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Ocular manifestations of chronic graft-versus-host disease in patients treated with extracorporeal photochemotherapy

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PURPOSE. *Eye involvement has long been appreciated in patients with chronic graft versus host disease (cGVHD). In particular, ocular complications are frequent and can be potentially severe in patients with steroid-refractory cGVHD, and therefore necessitate close monitoring. This prospective study was designed to describe eye manifestations of cGVHD in a large series of patients monitoring them before and after 1 year of extracorporeal photochemotherapy (ECP). ECP is a relatively new therapeutic approach based on the biological effects of psoralen 8-methoxypsoralen (8-MOP) and ultraviolet A light (UVA) on mononuclear cells collected by apheresis, and reinfused into the patient.*

METHODS. *Only patients with steroid-refractory cGVHD under treatment with ECP, who developed cGVHD-related eye symptoms, were selected for the study. Ophthalmologic examination was repeated every 3 months. Only patients with complete recovery of the ocular manifestations and symptoms were considered responsive.*

RESULTS. *In our study we observed eye alterations in 24 out of 140 patients (17%) with cGVHD. After 12 months of ECP, 10 out of 21 patients (48%) completely responded to the therapy. In all these cases the contribution of ECP was also essential in all the other organs subject to cGVHD.*

CONCLUSIONS. *Further studies are necessary to clarify the role of ECP in patients with cGVHD, especially in associated eye manifestations. Although our experience is limited, it suggests that ECP could be a safe and effective therapy for steroid-refractory eye manifestations of cGVHD. (Eur J Ophthalmol 2007; 17: 961-9)*

KEY WORDS. *Allogenic stem cell transplant, Chronic graft-versus-host disease, Ocular manifestations, Systemic immunosuppressants, Extracorporeal photochemotherapy*

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INTRODUCTION

About 20–80% of patients with chronic graft versus host disease (cGVHD) have ocular involvement (1, 2). Today the natural course of ocular cGVHD is well described and classified in four stages (3). The initial or subclinical stage manifests with lacrimation, mild nonspecific discomfort, and photophobia. This stage can last for a few days to as long as 1 month before patients start to develop other systemic manifestations of cGVHD or progress to a more severe form of ocular GVHD. A patient in the active stage of ocular cGVHD usually has other systemic manifestations of GVHD. During this stage the eye manifestations vary from mucopurulent conjunctivitis and pseudomem-

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branous conjunctivitis to punctate keratitis and corneal erosions. This stage is followed by the convalescent stage of the disease, characterized by secondary sicca syndrome, or progression to the necrotizing stage, with corneal melting and sometimes perforation. All these potentially severe eye problems in cGVHD patients call for close ophthalmic monitoring and sometimes multiple courses of systemic immunosuppressive therapy. Systemic corticosteroids and other immunosuppressants are also the mainstay of therapy for ocular manifestation of cGVHD. However, in addition to the well-known systemic side effects, some patients may develop bilateral cataracts and posterior subcapsular opacification, possibly caused by high-dose steroid medications, or keratoconjunctivitis sicca resulting from toxic reactions to methotrexate or azathioprine (4, 5). Other patients may have steroid-refractory disease with a particularly poor prognosis.

Extracorporeal photochemotherapy (ECP), also known as photopheresis, is now emerging as an alternative promising therapy for cGVHD, even in steroid-refractory patients (6).

ECP is an original immunoregulatory procedure introduced by Edelson et al in 1987 to treat cutaneous T-cell lymphomas (7). Since then, its application has been reported in the treatment of a variety of other T-cell-mediated disorders including not only GVHD but also organ transplant rejection (8). ECP consists of an extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen (8-MOP) and their subsequent return to the patient. ECP is performed with a UVAR® apparatus (Therakos Inc., West Chester, PA) and is used at a frequency suitable for disease and subject. Briefly, patients undergo discontinuous leukapheresis. The leucocytes are exposed to ultraviolet (UV) A irradiation (320–400 nm). Approximately 240 mL of leucocyte-enriched blood are mixed with 300 mL of the patient's plasma and 200 µg (5 mL) of the liquid form of 8-MOP. The buffy coat is then passed through a sterile cassette in a 1-mm film and is irradiated for 180 min with UVA, which provides an average leucocyte exposure of 2 J/cm^2. The buffy coat is then reinfused into the patient. ECP is now used in about 160 centers worldwide; however, the mechanism of action of ECP is not fully understood (9-13).

