The Use of Extracorporeal Photopheresis for the Treatment of Acute Graft Versus Host Disease

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Abstract

Acute graft versus host disease (aGVHD) is a key complication of haematopoietic stem-cell transplantation. The main first-line therapy is steroids, however less than half of patients respond to this treatment, and some patients relapse following an initial response. Extracorporeal photopheresis (ECP) is a therapy that has shown promising efficacy in several immune-mediated disorders, including aGVHD. Used as a second-line treatment, ECP has been associated with good rates of disease resolution, both overall and for individual organ systems involved in this disorder. The responses to ECP have commonly been seen soon after the start of treatment. Patients who respond to ECP have also been shown to have lower rates of transplant-related mortality and greater overall survival than those who do not respond. ECP is well tolerated by patients, including those with a low performance index and children of low body weight. Data on the use of ECP in treating aGVHD in both adults and children are reviewed here.

Keywords

Acute graft versus host disease (aGVHD), extracorporeal photopheresis, adult, paediatric, complete resolution, transplant-related mortality, survival, tolerability, safety

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Graft versus host disease (GVHD) is a major complication of haematopoietic stem-cell transplantation (HSCT). Historically, GVHD occurring within the first 100 days post HSCT was classified as acute GVHD (aGVHD). More recently, the National Institutes of Health (NIH) consensus criteria for clinical trials proposed that clinical manifestations rather than time after transplantation should be used to distinguish acute from chronic GVHD and introduced the term late acute GVHD, which includes persistent, recurrent, or late-onset aGVHD.[1] Clinical manifestations of aGVHD involve the skin, gastrointestinal tract and liver.[2] The incidence of aGVHD is reported to range from 10 to 80 %, depending on risk factors such as the use of unrelated donors, total body irradiation and transplant conditioning regimen.[3] Acute GVHD is, in turn, a strong risk factor for transplant-related morbidity and mortality (TRM), because of its own pathology and that associated with the immunosuppressive therapies generally used for its treatment. It is also a risk factor for the development of chronic GVHD.

Corticosteroids are the main first-line therapy for aGVHD, however these are associated with a response in less than 50 % of patients,[4] and some patients who initially respond subsequently relapse.[5] Response after short-term treatment with prednisolone (five days or 28 days) was significantly associated with a lower TRM than non-response.[6,7] New therapies are therefore being investigated that can quickly and effectively treat aGVHD, and prevent its relapse. One such therapy is extracorporeal photopheresis (ECP).

ECP is a therapy that was originally developed over 25 years ago to treat cutaneous T-cell lymphoma.[8] Since that time, its use has been investigated and shown promising efficacy in many other disorders with an auto- or alloimmune aetiology, including GVHD, systemic sclerosis, prevention and treatment of rejection in solid organ transplantation and Crohn's disease.[9] The treatment has three stages: first leukapheresis, following which the separated white blood cells are photoactivated with 8-methoxypsoralen and exposure to ultraviolet-A light, then return of the activated white blood cells to the patient. ECP has been found to be generally well tolerated, with a good safety profile, in patients with a variety of diseases.[10] This paper reviews studies with ECP in patients with aGVHD.

Early Data

Much of the early information on the use of ECP in aGVHD was recorded in case studies and series, and small studies (see *Table 1*).[11–21] The data on 76 patients (age range 5–55 years) from these early studies, all of whom were receiving ECP as second-line treatment for aGVHD, were collated and reviewed in 2002.[11] Overall patient survival was 53 %. ECP was associated with complete resolution (CR) of skin manifestations of aGVHD in 67 % of patients. Rates of CR for liver and gastrointestinal

Table 1: Summary of Results from Early Studies of Extracorporeal Photopheresis in aGVHD[11–21]

