Photopheresis in Adults and Pediatrics

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66.1 Introduction

Extracorporeal photopheresis (ECP) is a leukapheresis-based treatment that has been used during the last decades by many clinicians. Based on results of a prospective, multicenter, international clinical trial in patients with cutaneous T-cell lymphoma (CTCL), ECP was approved by the FDA as the first cellular immunotherapy for cancer in 1988 (Edelson et al. 1987). During the last decades, ECP has been investigated worldwide for prevention and treatment of a variety of T-cell-mediated diseases including acute and chronic GvHD, solid organ and tissue transplantation, systemic sclerosis, systemic lupus erythematodes, and Crohn's disease (Knobler et al. 2014). Administering ECP to patients suffering of these diseases revealed promising results both in prospective and retrospective single and multicenter clinical studies. Despite its frequent use, the mode of action of ECP remains elusive including reduction of pro-inflammatory cytokines and induction of anti-inflammatory cytokines and modulation of immune cell populations.

66.2 Technical Aspects

During ECP the patient's blood is collected via an antecubital vein or via a permanent catheter, and the white blood cells are separated from the red blood cells and plasma by centrifugation in a device that is specifically constructed for the procedure (Knobler et al. 2014; Schoonemann 2003). Collected mononuclear cells (MNCs) using either continuous or discontinuous cell separators are then exposed ex vivo to a photosensitizing agent, 8-methoxypsoralen (8-MOP), which is added directly to the buffy coat/plasma fraction followed by photoactivation with ultraviolet A (UV-A) irradiation and then reinfusion of the photoactivated product (Schoonemann 2003).

ECP has originally been developed as a single procedure which combines the separation of the MNCs from the whole blood with irradiation of the 8-MOP-treated leukapheresis products within a single machine ("closed system of ECP"). The "offline technique" (two-step method) of ECP treatment includes as the first step cell separation with a standard blood cell separator that can also be used for the collection of peripheral blood stem cells. The apheresis product is transferred into another disposable, 8-MOP is added, and irradiation is performed with a separate machine at a dosage of 2 J/cm^2. After irradiation transfusion of the treated cells is carried out manually by a standard transfusion set. Both ECP techniques have demonstrated clinical efficacy, but almost all clinical studies have been performed with the single

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ECP technique, and studies comparing both systems are almost completely lacking (Schoonemann 2003; Andreu et al. 1994; Brosig et al. 2016).

66.3 Results of ECP in Acute GvHD

To date, no consensus on the optimal choice of agents for salvage therapy of steroid-refractory acute GvHD has been reached, and treatment choices are based on physician's experience, risk of toxicity and potential exacerbation of pre-existing comorbidity, interactions with other agents, and ease of use (Martin et al. 2012). During the last years, more and more HSCT centers have administered ECP to patients with steroid-refractory acute GvHD. Results of larger prospective studies on the use of ECP in this indication are shown in Table 66.1. The intensified schedule of ECP with two to three treatments per week on a weekly basis significantly improved response rates in patients with GI involvement and grade IV acute GvHD (Greinix et al. 2006).

In a systematic review of prospective studies including 6 studies with 103 patients given ECP for steroid-refractory acute GvHD, an overall response rate (ORR) of 69% was achieved including ORR for skin, liver, and GI involvement of 84%, 55%, and 65%, respectively (Abu-Dalle et al. 2014). Compared to anticytokine treatment, administration of ECP for steroid-refractory acute GvHD not only achieved significantly higher ORR (66% vs 32%) and CR (54% vs 20%), but ECP was also an independent predictor of response and survival and was associated with significantly lower NRM and superior survival in steroid-refractory grade II acute GvHD (Jagasia et al. 2013). Compared to other IST, ECP has an excellent safety profile with limited toxicity concerns, no increased concerns for viral reactivations, and no documented interaction with other drugs (Martin et al. 2012).

66.4 Results of ECP in Chronic GvHD

Although many therapeutic options have been reported for salvage treatment of steroid-refractory chronic GvHD, no single class of IS agent has been established as standard therapy (Wolff et al. 2011). ECP represents a frequently used therapeutic approach for treatment of chronic GvHD patients failing corticosteroids (Table 66.2) (Knobler et al. 2014; Wolff et al. 2011; Greinix et al. 1998; Flowers et al. 2008; Jagasia et al. 2009; Greinix et al. 2011). Most of the clinical experience in ECP treatment of steroid-refractory chronic GvHD patients is based on retrospective analyses with consistently high response rates in up to 80% of patients with cutaneous manifestations and substantial improvement in scleroderma-tous skin involvement (Knobler et al. 2014; Wolff et al. 2011).

Table 66.1 Results of second-line treatment of acute GvHD using extracorporeal photopheresis

Author (year)	No. of patients	CR skin no. (%)	CR liver no. (%)	CR gut no. (%)	OS%
Salvaneschi (2001)	9	6/9 (67)	1/3 (33)	3/5 (60)	67
Dall'Amico (2002)	14	10/14 (71)	4/7 (57)	6/10 (60)	57
Messina et al. (2003)	33	25/33 (76)	9/15 (60)	15/20 (75)	69 at 5 y
Greinix et al. (2006)	59	47/57 (82)	14/23 (61)	9/15 (60)	47 at 5 y
Garban (2005)	12	8/12 (67)	0/2 (0)	2/5 (40)	42
Kanold (2007)	12	9/10 (90)	5/9 (56)	5/6 (83)	75 at 8.5 m
Calore (2008)	15	12/13 (92)		14/14 (100)	85 at 5 y
Perfetti (2008)	23	15/23 (65)	3/11 (27)	8/20 (40)	48 at 37 m
Gonzalez-Vicent (2008)	8	8/8 (100)	2/2 (100)	4/7 (57)	38
Perotti (2010)	50	39/47 (83) (1)	16/24 (67) (1)	8/11 (73) (1)	64 at 1 y
Jagasia (2013)	57	38/57 (67) (1)	38/57 (67) (1)	38/57 (67) (1)	59 at 2 y
Calore (2015)	72	50/64 (78)	10/12 (84)	42/55 (76)	71 at 5 y

Abbreviations: *No* number, *CR* complete resolution, *OS* overall survival, *y* years, *m* months
Results were provided as complete and partial resolution.

