcomes

The RCT by Flowers *et al.*[18] reported total skin scores; eye, oral, and joint changes associated with GVHD; and adverse events. Significant differences were detected only in eye GVHD, which showed improvement more often with ECP than with conventional treatment (30% for ECP vs. 7% for control, $p = 0.04$).

The case series by Seaton *et al.*[27] reported on change from baseline scores after 6 months for cutaneous, hepatic, pulmonary, mucosal, and neuromuscular cGVHD; significant improvements were detected only for cutaneous cGVHD scores [89% at baseline (skin median score: 131) vs. 52% at 6 months (skin median score: 61), $p = 0.003$].

4.2 Pediatric Population

4.2.1 Response

Only one of the pediatric studies, the case series by Calore *et al.*[7], reported response outcomes that were comparable for ECP and another treatment option. That study reported response rates for patients who received ECP and patients who remained on steroid treatment. The CR rate was higher in the ECP group (73% vs. 56%, *p* value not reported), but the PR rate was higher in the group that received steroid treatment (44% vs. 27%, *p* value not reported).

In the remaining studies, CR rates ranged from a low of 32%[25] to a high of 100% (grade II only)[20], and PR rates ranged from a low of 21%[10] to a high of 29%[10,26] in patients with aGVHD. For patients with cGVHD, CR rates ranged from a low of 21.7%[25] to highs of 44%[10,26], and PR rates ranged from a low of 29%[10] to a high of 56%[26].

4.2.2 Treatment-Related Mortality

Two of the studies, the case series by Calore *et al.*[7] and by Berger *et al.*[20], reported TRM outcomes. Calore *et al.* found a TRM of 6% in the group that had a good response to steroid treatment; mortality was zero in the ECP group (*p* value not reported). Berger *et al.* found an increase in TRM as aGVHD symptoms worsened (0% in grade II disease vs. 42% in grade III–IV disease, $p = 0.05$); they also found an increase in nonresponders to both treatments (0% in ECP responders vs. 50% in nonresponders to both treatments, $p = 0.022$).

4.2.3 Overall Survival

Six of the studies reported overall survival outcomes[7,10,20,23,25,26]. Only the study by Calore *et al.*[7] reported comparable survival rates for ECP and another treatment, with patients who received ECP having a survival rate of 85% and patients who received steroid-based treatment having a survival rate of 57% ($p = 0.2$).

For aGVHD, the study by Messina *et al.*[10] detected a significant survival benefit in ECP responders compared with nonresponders at a median follow-up of 5 years (69% vs. 12%, $p = 0.001$). Perotti *et al.*[25] reported a 62% survival rate in ECP responders compared with 6.3% in nonresponders at a median follow-up of 23.7 months (*p* value not reported). Berger *et al.*[20] reported a 100% survival rate in patients with grade II acute disease; the rate was 30% in patients with grade III or IV disease at a median follow-up of 1.6 years ($p = 0.006$).

In patients with cGVHD, Messina *et al.*[10] reported a survival rate of 96% in ECP responders compared with 58% in nonresponders (median follow-up: 5 years; $p = 0.04$), and Salvaneschi *et al.*[26] reported a survival rate of 79% in ECP responders compared with zero in nonresponders (median follow-up: 36 months; *p* value not reported). The study by Berger *et al.*[20] reported a survival rate of 100% in patients with limited symptoms, but the rate fell to 28% in patients with extensive symptoms (median follow-up: 2.6 years; $p = 0.03$).

4.2.4 Quality of Life

None of the studies reported quality of life.

4.2.5 Other Outcomes

In their case series, Calore *et al.*[7] presented 2-year progression-free survival, but no difference between the groups was reported (87% for ECP vs. 67% for steroid responders, *p* value not reported).