	Sniecinski et al., 1995	Besnier et al., 1997	Looks et al., 1997	Richter et al., 1997	Greinix et al., 1998	Miller et al., 1998	Smith et al., 1998	Girardi et al., 1999	Greinix et al., 2000	Salvaneschi et al., 2001	Dall'Amico & Messina 2002
Patients (n)	11	2	1	1	6	4	6	1	21	9	14
Age (years)		10–18	16	26	25–55	26–45	5–53	40	27–55	5–17	
Gender (M/F)		0/2	0/1	1/0		3/1		1/0	10/11		
BMT to ECP interval (days)		60	66	51	30–70	26–48	50–134	47	20–70	9–36	13–92
ECP cycles (n)		8–9	8	13	9–36		4–24		9–36		
CR skin (n)	1		1	1	4	2		1	13	6	10
CR liver (n)	1				2	2			8	1	4
CR gut (n)	3					3				3	6
Overall response		2 NR	1 CR	1 CR	4 CR, 2 PR	8 CR	6 NR	1 CR	8 CR		7 CR
Survival	7/11	0/2	1/1	1/1	6/6	2/4	0/6	0/1	12/21	6/9	8/14

aGVHD = acute graft versus host disease; BMT = bone marrow transplant; CR = complete resolution; ECP = extracorporeal photopheresis; M/F = male/female; NR = no resolution; PR = partial resolution.

Table 2: Results from a Phase II Study of Extracorporeal Photopheresis in Adult Patients with Severe aGVHD[22]

Patient Characteristic	Patients (n)	CR (%)
Grade of aGVHD at ECP		
II	36	86
III	13	55
IV	10	30
Organ Involvement at ECP		
Skin alone	31	87
Skin and liver	13	62
Skin, liver and gut	8	25
Skin and gut	5	40
Liver and gut	2	–

aGVHD = acute graft versus host disease; CR = complete resolution; ECP = extracorporeal photopheresis.

manifestations were 38 and 54 %, respectively. Best response rates were seen in patients with grade II–III aGVHD; lower rates were observed for grade IV disease. The maximal response to ECP was seen after 6–8 weeks of treatment (2–5 cycles of ECP).[11]

Extracorporeal Photopheresis in Adult Patients with aGVHD

The review described above included data from preliminary investigations[16] and a pilot study[20] conducted by Greinix and co-workers. The positive results achieved in these studies led this group to conduct a Phase II study of ECP in aGVHD.[22] This prospective study involved 38 adults with severe aGVHD (either steroid-refractory or -dependent disease), and results were compared with those obtained in the pilot study of 21 patients. In the pilot study, patients received ECP in cycles consisting of two consecutive treatment days at one- to two-week intervals until improvement, then every 2–4 weeks until maximal response; in the Phase II study, ECP was delivered in weekly cycles (two consecutive days) and stopped immediately after achieving maximal response. Overall, CR was shown by 82 % of patients with skin involvement, 61 % with liver involvement and 61 % with gastrointestinal involvement. Response rates for different combinations of organ involvement, and for individual grades of aGVHD are shown in *Table 2*. Results of the Phase II study were better than those of the pilot study, particularly for patients with gastrointestinal involvement and grade IV disease. This increase in efficacy was attributed to earlier initiation of ECP (15 days of steroid therapy before ECP in the Phase II study, compared with 21 days in the pilot study).[23] The best response to ECP was observed after a median of 1.3 (range 0.5–6) months; therefore, patients generally required a short duration of treatment and did not experience flare-ups of aGVHD after ECP was stopped.[23] In patients who responded to ECP, steroids could be discontinued a median of 55 (range 17–284) days after the start of ECP.

Univariate analysis of the response data showed that lower grades of aGVHD, fewer organs involved at the start of steroid therapy and of ECP, and lower cumulative doses of steroid before the start of ECP all significantly increased the probability of a CR following ECP.[22] Logistic regression analysis showed that only a lower grade of aGVHD at the start of ECP and later initiation of steroid therapy after transplant were associated with an increased probability of a CR following ECP.[22]

The overall cumulative incidence of TRM at four years was 36 % [95 % confidence interval (CI) 25–50 %], but this was only 14 % (95 % CI 10–31 %) for those who achieved a CR following ECP and was 73 % (95 % CI 56–94 %) for those who did not.[22] Corresponding data for overall survival at four years were 47 % for all patients, 59 % for those who experienced CR and 11 % for those who did not. Univariate analysis showed that a shorter interval between transplantation and ECP, a shorter duration of ECP, and lower cumulative doses of steroids were associated with lower TRM.