Table 66.2 Results of use of extracorporeal photopheresis in chronic GvHD

Author (year)	No of patients	CR/PR skin (%)	CR/PR liver (%)	CR/PR oral (%)	ORR (%)
Greinix et al. (1998)	15	80	70	100	na
Salvaneschi (2001)	14	83	67	67	64
Messina (2003)	44	56	60	–	57
Seaton (2003)	28	48	32	21	36
Apisarnthanarax (2003)	32	59	0	na	56
Foss (2005)	25	64	0	46	64
Rubegni (2005)	32	81	77	92	69
Greinix (2006)	47	93	84	95	83
Couriel (2006)	71	57	71	78	61
Kanold (2007)	15	75	82	86	50
Perseghin (2007)	25	67	67	78	73
Flowers (2008)	48	40	29	53	40
Jagasia (2009)	43				65
Perotti (2010)	23	96	100	80	69
Dignan (2012)	82	92	na	91	74
Greinix (2011)	29	31	50	70	na
Del Fante (2012)	102	na	na	na	81
Ussowicz (2013)	13	67	89	86	69
Hautmann (2013)	32	59	100	60	44
Dignan (2014)	38	65	-	29	50

Abbreviations: *No* number, *CR* complete resolution, *PR* partial resolution, *ORR* overall response rate, *na* not available

In a multicenter, randomized, controlled, prospective phase II study of ECP in 95 patients with steroid-refractory/dependent/intolerant chronic GvHD, significantly more patients in the ECP arm achieved a complete or partial response of cutaneous manifestations ($p < 0.001$) as well as a 50% reduction in steroid dose and at least a 25% decrease in total skin score ($p = 0.04$) by week 12 (Greinix et al. 1998). A steroid-sparing effect of ECP has also been reported by other investigators (Knobler et al. 2014; Wolff et al. 2011; Flowers et al. 2008; Jagasia et al. 2009).

In a systematic review of prospective studies on the use of ECP in patients with chronic GvHD, an ORR of 71% in cutaneous, 62% in GI, 58% in hepatic, 63% in oral mucosal, and 45% in musculoskeletal manifestations of chronic GvHD was reported (Abu-Dalle et al. 2014). Rate of IS discontinuation was 23% and ECP was tolerated excellently. In another meta-analysis high response rates in cutaneous and extracutaneous manifestations of chronic GvHD including 48% of responses in lung involvement were confirmed (Del Fante et al. 2016). The ECP schedule in chronic GvHD is empirical ranging from multiple treatments per week on a weekly basis to two treatments biweekly and in case of response prolongation of the treatment interval to 4–6 weeks, respectively. No clear association between ECP dose intensity and response has been reported. Higher response rates were achieved in steroid-refractory patients given ECP earlier in the course of their disease (Malik et al. 2014; Messina et al. 2003). Improvements in quality of life and survival in ECP responders have been reported (Knobler et al. 2014; Wolff et al. 2011; Greinix et al. 1998; Malik et al. 2014; Messina et al. 2003).

ECP is a safe and efficacious treatment for patients with chronic GvHD with steroid-sparing capacity. Transient hypotension during treatment and mild anemia and/or thrombocytopenia have been reported as side effects of ECP. Prospective clinical studies are warranted to assess the efficacy of ECP in well-defined cohorts of chronic GvHD patients treated earlier in the course of their disease. Recently, Jagasia and colleagues reported first results of a

randomized, controlled, multicenter study in NIH-defined moderate/severe chronic GvHD patients given ECP in the study arm in combination with standard of care IS (Jagasia et al. 2017). Besides an ORR of 74%, and thus, a promising efficacy ECP demonstrated to be safe and tolerated well.

66.5 Conclusions

ECP has been used for over 30 years in the treatment of CTCL, acute and chronic GvHD, and solid organ transplant rejection. Multiple scientific organizations recommend its use due to ECP's efficacy and excellent safety profile (Knobler et al. 2014). Due to the lack of interactions with other agents and the avoidance of general IS, ECP compares favorably with other IS strategies, supporting its increasingly frequent use as second-line therapy of steroid-refractory/dependent acute and chronic GvHD. Of note, the corticosteroid-sparing potential of ECP has been confirmed in numerous retrospective and prospective studies and translates into immediate clinical benefit for patients with GvHD as well as a reduction of transplant-associated morbidity and mortality.

No general recommendation can be made on treatment schedule due to missing evidence. Ideally, ECP treatment should be initiated as early as possible after the indication is confirmed. Especially in patients with steroid-refractory acute GvHD, earlier treatment onset and an intensified weekly ECP schedule resulted in improved response rates and patients' outcome. Prospective studies on the use of ECP as upfront treatment in GvHD are warranted as well as its investigation for prophylactic/preemptive use during allo-HSCT.

Key Points

- ECP is a safe and efficacious adjunct therapy of steroid-refractory acute and chronic GvHD.
- Results in upfront therapy of chronic GvHD are promising.

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