5. REVIEW PROCESS

The clinical lead author wrote the initial recommendations and qualifying statement pertaining to the benefit associated with the use of ECP for patients experiencing GVHD. This report was circulated to the members of the Stem Cell Transplantation working group and discussed during a teleconference. The draft recommendations were then generated. The ensuing recommendation report was presented to the entire Stem Cell Transplantation Steering Committee to ensure the clinical relevance and utility of the recommendations, the absence of obvious defects in the evidence base, and the reasonableness of the recommendations derived through expert opinion. Refined recommendations and a summary of the key evidence were first reviewed by the PEBC's Report Approval Panel (Scientific Director and the

PEBC Assistant Director) to ensure that the guideline development was methodologically rigorous and that the evidence-based recommendations are indeed supported by the evidence in a transparent way. Upon completion of preliminary review and feedback provided by the PEBC Assistant Director, the recommendation report was presented to the PEBC Scientific Director for final review.

Practice guidelines and recommendation reports developed by the PEBC are reviewed and updated as needed. Please visit the Cancer Care Ontario Web site (http://www.cancercare.on.ca) for the full report and subsequent updates.

6. PRACTICE GUIDELINE

Evidence from a systematic search of the primary literature, consensus of expert opinion, feedback obtained through the review process, and a final approval given by the Stem Cell Transplant Steering Committee and the PEBC's Report Approval Panel collectively form the basis of this recommendation report, completed in August 2013.

6.1 Target Population

The following recommendations apply to adult and pediatric patients who have received allogeneic transplantation and are experiencing GVHD.

6.2 Recommendations

- Extracorporeal photopheresis is an acceptable therapy for the treatment of steroid-dependent or refractory aGVHD in adult and pediatric patients.

  This recommendation is based on results of three non-comparative studies in adult patients (one prospective single cohort[23] and two case series[6,11]) and six studies in pediatric patients (one clinical trial[10], one prospective cohort[26], and four case series[7,20,23,25]) that reported response rates ranging from 32% to 100% in favour of ECP. Only one of the pediatric studies reported comparable response rates for patients who received ECP and patients who remained on conventional treatment[7].

  In the opinion of the Expert Panel, although the quality of the data for steroid-refractory aGVHD is limited, patients with refractory skin GVHD primarily should be considered for ECP treatment.

- Extracorporeal photopheresis is an effective therapy for the treatment of steroid-dependent or refractory cGVHD in adult and pediatric patients.

  This recommendation is supported by the evidence obtained from two studies (an RCT[18] and a crossover RCT[19]) because, in both studies, a significant increase in the response rate favours ECP over conventional corticosteroid treatment.

  Five additional comparative studies[8,10,16,17,26] and six noncomparative studies[6,20,21,23–25] reported response rates ranging from 50% to 80%.

6.3 Key Evidence

Although the proof for efficacy of ECP is of mixed quality, the weight of the evidence supports that ECP works in certain patients and that, when it works, it can provide clinical improvement. The best data, as summarized earlier, support the use of ECP for steroid-refractory cGVHD that is affecting primarily skin or subcutaneous tissue, lung, and liver[3,8,9,18,19,21,22,24]. The data for steroid-refractory aGVHD are more limited, but patients with refractory skin GVHD primarily should also be considered[8,9,23]. 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 individuals who tolerate corticosteroids poorly. Definitive randomized trial data defining second-line therapy for either aGVHD or cGVHD is, for a variety of reasons, many years away (no good candidates, complexity of trials, cost to conduct trials, limited peer funding for such trials, a small market discouraging industry pursuit of 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 in whom front-line therapy fails[4,5,8,15]. Appropriate application of photopheresis combined with data collection and reporting will enable ongoing evaluation of this therapy compared with other emerging options for GVHD patients in Ontario.

6.4 Qualifying Statement

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

7. ACKNOWLEDGMENTS

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8. CONFLICT OF INTEREST DISCLOSURES

The authors of this recommendation report disclosed potential conflicts of interest relating to the topic. The lead author (CB) 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 (RBR, NPV, JK, CTK) reported no conflicts of interest.