Two small studies also support the results of this Phase II trial (see *Table 3*). Garban et al. reported the treatment of 12 adults with steroid-refractory aGVHD, who received three weekly cycles of ECP and were then assessed for treatment response.[24] At that time, 9/12 patients had responded and seven showed a CR. Those seven patients were able to stop treatment immediately, whereas the patients who had experienced partial resolution (PR) underwent further therapy until CR. ECP was particularly effective for patients with skin involvement and some gastrointestinal involvement; in this study, patients with liver disease did not respond to ECP. All of the patients with skin involvement who responded to treatment showed a CR after the first three weeks of treatment. In addition, the patients who responded were able to stop steroid treatment one–two months after the start of ECP. The authors concluded that ECP treatment should be started early after the onset of aGVHD, and a short course of treatment followed by evaluation of response would identify those patients who could stop ECP at that stage and those who required further treatment.[24]

Table 3: Results of Studies of the Use of Extracorporeal Photopheresis in Adult Patients with aGVHD[22,24,25]

	Patients (n)	CR Skin [n (%)]	CR Liver [n (%)]	CR Gut [n (%)]	OS (%)
Garban et al., 2005	12	8/12 (67)	0/2 (0)	2/5 (40)	42
Greinix et al., 2006	59	47/57 (82)	14/23 (61)	9/15 (60)	47 at five years
Perfetti et al., 2008	23	15/23 (65)	3/11 (27)	8/20 (40)	48 at 37 months

aGVHD = acute graft versus host disease; CR = complete resolution; OS = overall survival.

A retrospective series of 23 patients with steroid-unresponsive aGVHD was reported by Perfetti et al.[25] These patients received weekly cycles of ECP for the first month, then every other week for two months, followed by monthly cycles until CR or stabilisation of GVHD. Patients received a median of 10 cycles of ECP and the overall CR rate was 52 % (12/23 patients). As shown in *Table 3*, responses were better for patients with skin involvement at the start of treatment, and for those with grade II disease (66 % CR) compared with grades III and IV disease (27 and 40 %, respectively). ECP was started a median of 56 days after the onset of aGVHD; the authors noted a trend towards improved responses for patients who started ECP less than 35 days after aGVHD onset, compared with those starting after this time. Once ECP was started, the mean dose of intravenous (iv) steroids that patients were receiving could be reduced over time; and after three months of treatment only four of the original 23 patients were still receiving iv steroids.

Recently, data have been reported in abstract form from a large, multicentre, retrospective comparison of ECP (86 patients) and anticytokine therapy (inolimomab or anti-tumour necrosis factor-alpha, 41 patients) for second-line treatment of adult patients with steroid-dependent and -refractory aGVHD.[26] Patients received a median of 12 ECP treatments, over a median of 50 days. The aGVHD response was higher in the ECP group (73 versus 32 %; p<0.001) and was associated with a superior survival (not reached versus 4.9 months; p<0.001). The cumulative incidence of two-year non-relapse mortality was higher in the non-ECP group compared with the ECP group (82 versus 37 %; p<0.001). This international, multicentre study suggests that ECP is an effective second-line therapy for aGVHD and may be superior to non-ECP intervention.

