Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD

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Chronic graft-versus-host disease (GVHD) is a major limitation of successful allogeneic hematopoietic stem cell transplantation (HSCT). Extracorporeal photochemotherapy (ECP) has been tested extensively in small cohorts of patients with chronic GVHD. In this study, we retrospectively evaluated 71 patients with severe chronic GVHD treated with ECP. Response rate was 61% (n = 43), and 14 patients had complete responses (CRs). The best responses were observed in skin, liver, oral mucosa, and eye. Factors affecting outcomes were assessed in the less heavily pretreated subgroup (n = 63). Thrombocytopenia was associated with a lower response rate (P = .04), and there was a trend toward a higher response rate in de novo chronic GVHD. At 6 months, a total of 27 (69%) of 39 patients who were alive continued to have a sustained response (CR 4 [10%] of 39, and partial response [PR] 23 [59%] of 39). The cumulative incidence of steroid discontinuation at 1 year was 22%. The overall survival since initiation of therapy was 53% at 1 year. Response to ECP and platelet count at initiation of therapy were the strongest predictors of nonrelapse mortality (NRM) on univariate analysis. Objective responses were observed in a substantial number of patients with both skin and visceral chronic GVHD failing corticosteroids and other immunosuppression. (Blood. 2006;107:3074-3080)

Introduction

Chronic graft-versus-host disease (GVHD) is a major limitation of successful allogeneic hematopoietic stem cell transplantation (HSCT), and it affects the majority of patients who develop acute GVHD.[1,2] Chronic GVHD is a disease of deregulated immunity with protean manifestations similar in many ways to autoimmune diseases. The relative uncommonness of the disease, the lack of consensus on what represents true manifestations of chronic GVHD, the very limited understanding of its pathophysiology, and the clinical complexity of these patients are all factors that have hindered a systematic approach to this problem.

Chronic GVHD has a negative impact on the morbidity and quality of life, as well as in nonrelapse mortality (NRM).[2,3] Corticosteroids are considered the standard of care for initial treatment of chronic GVHD, but only a minority of patients durably responds to them. So far, there are more questions than answers regarding chronic GVHD. These patients are subject to long-term complications of corticosteroid treatment, and management of steroid-resistant chronic GVHD is not well defined.[4] A variety of different immunosuppressive and immunomodulating modalities have been tested in chronic GVHD, among them extracorporeal photochemotherapy (ECP), or photopheresis. Photopheresis is currently indicated and Food and Drug Administration (FDA) approved for the treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL), which is a clonally derived skin malignancy of $CD4^+$ cells with the phenotype of mature helper T cells. CTCL responds to biological response modification,[5] and ECP produces a high clinical response rate.[6-8] It is felt that this therapy not only augments the function of monocytes but also induces the malignant T cells to undergo a high rate of apoptosis, exerting an antitumor effect through cytokine modulation and modification.[9,10]

In chronic GVHD, ECP has been tested quite extensively in small cohorts of patients, and responses were observed in skin, liver, gastrointestinal (GI) tract, mouth, eye, and lung.[11-16] Unfortunately, the literature is difficult to interpret due to the heterogeneity of treatment schedules and diagnostic and response assessment criteria.

In this study, we evaluate the efficacy and safety of ECP in a group of patients with a clinical diagnosis of chronic GVHD failing corticosteroids and who were treated with similar ECP schedule.

Patients, materials, and methods

Patient population

We evaluated a total of 246 patients who received systemic immunosuppression for the treatment of steroid refractory chronic GVHD between 1/98 and 10/02. Of these, we analyzed all patients treated with ECP (n = 71) during this time period. Referral to ECP therapy was at the discretion of the primary transplantation physician. Results were presented for the whole group and separately for patients treated with 3 or fewer versus more than 3 lines of immunosuppression prior to initiation of ECP. Results and outcomes are presented for all patients. Considering that in patients receiving multiple lines of immunosuppression it is impossible to discriminate the effects of each particular treatment, our analysis of outcomes and

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prognostic factors was focused on the 63 patients who had 3 or fewer lines of immunosuppression, including tacrolimus and steroids.