In this study we reported eye manifestations in a large number of patients with cGVHD, monitoring them before and after 1 year of ECP.

MATERIALS AND METHODS

Patients

Patient data are shown in Table I. Between 2002 and 2006, 140 patients treated with allogeneic stem cell transplant (SCT) for various malignant blood disorders developed steroid-refractory cGVHD diagnosed on the basis of clinical, laboratory, and histologic data, according to published criteria (14, 15). After SCT, patients were treated with ECP at the Department of Clinical Medicine and Immunological Sciences, Dermatology Section, University of Siena. The mean time between SCT and ECP was 13 months (Tab. I). In this cohort, 24 patients (15 male, 9 female; average age at SCT, 41 years) developed cGVHD-related eye symptoms and/or ocular side effects of previous therapies. All these patients had been routinely examined 7 days before SCT and did not show eye manifestations. As shown in Table I, all patients were on immunosuppressants at the start of ECP: 10 patients were treated with one agent, 9 patients with two agents, 4 patients with three agents, and 1 patient with four agents.

All the patients selected for the present study gave their informed consent. The study was approved by the local ethics committee.

ECP procedure

Three identical UVAR® photopheresis units (Therakos Inc.) were used for ECP. At each treatment cycle, 240 mL buffy coat and 300 mL plasma were obtained in special bags by standard leukapheresis, and diluted in 200 mL saline. A solution containing 100,000 ng 8MOP (Gerot Pharmazeutika, Vienna, Austria) was added directly to the bags. Bag contents were run as a thin layer through the sterile cassette in a 1-mm film and then irradiated with UVA (2 J/cm2) for 90 min. Treated cells were then immediately reinfused.

Treatment protocol

Patients underwent two treatment sessions on consecutive days every 2 weeks for the first 3 months and then two sessions on consecutive days every 3 weeks for an additional 3 months. In the following 6 months, patients underwent two treatment sessions on consecutive days every 4 weeks.

Ophthalmologic evaluation and assessment of the severity of disease

Ophthalmologic examination included visual acuity, slit-lamp examination of the anterior segment, evaluation of the eye surface with Bengal rose staining, assessment of lacrimal dynamics with tear break up time (BUT), Schirmer test (with and without nasal stimulation), and tonometry. The lens and fundus were examined after pupil dilation with 1% tropicamide. Patients were then staged as described by Claes and Kestelyn (3).

Ophthalmologic examination was repeated every 3 months. Only patients with complete recovery of the ocular manifestations and symptoms were considered responsive (R). Patients in convalescent stage were considered partially responsive (PR). Patients in persistent active stage and in necrotizing stage were considered nonresponsive (NR).

Assessment of the extent and severity of GVHD in other organs and systems

On enrollment, patients underwent detailed clinical examination, analysis, and other procedures to document and assess involvement of the various organs and systems. Complete blood count, differential white cell count, and biochemical profile were performed at each cycle of ECP.

Cutaneous cGVHD. Skin involvement was assessed every 3 months by the same observer for each patient. Skin biopsies were obtained in representative areas prior to starting ECP and were repeated 6 and 12 months after the start of treatment, when possible near the site of the

