Extracorporeal chemophototherapy for the treatment of graft-versus-host disease: hematologic consequences of short-term, intensive courses

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Background and Objectives. Extracorporeal chemophototherapy (ECP) is considered an immunomodulatory agent useful in both acute and chronic graft-versus-host disease (GVHD). Little is known about the best treatment schedule, and there are no data concerning hematologic parameters and cellular compositions of products during the treatment.

Design and Methods. This was a single-center study of 27 patients treated with ECP for corticoresistant GVHD. Treatment was given in a short-term series of six courses over 3 weeks, and in case of response, consolidation treatment was given until complete response or stabilization of lesions.

Results. Nine out of 12 patients with acute GVHD responded to treatment. In patients with chronic GVHD, 13 out of 15 patients responded (11 complete and 2 partial responses). Responses were obtained essentially in skin or gut lesions; ECP was of particular effect in three cases of bronchiolitis obliterans associated with transplantation, with all three patients responding. Hematologic consequences were studied in patients with chronic GVHD: hemoglobin levels increased significantly after treatment and a reduction in red blood cell transfusion requirements was also observed.

Interpretations and Conclusions. ECP is effective in both chronic and acute GVHD, particularly in lung forms. ECP can reduce the duration of immunosuppressive therapy and improve erythroid recovery. ECP product quality, including standardization for the number of mononuclear cells for each patient, needs further investigation.

Key words: extracorporeal chemophototherapy, graft-versus-host disease, intensive courses.

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Allogeneic stem cell transplantation can create a conflict between the immune systems of the donor and the host. A strong anti-malignancy effect (GVM effect) results from this conflict as does an immunological complication called graft-versus-host disease (GVHD). Despite progress in the management of patients who receive transplants, GVHD remains one of the major causes of non-relapse mortality.[1,2] GVHD principally affects the skin, gut and liver in its acute form, whereas chronic GVHD has various clinical manifestations among which cytopenia is frequent and anemia may require blood transfusion. Various therapies have been proposed for the treatment of patients with GVHD, such as cyclosporine, tacrolimus, mycophenolate mofetil, monoclonal antibodies and corticosteroids.[3] All these approaches lead to prolonged immunosuppression and an increased risk of infectious complications.[4] Extracorporeal chemophototherapy (ECP) was initially used successfully to treat Sézary's lymphoma[5] and later to treat graft rejection in organ transplantation,[6] as an immunomodulating strategy in other immunological disorders involving T cells[7,8] and in type 1 diabetes.[9] ECP has been successfully used to treat both acute[10] and chronic forms of GVHD.[11-14] Several studies both in children[15] and adults[12] suggest that ECP is effective either in combination with other immunosuppressive drugs or alone in steroid-resistant GVHD.[10] However, little is known about the optimal conditions for conducting apheresis and the schedule that could be applied to patients. The best mononuclear cell dose to use for clinical benefit is unknown. As previously reported, ECP is a well-tolerated procedure that could be an alternative treatment with the aim of avoiding some of the hematologic and immune complications of conventional therapies for GVHD.

Here we report our single-center experience with 27 consecutive patients treated for acute or chronic GVHD, with an inten-

sive, promptly instituted series of courses of ECP. We explored the consequences of this treatment on hematologic parameters and the composition of the cell product infused into the patients.