9. REFERENCES

1. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet* 2009;373:1550–61.
2. Flowers ME, Inamoto Y, Carpenter PA, *et al.* Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood* 2011;117:3214–19.
3. Pavletic SZ, Fowler DH. Are we making progress in GVHD prophylaxis and treatment? *Hematology Am Soc Hematol Educ Program* 2012;2012:251–64.
4. Martin PJ, Inamoto Y, Flowers ME, Carpenter PA. Secondary treatment of acute graft-versus-host disease: a critical review. *Biol Blood Marrow Transplant* 2012;18:982–8.
5. Martin PJ, Rizzo JD, Wingard JR, *et al.* First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 2012;18:1150–63.
6. Greinix HT, Volc–Platzer B, Rabitsch W, *et al.* Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood* 1998;92:3098–104.
7. Calore E, Calo A, Tridello G, *et al.* Extracorporeal photochemotherapy may improve outcome in children with acute GVHD. *Bone Marrow Transplant* 2008;42:421–5.
8. Couriel D, Hosing C, Saliba R, *et al.* Extracorporeal photopheresis for acute and chronic graft-versus-host disease: does it work? *Biol Blood Marrow Transplant* 2006;12(suppl 2):37–40.
9. Greinix HT, Knobler RM, Worel N, *et al.* The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica* 2006;91:405–8.
10. Messina C, Locatelli F, Lanino E, *et al.* Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. *Br J Haematol* 2003;122:118–27.
11. Perfetti P, Carlier P, Strada P, *et al.* Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. *Bone Marrow Transplant* 2008;42:609–17.
12. Couriel D, Carpenter PA, Cutler C, *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;12:375–96.
13. Wolff D, Gerbitz A, Ayuk F, *et al.* Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. *Biol Blood Marrow Transplant* 2010;16:1611–28.
14. Inamoto Y, Flowers ME. Treatment of chronic graft-versus-host disease in 2011. *Curr Opin Hematol* 2011;18:414–20.
15. Wolff D, Schleuning M, von Harsdorf S, *et al.* Consensus Conference on Clinical Practice in Chronic GVHD: second-line treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2011;17:1–17.
16. Apisarnthanarax N, Donato M, Korbling M, *et al.* Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone Marrow Transplant* 2003;31:459–65.
17. Bisaccia E, Palangio M, Gonzalez J, *et al.* Treatment of extensive chronic graft-versus-host disease with extracorporeal photochemotherapy. *J Clin Apher* 2006;21:181–7.
18. Flowers ME, Apperley JF, van Besien K, *et al.* A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood* 2008;112:2667–74. [Erratum in: *Blood* 2009;113:4478]
19. Greinix HT, van Besien K, Elmaagacli AH, *et al.* Progressive improvement in cutaneous and extracutaneous chronic graft-versus-host disease after a 24-week course of extracorporeal photopheresis—results of a crossover randomized study. *Biol Blood Marrow Transplant* 2011;17:1775–82.
20. Berger M, Pessolano R, Albiani R, *et al.* Extracorporeal photopheresis for steroid resistant graft versus host disease in pediatric patients: a pilot single institution report. *J Pediatr Hematol Oncol* 2007;29:678–87.
21. Dignan FL, Greenblatt D, Cox M, *et al.* Efficacy of bimonthly extracorporeal photopheresis in refractory chronic mucocutaneous GVHD. *Bone Marrow Transplant* 2012;47:824–30.
22. Hildebrandt GC, Fazekas T, Lawitschka A, *et al.* Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. *Bone Marrow Transplant* 2011;46:1283–95.
23. Kanold J, Merlin E, Halle P, *et al.* Photopheresis in pediatric graft-versus-host disease after allogeneic marrow transplantation: clinical practice guidelines based on field experience and review of the literature. *Transfusion* 2007;47:2276–89.
24. Lucid CE, Savani BN, Engelhardt BG, *et al.* Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT. *Bone Marrow Transplant* 2011;46:426–9.
25. Perotti C, Del Fante C, Tinelli C, *et al.* Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. *Transfusion* 2010;50:1359–69.
26. Salvaneschi L, Perotti C, Zecca M, *et al.* Extracorporeal photochemotherapy for treatment of acute and chronic GVHD in childhood. *Transfusion* 2001;41:1299–305.
27. Seaton ED, Szydlo RM, Kanfer E, Apperley JF, Russell–Jones R. Influence of extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response. *Blood* 2003;102:1217–23.

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