TABLE I - STUDY POPULATION

Patient	Age, yr	Sex	Blood disorder	Cutaneous cGVHD/Score	Systemic therapy before ECP (mo)	Referred symptoms before ECP	Months between SCT and first cycle ECP
1	40	M	CML	L/100	C (6)	De, P	6
2	42	F	CLL	Sc (Ef)/210	C (2), ME (1)	De, Lh	2
3	34	M	CLL	L/30	PR (3), C (3)	↓v, De 3	
4	42	M	CML	L/160	C (11)	P, De, ↓v	11
5	46	F	MM	Sc (Ef)/210	C (50)	P, De	50
6	53	F	NHL	L/140	C (4), PR (4), TH (2)	↓v, P	4
7	33	M	CML	/	PR (7), C (7) , TH (4)	↓v, P	7
8	38	M	AML	L/180	C (5), PR (5)	De	5
9	33	M	NHL	L/80	C (5), PR (5)	↓v, P	5
10	59	M	ALL	L/90	C (3)	De, Lh	3
11	43	M	NHL	/	C (7), A (4), PR (7)	↓v, De, Lh	7
12	35	M	NHL	L/30	C (4)	Fs	4
13	16	F	ALL	L/40	PR (10)	De, Lh	10
14	38	M	MA	Sc /120	C (5), MM (51)	↓v, De	56
15	30	M	MM	Sc/120	PR (8)	De, P, Lh	8
16	30	M	CML	L/60	C (8) C (8), MM (30), A (2)	De	8
17	42	M	AML	Sc/60	PR (2)	De, P, Lh	44
18	54	F	MM	L/160	TH (1), PR (2)	Lh, ↓v	2
19	48	F	AML	L/160	TH (3), PR (6)	Lh, ↓v, De, Ps	6
20	28	F	AML	L/140	C (3)	De	3
21	48	M	MM	L/80	C (5), PR (5)	De	5
22	49	M	MM	/	MM (5), ME (6)	De, P, ↓v	10
23	55	F	AML	L/160	MM (20)	Acute pain	45
24	49	F	CLL	L/120	ME (2), MM (4), C (9)	De, ↓v	9

cGVHD = Chronic graft versus host disease; ECP = Extracorporeal photochemotherapy; SCT = Stem cell transplant; CML = Chronic myelogenous leukemia; L = Lichenoid; C = Cyclosporin; De = Dry eye; P = progression; CLL = chronic lymphocytic leukemia; Sc (Ef) = Sclerodermoid; ME = Methotrexate; Lh = Lachrimation; PR = Partially responsive; v = Decreased visual acuity; MM = Mycophenolate mofetile; NHL = Non-Hodgkin lymphoma; TH = Thalidomide; AML = Acute myelogenous leukemia; ALL = acute lymphocytic leukemia; Fs = Fosfeni; MA = Multiple myeloma; Ps = Palpebral swelling

first biopsy. Activity of cutaneous cGVHD was quantified during treatment on the basis of surface area involved and severity. The measuring technique was adapted from Child et al's grading method which associates quantification of skin area involved with qualitative evaluation of clinical manifestations (16). Regarding the evaluation of lichenoid cGVHD, clinical evaluation was based on the percentage of skin area involved and severity assessment was based on the intensity of erythema and maculopapular lesions (Tab. II). For sclerodermoid lesions, the percentage of skin involved was evaluated clinically as described for lichenoid cGvHD. Unlike Seaton et al (17), we used a grading scale from 0 to 3 based on elastometry for the quantitative assessment of severity of sclerosis (Tab. II). Computerized elastometry (Cutometer SEM 474, Courage + Khazaka Electronic GmbH, Cologne, Germany) was done in three sites of significantly involved skin. The instrument measures skin deformation after repeated cycles of suction and release (mm/s). Tensile distensibility, resilience, and hysteresis were monitored. Tensile distensibility is mainly related to the distensibility of collagen fibers. Resilience expresses the distensibility of elastic fibers. Hysteresis reflects the state of the extracellular environment. Each patient was assigned a score based on the ratio of the mean elastometric values of lesional skin (l-MEV) to the mean elastometric values of nonsclerotic skin in the same part of the body, or if not possible, in an adjacent uninvolved part (n-MEV). Grade 0 was assigned for l-MEV/n-MEV between 2/3 and 1, grade 1 for values between 1/3 and 2/3, and grade 2 for values below 1/3 (Tab. II). The skin score was calculated using the following formula: total skin score = [(percentage of body surface with lichenoid lesions × grade of erythematous and/or lichenoid lesions) + (percentage of body surface with sclerodermoid manifestations × grade of sclerodermoid changes)]. Clinical response of skin involvement was defined on the basis of skin score: complete response (R) when skin score returned to 0; partial response (PR) when skin score decreased by at least 25% with respect to the score before ECP; stabilization (ST) when it decreased by less than 25% or did not change; progression (P) when the score increased.