Design and Methods

Patients

This was a pilot study based on 7 years of experience (1997-2004) with the use of ECP. Twenty-seven adult patients were treated for acute (12 patients) or chronic GVHD (15 patients). All patients gave their informed consent. Diagnosis was assessed by skin, gut or liver biopsies. Lung disease was explored by immunological and cytological examinations of bronchoalveolar fluid, computed tomography and pulmonary function tests. All the patients with acute GVHD had grade II–IV disease (according to the Glucksberg scale), and were refractory to corticosteroids (2-3 mg/kg/day of prednisone for a minimum of 5 days associated with either cyclosporine or cyclosporine + mycophenolate mofetil). All patients with chronic GVHD presented an extensive form of the disease resisting immunosuppressive therapy with associated corticosteroids given at a minimum dose of 2 mg/kg/day for at least 1 month. The results of ECP treatment in both acute and chronic GVHD were evaluated as previously described.[12] Complete response was defined as complete resolution of all manifestations of chronic GVHD with discontinuation of the immunosuppressive drug. For skin involvement, a partial response was considered to have occurred when at least 50% of the skin involvement appeared to be non-inflammatory or fixed; a complete response was defined as either the disappearance of all lesions or the presence of fixed and pigmented lesions; in cases in which immunosuppressive drugs were maintained, the response was considered as partial. Improvement of 50% in one organ involved was considered as a partial response. Evaluations were systematically scheduled for 1 month, 3 months and 6 months after the beginning of ECP. The patients' characteristics are listed in Table 1.

Table 1. General characteristics of the patients treated with ECP.

	Acute GVHD	*Chronic GVHD*
N	12	15
Age	40 (23-63)	45 (14-62)
Diagnosis		
Acute leukemia	7	2
Chronic myeloid leukemia	2	5
Multiple myeloma	1	4
Myelodysplastic syndrome	2	
Myeloproliferative disease		1
Fanconi's anemia		1
Solid tumor		1
Transplant		
Standard conditioning/RIC	10/2	6/9
Source PB/BM	8/4	11/4
donor type		
match sibling	8	13
unrelated	4	2
GVH prophylaxis		
CSA MTX	9	10
CSA MMF	2	1
CSA	1	4
Previous acute GVHD	–	6 /15

RIC: reduced intensity conditioning; CSA: cyclosporine A; MTX: methotrexate (days 1, 3, 6); MMF: mycophenolate mofetil; PB: peripheral blood; BM: bone marrow.

ECP procedure

Patients were treated according the Vilbert Lourma procedure, as previously described.[16,17] Briefly, leukapheresis was performed using a Spectra cell separator (Cobe, USA) with treatment of three whole blood masses. Mononuclear cells were transferred to a bag specially adapted for UVA irradiation (MacoPharma, France) and 8-methoxypsoralen was added *ex vivo*. Thereafter, cells were UVA-irradiated at 2 J/cm^2 (UV matic irradiator, Vilbert Lourma, France), except in cases with a hematocrit >5%, when the irradiation was 2.5 J/cm^2). The final product was intravenously infused in the patient within 3 hours after irradiation. Six courses were given during the first 3 weeks, then, after clinical evaluation, ECP was stopped if there was complete response; in cases of partial response, maintenance therapy was one course per week until complete response. In the case of no response, ECP was interrupted after six courses. Each patient's blood count was obtained before apheresis and all products were tested: the quality control included cell count and hematocrit.

Results

Acute GVHD

For the patients with refractory acute GVHD, the ECP was added to immunosuppressive treatment with cyclosporine and/or mycophenolate mofetil and corticosteroids. All patients had a stable skin response when evaluated after six courses of ECP, except two patients in whom responses appeared to be transient, noted as *no response* in Table 2A. These two non-responding patients developed rapidly progressive, severe grade IV GVHD with skin, liver and gut involvement, leading to death despite additional

treatment with anti-thymocyte globulins. Nine of the patients did not require a complementary immunosuppressive regimen. The others rapidly progressed and two died from liver failure (see above), one from multiorgan failure with GVHD lesions. Corticosteroids were stopped between 1 and 2 months after ECP initiation in all responding patients. Among the patients evaluable for chronic GVHD, three developed signs of chronic GVHD leading either to new ECP courses or conventional treatment by immunosuppressive drugs associated with steroids. To avoid complicating the interpretation of the ECP results, these patients were not reported in the chronic GVHD series of patients and were only evaluated for acute GVHD. Two patients relapsed early (<6 months) after transplantation and died of refractory disease. In our experience, it appears that ECP is better if performed as soon as possible after the diagnosis of acute GVHD, particularly when lesions are limited to the skin or when there is minimal gut injury. In case of liver disease, ECP did not alleviate the requirement for more potent immunosuppressive therapies.