Patients had received an allogeneic transplant for hematologic malignancies (n = 67), benign hematologic disorders (n = 3), and breast cancer (n = 1). At the time of initiation of ECP, all patients were steroid refractory as defined in the next section. Patients were started on 2- to 3-times-weekly ECP treatments and tapered according to clinical response at the discretion of the managing physician. Patient characteristics are summarized in Table 1. The information used in this analysis was obtained through a retrospective chart review approved by the University of Texas M.D. Anderson Cancer Center Institutional Review Board. Informed consent for extracorporeal photopheresis was provided according to the Declaration of Helsinki. The University of Texas M.D. Anderson Cancer Center Institutional Review Board approved the retrospective chart review for these patients.

Definition of chronic GVHD and steroid refractoriness

For the purpose of this analysis, we defined chronic GVHD based upon clinical manifestations and independently of the date of diagnosis. Thus, patients were considered to have chronic GVHD only if they had 1 or more of the characteristic chronic, long-standing manifestations of GVHD,[2] including lichenoid or sclerodermal skin involvement, ocular dryness that could not be relieved by artificial tears, dryness or lichenoid involvement of oral and vaginal mucosa, and GI strictures. Hyperbilirubinemia or alkaline phosphatase elevations were considered to be secondary to chronic GVHD of the liver if biopsy-proven and in the setting of other manifestations of chronic GVHD as described. Diarrhea, nausea, and vomiting were considered secondary to chronic GI GVHD if biopsy-proven and in the setting of other manifestations of chronic GVHD. All of our patients with lung GVHD had bronchiolitis obliterans (BO), which was diagnosed by the presence of symptoms (dyspnea, cough, wheezing) and all 3 of the following: (1) decrease in FEV1 by more than 20% within 1 year; (2) evidence of air-trapping or small-airway thickening or bronchiectasis on high-resolution chest computed tomography (CT) or pathologic confirmation of constrictive bronchiolitis; and (3) no evidence of active infection in the respiratory tract, documented with investigations directed by clinical symptoms, including radiologic studies or microbiologic cultures.

Chronic GVHD was considered to be "de novo" if there was no prior history of acute GVHD. Relapsing chronic GVHD occurred if there was a prior history of successfully treated acute GVHD. Progressive chronic GVHD was defined as acute GVHD that failed to respond completely to treatment and evolved into chronic GVHD. Patients were also classified as having limited or extensive chronic GVHD according to Sullivan et al.[17]

Patients in this analysis were initially treated for GVHD with a combination of tacrolimus and methylprednisolone starting at 1 to 2 mg/kg/d. Tacrolimus doses were adjusted to maintain trough levels of 5 to 15 ng/mL. Corticosteroids were generally continued until evidence of a clinical response and then tapered as tolerated. Chronic GVHD was considered refractory or resistant to therapy if: (1) patients had stable disease (ie, no response [NR]) after 1 month of treatment; (2) no more than a partial response (PR) occurred after 2 months of treatment; or (3) progressive disease occurred after 2 weeks of initiation of steroid treatment or during the methylprednisolone taper. These same criteria were used to define steroid refractoriness prior to inclusion in this retrospective study.

Table 1. Patient characteristics

Characteristics	Data
No. male/no. female	33/38
Median age, y (range)	39 (5-70)
Donor type, no. (%)	
Matched sibling	43 (61)
Matched, unrelated	19 (27)
Mismatched, related	5 (7)
Mismatched, unrelated	4 (6)
Diagnosis, no. (%)	
ALL	2 (3)
AML/MDS	29 (41)
CLL	1 (1)
CML/MPD	21 (30)
Lymphoma	14 (20)
Aplastic anemia	2 (3)
Sickle-cell anemia	1 (1)
Breast cancer	1 (1)
GVHD prophylaxis, no. (%)	
Tacrolimus/MTX	65 (91)
Tacrolimus/steroids	5 (7)
Cyclosporine/MTX	1 (2)
Grades 2-4 acute GVHD, no. (%)	39 (55)
Type of chronic GVHD, no. (%)	
De novo	18 (25.5)
Progressive	18 (25.5)
Relapsing	35 (49)
Extensive chronic GVHD, no. (%)	52 (73)
Corticosteroids at the time of ECP, no. (%)	59 (83)