TABLE II - GRADING SYSTEM FOR CUTANEOUS CGVHD

Score	Grading for lichenoid manifestations
0	No lesions
1	Erythema or macular lesions
2	Erythema and maculopapular lesions
Score	**Grading for sclerodermoid manifestations**
0	l-MEV/n-MEV = 2/3–1
1	l-MEV/n-MEV = 1/3–2/3
2	l-MEV/n-MEV = <1/3

cGVHD = Chronic graft versus host disease; n-MEV = Median elastometric value of normal skin; l-MEV = Median elastometric value of lesional skin

Oral mucosal cGVHD. Diagnosis of oral mucosal cGVHD was based on clinical and histologic examination. Involvement was quantified on the basis of clinical criteria: grade 0, absence of lesions; grade 1, presence of lichenoid lesions (erythema, striae); grade 2, presence of lichenoid lesions associated with erosion, according to Child et al. Clinical and photographic assessment was repeated every 3 months. Response was evaluated as follows: R when clinical manifestations disappeared, PR when manifestations decreased from grade 2 to 1, ST when there was no clinical improvement, and P when grade increased.

Liver cGVHD. Liver involvement was diagnosed on the basis of liver function parameters (total bilirubin, SGPT, gamma-GT, and alkaline phosphatase). Biopsies were not performed before or after therapy in all patients because the ethics committee denied approval. Liver function parameters were evaluated before each treatment cycle. Response was assessed as follows: R when all parameters returned to normal, PR when at least one of the parameters decreased by 25% or more with respect to initial value, ST when values neither increased nor decreased significantly, and P when one parameter increased.

Lung cGVHD. Lung involvement was assessed by a pneumologist. Lung function tests – forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and total carbon monoxide transfer (CO transfer) – were assessed at the start of treatment in all patients and every 6 months thereafter only in those showing altered respiratory function. These patients also underwent CAT scans before and 12 months after ECP. After 1 year of therapy patients were assessed as complete responders (R), partial responders (PR), stabilized (ST), or with progression of the disease (P) according to the criteria of Dall'Amico and Zacchello (18).

Neuromuscular cGVHD. Patients with subcutaneous involvement (fascia and/or muscle) and signs of myopathy and reduced joint movement underwent full thickness biopsy (skin, subcutaneous layer, fascia, and muscle), echotomography, and electromyography. Clinical evalua-

tions of neuromuscular involvement, echotomography, and electromyography were repeated every 6 months and response was classified as complete responders, partial responders, stabilized, or with progression of the disease according to the criteria of Dall'Amico and Zacchello (18).

Thrombocytopenia. This hematologic parameter was evaluated as follows: R when platelet count returned to the normal range (130–400 thousand/mm^3), PR when initial value improved by more than 25% but did not become normal, ST when an increase did not exceed 25%, and P when platelet count decreased.

Overall outcome

As previously described (6), to assess the role of ECP in the various organs and systems subject to reject, we introduced the parameter overall outcome, which was determined as follows. The contribution of ECP was consid-

TABLE III - EYE MANIFESTATIONS, OCULAR, SYSTEMIC, AND CUTANEOUS CLINICAL RESPONSE BEFORE AND AFTER 12 MONTHS OF ECP IN OUR STUDY POPULATION