Chronic GVHD

Only patients with chronic GVHD who had not been previously treated with ECP for acute GVHD were evaluated. Data concerning the delay from graft to chronic GVHD and from graft to the beginning of ECP, and immunosuppressive therapy are presented in Table 2B. Most of our patients were treated before the first year after transplantation, two were treated at 13 and 17 months, and two others 3 and 9 years after transplantation. Only 4 of 15 patients developed thrombocytopenia and 6 of 15 had experienced previous acute GVHD. Twelve out of 15 patients had chronic skin involvement (sclerodermoid or lichenoid), all patients responded and most of the responses occurred in the first weeks of treatment. Evaluation of these patients after the induction regimen of four to six courses indicated at least a partial response and, after the consolidation sequence (eight to ten courses), responses became progressively complete. Control of gut involvement appeared to parallel skin improvements, but chronic hepatic lesions seemed to be dissociated, and improvement in liver test results was only transient.

The control of the bronchiolitis obliterans associated with GVHD was a more noteworthy finding. Our three patients with documented severe bronchiolitis obliterans were treated with ECP, associated for the first weeks with steroids, leading to a stabilization of pulmonary function test results without corticosteroids (vital capacity and forced expiratory volume in 1 second improved to 15%, 32% and 35% for each of these patients and stabilized at 52–65% of the normal value without steroids). Although, our three patients recovered good quality of life (Karnofsky score up to 80%) and improvement of pulmonary function tests, the stable, fixed obstructive lesions could only be evaluated as a partial response. Clinical

Table 2A. Organ involvement in patients with acute GVHD and clinical responses.

	Staging pre- ECP	*post ECP*
Skin		
Acute grade 0	0	8
Acute grade I-II	4	1
Acute grade III-IIV	8	3
Chronic fixed lesion or no lesion	12	
Chronic limited lesion	0	0
Chronic extensive	12	0
Gut		
Acute grade 0	0	2
Acute grade I-III	4	2
Acute grade III-IV	1	0
Chronic no lesion		7
Chronic extensive	9	2 (2 NR)
Liver		
Acute grade 0	0	0
Acute grade I-II	0	0
Acute grade III-IV	2	2
Chronic extensive	3	3 (1 PR, 2 NR)
Lung		
Chronic extensive	3	3 (3 PR)
Neuropathy		
Chronic extensive	3	3 (1 PR, 2 NR)

CR: complete response; PR: partial response; NR: no response.

Table 2B. Response and immunosuppressive therapy (IS) in chronic GVHD patients.

	Time from graft to chronic GVHD (months)	*Time from graft to ECP (months)*	*Immunosuppressive therapy*		*Duration of response*
			before ECP	*after ECP*	
P1	3	4	C+tacro	none	6 months
P2	12	17	C	none	30 months
P3	3	4	C+CSA	none	20 months
P5	11	13	C + chloram	MMF	no response
P9	5	6	C + CSA	none	4 months
P12	5	7	C	none	15 months
P13	9	11	C+MMF	none	24 months
P14	6	110	C	none	72 months
P15	6	8	C	none	no response
P16	3	36	C+MMF	MMF	36 months
P17	7	9	C+MMF	none	3 months
P19	4	7	C+CSA	none	12 months
P23	3	3	C+CSA	none	12 months
P24	4	6	C+MMF+tacro	C+MMF	no response
P26	4	5	C+ CSA	none	4 months

CSA: cyclosporine A; MMF: mycophenolate mofetil; Tacro: tacrolimus; CS: corticosteroids. Chloram: chlorambucil.

Table 3. Cellular composition of ECP products in terms of lymphocytes, monocytes, granulocytes and total cells.