Extracorporeal Photopheresis in Children with aGVHD

The efficacy of ECP as a treatment for aGVHD in adult patients has largely been replicated in paediatric patients (see *Table 4*). An early multicentre, retrospective study involving 33 children with steroid-resistant aGVHD showed an overall CR rate of 54 % (21 % PR).[27] Patients received a median of eight cycles of ECP and maximal response was seen after eight weeks' treatment (weekly cycles for the first month, then every other week in months two and three). CR rates for different organ involvement were as follows: skin symptoms 76 %, gastrointestinal symptoms 75 %, and liver involvement 60 %. Overall survival at five years was significantly better for ECP responders (69 %) than non-responders (12 %). In addition, as a result of ECP, it was possible to discontinue immunosuppressive therapy in eight patients (42 %) and reduce the dose in seven patients (36 %).

Berger et al. reported a series of 15 paediatric patients with steroid-resistant aGVHD treated with ECP.[28] Patients received a median of six cycles of ECP, starting a median of 25 days after diagnosis of aGVHD. At the end of the scheduled ECP treatment, 62 % of patients were aGVHD-free. All of the patients with grade II disease at the start of ECP showed a CR; 50 % of those with grade III disease experienced CR and 25 % PR. For any grade of organ involvement, CR was seen for 8/12 patients with skin involvement (67 %), 3/4 patients with liver involvement (75 %) and 5/7 patients with gastrointestinal involvement (71 %). The strongest predictor of treatment response was disease grade. Significant predictors of TRM were grade of aGVHD and response to ECP.

Similar good results for individual organ systems were reported in a series of eight paediatric patients with steroid-refractory aGVHD.[29] CR was shown for 8/8 patients with skin involvement, 2/2 patients with liver involvement and 4/7 patients with gastrointestinal involvement (3/7 experienced PR). Likewise, in a study of 12 patients with aGVHD, the overall response rate was 83 % (10/12; 58 % CR; 25 % PR).[30] Rates of CR for individual organ systems were 90 % for skin (9/10 patients), 56 % for liver (5/9) and 83 % for gastrointestinal involvement (5/6). Overall, the steroid-sparing rate after 10 sessions of ECP was 63 %, and corticosteroids could be stopped during ECP in six patients.

Calore et al. reported a comparison of ECP and steroid therapy in paediatric patients (15 and 16 patients, respectively) with grade II–IV aGVHD.[31] The overall response rates were 73 % CR and 27 % PR for ECP and 56 % CR and 31 % PR for steroid therapy. Response rates for individual organ involvement were also somewhat higher for ECP compared with steroid therapy: for skin involvement CR rates were 92 % for ECP and 46 % for steroids; for gastrointestinal involvement the rates were 71 and 57 %, respectively; for liver involvement the rates were 100 and 67 %, respectively. At day 100, TRM was 6 % for patients who had received steroid therapy and 0 % for patients in the ECP group. In addition, at two years, overall survival rates were somewhat higher for ECP (85 %) than steroid therapy (57 %).

A longitudinal study of 50 paediatric patients with aGVHD showed an overall response rate of 68 % (32 % CR, 36 % PR).[32] Overall response rates (CR+PR) for individual organ systems were: skin 83 %, liver 66.7 %, gastrointestinal system 72.7 %. It was possible to stop steroid therapy in 16 % of patients with aGVHD, and tapering of steroid dose after 30 days of ECP therapy was positively associated with survival of patients in this study. Non-response to ECP was significantly associated with risk of death.

Tolerability of Extracorporeal Photopheresis

There are several challenges inherent in treating children with ECP, such as low body weight and extracorporeal volume during treatment. Nevertheless, several studies have addressed these issues directly and reported good treatment tolerance, even in children with body weight as low as 10 kg.[27,30,33] Similarly, the tolerability of ECP appears to be good in adult patients. Indeed, one group commented that the low toxicity of ECP allowed the use of this treatment in patients with a low performance index.[25] Furthermore, the efficacy of ECP in reducing patients' doses of steroid therapy may produce some long-term benefits in terms of toxicity, although it would require continued follow-up of patients to establish whether there is such a treatment advantage.