Patient of systemic	Possible ocular side effects therapy	Stage of ocular cGVHD before ECP	Stage of ocular cGVHD after ECP	Ocular response	Overall outcome	Cutaneous response
1		Active (punctate keratitis)	Convalescent (sicca syndrome)	PR	+	R
2		Active (mucopurulent conjuntivis)	Complete recovery	R	++	R
3	Initial cataract (left eye)	Initial	Complete recovery	R	++	R
4		Active (mucopurulent conjuntivis)	Necrotizing (pseudomembranous conjiuntivitis)	NR	-	NR
5		Initial	/	/	/	/
6	Initial bilateral cataract, ↑ ocular pressure	↑ Active (punctate keratitis)	Complete recovery	R	++	R
7	Initial cataract (right eye) ↑ ocular pressure	Initial	Complete recovery	R	++	/
8		Active (corneal erosion)	Complete recovery	R	++	R
9	Initial bilateral cataract	Active (corneal erosion and punctate keratitis)	/	/	/	/
10	Initial bilateral cataract	Active (mucopurulent conjunctivitis)	Complete recovery	R	++	R
11	Initial cataract (right eye)	Initial	Complete recovery	R	++	/
12	Bilateral cataract	Initial	Complete recovery	R	++	R
13		Initial	Convalescent (sicca syndrome)	PR	+	PR
14		Active (mucopurulent conjuntivis)	Convalescent (sicca syndrome)	PR	+	ST
15	Initial bilateral cataract, ↑ ocular pressure	↑ Active (punctate keratitis)	Active (punctate keratitis)	NR	–	ST
16		Initial	Active (punctate keratitis)	NR	–	ST
17	Initial bilateral cataract	Active (punctate keratitis)	Convalescent (sicca syndrome)	PR	+	R
18	Initial bilateral cataract	Necrotizing (corneal epithelial defects)	Convalescent (corneal epithelial defects)	PR	+	R
19	↑ Ocular pressure, bilateral disc o–edema	Necrotizing (corneal epithelial defects)	Convalescent (sterile conjunctivitis, corneal epithelial defects)	PR	+	R
20		Active (punctate keratitis)	Complete recovery	R	++	R
21	↑ Ocular pressure	Initial	Complete recovery	R	++	R
22		Active (punctate keratitis)	Active (punctate keratitis)	NR	—	/
23		Necrotizing (pseudo-membranous conjunctivitis)	/	/	/	/
24	Initial right cataract	Active (punctate keratitis)	Convalescent (sicca syndrome)	PR	+	R

ECP = Extracorporeal photochemotherapy; cGVHD = Chronic graft versus host disease; PR = Partially responsive; R = Responsive; NR = No response; ST = Stabilization

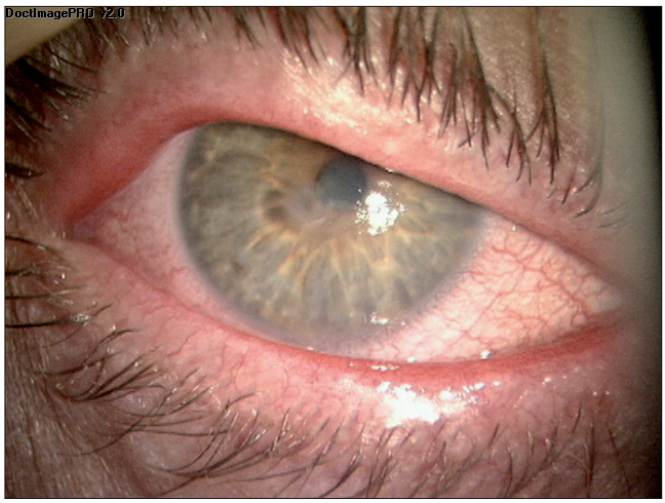

Fig. 1 - *Keratoconjunctivitis sicca in patient with chronic graft versus host disease associated with keratopathy.*

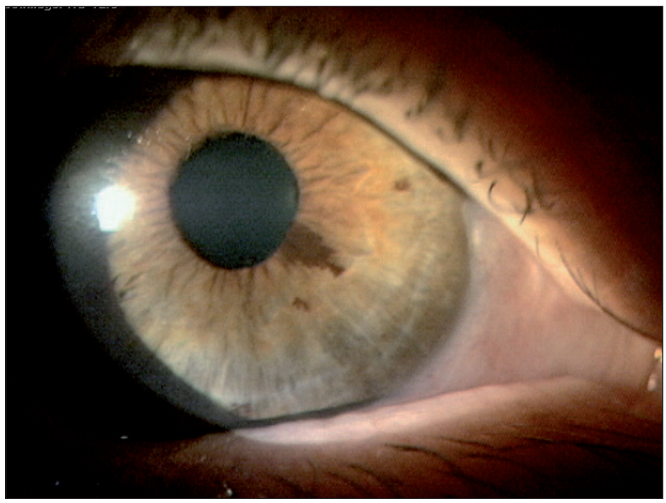

Fig. 2 - *Dry eye in chronic graft versus host disease without keratopathy.*

ered essential (++) when complete recovery was observed in all organs involved after the start of ECP and when the dose of immunosuppressants could be reduced by at least 50% with respect to initial therapy. The contribution of ECP was considered inefficacious (–) when patients remained in a persistent active stage, when it was necessary to increase the dose of immunosuppressants, or when immunosuppressants could not be reduced by more than 50%, and good (+) in all other cases when a meliorative response was observed. This provided a realistic though somewhat arbitrary line between responders and nonresponders.