	No. of courses	*Lymphocytes %*	*Monocytes %*	*Granulocytes %*	*Total cells $\times 10^6$*
P1	15	48	20	24	9,275
P2	23	66	18	17	7,159
P3	33	68	28	3	7,044
P5	10	72	17	1	7,759
P9	37	49	37	12	2,122
P12	17	66	30	4	15,267
P13	13	38	39	20	9,535
P14	18	31	27	39	10,529
P15	18	68	26	12	5,361
P16	15	50	31	18	6,138
P17	7	38	19	30	6,006
P19	4	69	25	11	4,816
P23	10	65	25	12	6,965
P24	7	0	0	0	3,652
P26	6	67	12	20	5,815
Average	16	53	24	15	7,163

results have been stable for several months and for one patient for more than 2 years. The improvements in respiratory function tests appeared to be delayed up to 3 months.

Our results in chronic extensive GVHD also showed that immunosuppressive therapy could be stopped or suspended in most cases, a major finding. Four patients were totally free of immunosuppression for more than 1 year. Six patients had a relapse of their malignant disease (three myeloma, one ALL, one AML, one solid tumor), but all undergone transplantation in an advanced phase (relapse or refractory).

ECP and transfusion requirements in chronic GVHD

Our institutional policy on transfusion requirements is to transfuse red blood cells in cases of hemoglobin under 80 g/L and units of single-donor platelets from apheresis in cases of platelet counts under 20×10^9/L. All products were irradiated. In this study, none of the patients was treated with recombinant erythropoietin. In 14 patients we noted that hemoglobin levels were significantly improved 3 months after ECP, with a corresponding reduction in red blood cell requirements (*data not shown*). It should be noted that most of the patients, despite the intensive series of aphereses, did not receive transfusions, and in some cases showed dramatic improvement of anemia. However, these data concern a limited number of patients.

Cellular composition of the ECP product infused

In order to gain some insights into the cell populations most involved in ECP, we conducted a systematic analysis of each product infused into the patients. For this part of the study we considered only the patients with chronic GVHD, so as to minimize the interference in blood counts that could be related to other immunosuppressive therapies, infections, or relapse. Results of the evaluable patients are shown in Table 3. It was found that the composition of monocytes, granulocytes, and lymphocytes of each product did not vary greatly from one course to another. The proportions of lymphocytes, monocytes and granulocytes were, respectively, 53% (31-72%), 24% (12-39), and 15% (1-39%). These data must be considered as preliminary.

Discussion

Following its use in rejection after organ transplantation, several years ago, ECP was proposed as treatment for chronic GVHD. The first clinical successes were obtained in cutaneous sclerodermoid lesions. The use of ECP has now been extended to management of both acute and chronic GVHD. As previously reported, we observed that both skin and to a lesser extent gut allogeneic injuries were highly sensitive to ECP. Our data suggest that in acute GVHD only four to six courses are necessary to obtain clinical results and enable interruption of corticosteroid therapy, with nine of the 12 patients responding (seven had complete responses). However, in our two cases of rapid onset, acute liver GVHD, ECP did not appear to help control the disease even when added to antithymocyte globulins and high doses of steroids. Our small number of patients does not allow a firm interpretation to be made on the role of ECP in the prevention of chronic GVHD.

Our investigation of patients with already established chronic GVHD provided some original findings. First, there were very high response rates, especially among the patients with skin involvement. These results are undoubtedly related to our population of GHVD patients, who could be considered as good risk. Most of the patients were treated during the first year after transplantation, so the chronic cutaneous GVHD appeared to comprise more inflammatory lesions than fibrotic or retractile ones. However, we also obtained good responses even in those patients who manifested GVHD years after transplantation. Second, we observed good results in three patients with severe bronchiolitis obliterans after at least 2 months of steroid therapy. These three patients responded with improvements in quality of life and spirometric tests; the responses, in terms of clinical signs and pulmonary function tests, occurred within 3 months of the beginning of ECP and appeared to be stable, allowing corticosteroid thera-