Table 4: Results of Studies of the Use of Extracorporeal Photopheresis in Paediatric Patients with aGVHD[27–32]

	Patients (n)	CR Skin [n (%)]	CR Liver [n (%)]	CR Gut [n (%)]	OS (%)
Messina et al., 2003	33	25/33 (76)	9/15 (60)	15/20 (75)	69 at five years
Berger et al., 2007	15	8/12 (67)	3/4 (75)	5/7 (71)	
Kanold et al., 2007	12	9/10 (90)	5/9 (56)	5/6 (83)	75 at 8.5 months
Calore et al., 2008	15	12/13 (92)		14/14 (100)	85 at five years
Gonzalez-Vicent et al., 2008	8	8/8 (100)	2/2 (100)	4/7 (57)	
Perotti et al., 2010	50	39/47 (83)*	16/24 (67)*	8/11 (73)*	64 at one year

*aGVHD = acute graft versus host disease; CR = complete resolution; OS = overall survival. *Results were provided as complete and partial resolution.*

Prophylactic use of Extracorporeal Photopheresis in aGVHD

In addition to the studies described above, in which ECP was used to treat aGVHD, some preliminary studies have investigated the use of ECP as part of the myeloablative conditioning regimen, prior to HSCT, in an attempt to reduce the onset of aGVHD. In one study, 55 patients at high risk or ineligible for a conventional allogeneic HSCT received a reduced-intensity conditioning regimen consisting of ECP, pentostatin, and reduced-dose total-body irradiation.[34] GVHD prophylaxis consisted of cyclosporine and methotrexate. The results showed a 9 % incidence of greater than grade II aGVHD in these patients, with no negative effects on engraftment or disease relapse. Contradictory results were obtained in a Phase II study, in which ECP was added to cyclosporine and methotrexate for aGVHD prophylaxis in a standard myeloablative regimen.[35] In these 66 patients, the incidence of aGVHD was similar to that found in other studies following conventional conditioning and HSCT; however, there did appear to be a somewhat lower incidence of grades II–IV aGVHD and a longer overall survival for patients when ECP was included in conditioning. Therefore, the preventive use of ECP is an interesting area that requires further exploration, and data from more patients with a longer duration of follow-up will be required to establish a role for ECP in this setting.

Discussion

Data reviewed here demonstrate that ECP is an effective therapy for aGVHD, with CR rates reported to be as high as 73 %.[23,36] The use of ECP and response to ECP have been significantly associated with longer survival of both adult[22,26] and paediatric patients[28,31,32] with aGVHD following transplantation. These reports also show that the results of ECP can be seen after only a short course of treatment (best response was observed after 1.3 months by Greinix et al.[22] and after three treatment cycles by Garban et al.[24]). Thus, patients may be reviewed after a small number of treatment cycles and ECP stopped or modified according to an individual's response. In addition, a number of studies appeared to indicate that earlier initiation of treatment with ECP was associated with better responses than if this treatment was delayed.[23,25,27] Therefore, patients may experience better responses if ECP treatment is started promptly when it is clear that first-line therapy is producing a sub-optimal response. One study reported that a lack of response of aGVHD after only five days of first-line prednisolone therapy was predictive of a higher TRM,[7] so the results of early steroid therapy may be of use in guiding the initiation of ECP in appropriate patients.

Responses to ECP of aGVHD in individual organ systems are generally good, with reported CR rates for skin involvement as high as 92 % and those for gastrointestinal or liver involvement of up to 100 %. Responses for aGVHD affecting combinations of organ systems are less well reported, as many studies have included only small numbers of patients. Greinix et al. did report the outcome of GVHD affecting combinations of systems in their Phase II study. This showed that responses of patients with skin only, or skin and liver involvement were superior to those with skin and gastrointestinal involvement, and that the poorest responses were seen in patients with symptoms in all three of these organs.[22]

The safety and tolerability of ECP are reported to be good, even in patients with a low performance index[25] and low-weight children.[27] In addition, the fact that ECP treatment reduces patients' cumulative exposure to steroids in both adults[24–26] and children[27,30,32] holds promise for the long-term sequelae for such patients. ■

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