RESULTS

Three patients (including Patient 23 with orbital secondary localizations) died due to progression of the original blood disorder in less than 12 months from the first ECP session. During ECP, the dose of medication was reduced in 16 patients (6 of whom are currently treated with cyclosporin alone at <2 mg/Kg bw), remained unmodified in 4, and had to be increased in 1 (Case 4) (Tab. III).

Ocular cGvHD before ECP

Symptoms and ophthalmologic findings before treatment are summarized in Tables I and III. The most common eye manifestations were typical of the active stage (13 cases) (Fig. 1). Eight patients were in initial stage (Fig. 2) and three in necrotizing stage with severe corneal epithelial defects and pseudomembranous conjunctivitis. One of these patients (Case 23) had bilateral optic disc edema secondary to orbital metastases. Thirteen patients had possible side effects of systemic immunosuppressive therapy, namely cataract and increased intraocular pressure, presumably steroid-related. Another case (Case 19) with bilateral optic disc edema, presumably due to toxic effects of cyclosporin therapy, was also detected (Fig. 3).

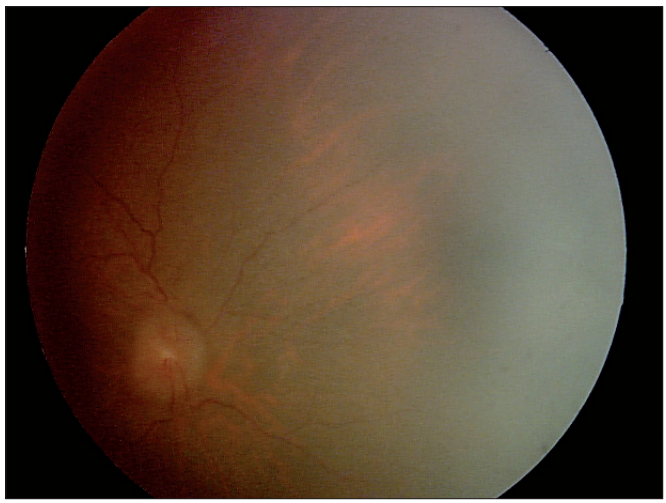

Fig. 3 - *Optic disc edema.*

Overall outcome

We observed a negative outcome (–) in four patients; in particular progression was observed in Case 4 and stabilization in the other cases. A positive outcome was observed in 17 patients (80%): in 10 patients the contribution of ECP was essential (++) and in 7 patients good (+).

Ocular cGvHD after ECP

After 12 months of ECP we obtained complete recovery in 10/21 patients (48%). In these patients, Schirmer test was within normal limits and they no longer complained of eye symptoms or needed any kind of local therapy; these patients were considered R. Seven of 21 patients (33%) went into convalescent stage, and they were considered PR. These patients continued to have sicca syndrome and to complain of dry eye symptoms. Their Schirmer test values remained <5 mm. Only one of them (Case 22) has sterile conjunctivitis and corneal epithelial defects. They are currently treated with artificial tears only. Only 5 patients were considered NR: Case 13, who was in initial stage and went into active stage; Case 4, who went into necrotizing stage (pseudomembranous conjunctivitis); and 3/21 (14%) patients who remained in active stage (persistent active stage). In all cases in which overall outcome was essential (++) we observed complete recovery of the eye. In seven patients (Cases 1, 13, 14, 17, 18, 19, 24) with good (+) overall outcome, eye condition improved (convalescent sicca syndrome) but did not recover completely. In patients with negative overall outcome (–), the eye response was also negative. This confirms the close relationship between evolution of cGVHD in general and also in regard to the eyes.

Side effects of ECP

The 32 patients in this study received a total of more than 1000 cycles of ECP, with only minor side effects. The most frequent (albeit rare) side effect was slight hypotension resulting from volume shifts during the leukapheresis phase of treatment. Hematomas at antecubital venipuncture sites were another side effect. None of these side effects required interruption of treatment, and there was no evidence of cumulative toxicity from ECP.