py to be stopped. Considering the very poor prognosis of bronchiolitis obliterans after allogeneic transplantation, our intensive strategy of at least six courses of ECP in 1 month may be of particular interest in this setting. Indeed, given the poor efficiency of immunosuppressive drugs in this late complication of chronic GVHD, often further complicated by bacterial or viral infection,[4] ECP, a well-tolerated procedure, appears to be a reasonable treatment option in bronchiolitis obliterans. Data on ECP treatment of bronchiolitis obliterans are scarce. Seaton observed only small changes in pulmonary function tests during ECP.[18] However, Seaton's study was quite different from ours: it was prospective and no patients with severe bronchiolitis obliterans were included; evaluation concerned only systematically studied spirometric parameters. We used ECP in concordance with steroids in severe clinical disease and recorded improvements in the obstructive defect, and resolution of the restrictive syndrome.

Besides studying the changes in clinical manifestations of GVHD induced by ECP, we also investigated hematologic parameters. Changes in hemoglobin levels and platelet counts were studied before ECP, at 3 months and at the end of ECP. A statistically significant change was observed in hemoglobin level in the chronic GVHD group of patients. The improvement was significant as early as 3 months and at the end of the ECP procedure. This finding was confirmed by a decrease in red blood cell transfusion requirements. Changes in platelet counts were correlated with hemoglobin levels but were not statistically significant. Our study provides the first data concerning the effects of ECP on hemoglobin changes and their consequences on blood transfusion requirements. These results are all the more important considering the intensive series of courses during the first months of treatment, and the resulting red blood cell depletion induced by apheresis.

Taken together our data also suggest that an intensive sequential regimen of ECP followed by consolidation courses is an alternative schedule for ECP that improves clinical response and obtains earlier responses. The ECP regimen we used allows a higher number of mononuclear cells to be processed than in the regimens used by Seaton *et al.*[18] or by Greinix,[12] although it is not yet known whether these parameters are relevant to ECP results. Our study argues for an early implementation of ECP in GVHD, with a minimum of six to ten courses over a short period. In our opinion, if no response has occurred after four to six courses, ECP cannot be considered as effective and should be stopped. The recent studies by Seaton *et al.* and Greinix reported a less intensive ECP procedure, with eight courses in 4 months. Unfortunately, data concerning the cells treated by ECP in these last two studies were not reported, but in 1994 Andreu *et al.*[16] compared the two available ECP techniques and demonstrated that the Vilbert Lourma procedure made it possible to process more mononuclear cells (nearly double the number).

Our group tried to define parameters for quality control for ECP, only based on the known effect on lymphocytes.[17] The mechanism of action of ECP remains largely unknown. It has been clearly demonstrated that lymphocytes irradiated with UV light undergo early and substantial apoptosis,[19] probably explained by enhanced CD95 expression on circulating treated T cells.[20] However, effects on antigen-presenting cells, which can play a key role in the initiation of acute GVHD,[21,22] have also been reported in patients with chronic GVHD treated by ECP.[23] A more extensive definition of the technical process is now required so that the results between studies can be compared. Further studies are also needed to determine the best cellular target of ECP, focusing not only on lymphocytes and dendritic cells, but also on freshly irradiated monocytes obtained from patients.

FG: conception and design, acquisition of data, drafting, revising and final approval; PD: acquisition of data, interpretation, drafting, revising and final approval; CM, M-CJ, M-JR: acquisition of data, revising critically and final approval; MF: analysis and interpretation of data, revising critically and final approval; JJS and JCB: conception and design, revising critically and final approval; JYC: conception and design, interpretation of data, drafting and revising critically and final approval.

All authors approved the manuscript, declare they have no potential conflict of interest and in particular for the past two years and the known future, they had and will have none of the financial relationships as mentioned in points 1 to 7 of Haematologica's policy concerning conflict of interest, with companies whose products are considered in this paper or relevant to its subject or with their competitors.

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