DISCUSSION

Recent advances in the prevention of GVHD have considerably reduced the incidence of complications of SCT. Though GVHD is still not rare, it occurs in 20–50% of long-term SCT survivors and is fatal in 20–70% of them despite aggressive therapy (19-22).

The incidence of eye manifestations in patients with cGVHD reported in the literature varies. The concentration of many life-threatening problems in these kinds of patients may explain the delay in presentation to the ophthalmologist and the sparse documentation of ocular complications of the disease in the literature. According to Claes and Kestelyn (3), eye problems occur in 45 to 60% of patients with GVHD, whereas Mohty et al (22) report a slightly lower incidence, distinguishing patients with cGVHD after bone marrow SCT (22/71) from those after peripheral SCT (7/37). In our study, we observed eye problems in 24/140 (17%) patients treated with allogeneic SCT, which is in line with the incidence reported by Mohty et al.

Treatment of GVHD is not yet satisfactory, being relatively ineffective and/or associated with side effects in many patients. The same is true of eye manifestations. In these cases, ECP has proven to have a positive effect on the course of the disease, with few or no side effects, as shown in many other studies (23-25). The fact that we were able to reduce the quantity of systemic immunosuppressants, in some cases suspending them, confirms the overall efficacy of ECP in modifying the course of cGVHD (6). With regard to eye involvement, we observed a response (R+PR) in 17/21 (80%) of our patients after 1 year of treatment.

The etiopathogenesis of eye manifestations of cGVHD is also controversial. This is partly due to the fact that eye complications in cGVHD patients may be difficult to determine, as the patient's underlying disease process, pharmacologic therapy, and radiation therapy may all contribute (26). However, it is believed to be an extension of acute GVHD (characterized by acute alloreactivity) and/or a result of dysfunctional immune reconstitution with generation of autoantibodies and autoreactive T-cell clones. Ogawa and Kuwana (27) reported a significant role of stromal fibroblasts in the pathogenic processes of dry eye, the most frequent complication of cGVHD. In these patients the lacrimal glands undergo fibrosis with an increase in $CD34^+$ stromal fibroblasts in the interstitium and infiltration of periductal areas by T cells ($CD4^+$ $CD8^+$).

Periductal areas are involved in fibrogenic and immune processes through interaction with T cells in the lacrimal glands of patients with cGVHD, resulting in rapidly progressive dry eye. More recently, Yoshida et al (28) suggested that apoptosis and infiltrating leukocytes may be involved in the corneal perforation in patients with cGVHD. On the other hand, ocular cGVHD should not differ from cutaneous and gastrointestinal cGVHD where it is well known that cytotoxic T-lymphocyte-mediated apoptotic processes are predominant (29).

Although the mechanism of action of ECP is still not fully understood, some hypotheses have been suggested such as the generation of clone-specific suppressor T cells (9), the release of cytokines by the reinfused white blood cells (10), and shifting of T-cell phenotype (11). Recent research indicates that the monocyte/macrophage plays a central role in the mechanism of action of ECP (12). Monocytes and dendritic cells show an increased avidity for the phagocytosis of apoptotic lymphocytes. These cells acquire antigens from apoptotic lymphocytes and induce expression of adhesion molecules and antigens on their surface (13, 30). Moreover, some authors recently showed that ECP is able to induce a downregulation of the immune response probably mediated by CD4+CD25+ cells (31-34). We believe that these mechanisms could be, at least in part, responsible for the clinical effects we observed. In particular, we can speculate that ECP-induced immunoregulatory/suppressive cytokines could prevent the proliferation of fibroblasts and the consequent (27) lacrimal gland involvement and dry eye. We can also hypothesize that the phagocytosis of apoptotic lymphocytes could prevent the corneal perforation.

Further studies are necessary to clarify the role of ECP in cGVHD patients, especially in associated eye manifestations. Although our experience is limited, it suggests that ECP could be a safe and effective therapy for steroid-refractory eye manifestations of cGVHD. It would therefore be interesting to do early ECP also in patients with nonrefractory disease and compare ECP-treated patients with a non-ECP-treated control group. This would allow us to assess the actual role of ECP as a steroid sparing treatment, which could limit the development of all the potential ocular side effects of traditional immunosuppressants.

The authors report no conflicts of interest.

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