ALL indicates acute lymphoblastic leukemia; AML/MDS, acute myelogenous leukemia/myelodysplastic syndrome; CML/MPD, chronic myelogenous leukemia/myeloproliferative disorders; ECP, extracorporeal photopheresis; and MTX, methotrexate.

Chronic GVHD response criteria

Complete response (CR) was defined as resolution of all manifestations of chronic GVHD. Partial response (PR) was defined as at least a 50% improvement of clinical manifestations without a CR. In this case, due to the complexity inherent to the assessment of response in chronic GVHD, we defined PR for each organ as follows. (1) Skin: for lichenoid rashes, a minimum reduction in the body surface area involved by 50%. For sclerodermatous involvement, any improvement in the skin score or range of motion, with an improvement in Zubrod performance status by 1. (2) Ocular GVHD: subjective improvement and reduction in the frequency of artificial tear administration by 50%, or improvement in Schirmer test for 1 or both eyes. (3) Oral GVHD: improvement by 50% in the mucosal area involved with lichenoid and/or ulcerative changes. (4) GI and liver: Decrease by 50% in the volume of diarrhea, bilirubin, or alkaline phosphatase. (5) BO: Sustained improvement in pulmonary function tests (FEV1) and/or the ability to taper corticosteroids by 50% without deterioration of pulmonary function.

No response (NR) was no change in GVHD. Patients who experienced early deaths due to GVHD prior to assessment of response were considered NR as well. Progressive disease (PD) was any worsening while on treatment or steroid taper. Patients with a CR or PR in one organ and simultaneous NR or PD in another were considered to have a mixed response (MR).

The timing of the response was analyzed as best response of at least 2 weeks duration, occurring within 3 months after initiation of therapy, and response at 6 months following initiation of therapy.

Extracorporeal photochemotherapy

ECP was performed both on an outpatient and inpatient basis. Extracorporeal photopheresis (ECP) was performed using the UVAR TS machine (Therakos, Exton, PA) Whenever feasible, 6 cycles were performed for each treatment using the 125-mL bowl. Liquid methoxsalen (UVADEX) was injected into the recirculation bag of the ECP circuit after collection of the buffy coat was complete, but prior to the photoactivation process. The methoxsalen dosage was calculated based on the volume of buffy coat collected using the following formula: treatment volume collected $\times$ 0.017 = milliliters of methoxsalen (20 g liquid mL Therakos).

After completion of photoactivation the product was reinfused into the patient. Liquid methoxsalen is a psoralen derivative and photoactive agent. The advantage of using liquid methoxsalen is that the drug does not need to be ingested by the patient or injected directly into the patient but can be added directly to the collection product prior to the photoactivation. This allows for a reduction in the human exposure to the drug, as only 1/200 of the oral dose is required to inoculate the cells.

All patients initiated therapy with 2 to 4 treatments per week, and tapered when partial response was observed. Treatments were decreased by 1 per week when a partial response was observed, and subsequently the patients were placed on a maintenance regimen of 2 treatments every 2 weeks. Discontinuation and duration of treatment was at the discretion of the treating physician, titrating the ECP treatments to control of symptomatic manifestations of chronic GVHD.

Statistical analysis

The main endpoints were response to therapy, nonrelapse mortality, and overall survival. The effects of patients' and clinical characteristics on response were evaluated using logistic regression analysis. The cumulative incidence of complete or partial responses (CRs/PRs) since initiation of ECP was estimated using death without a response as a competing risk. The cumulative incidence of nonrelapse mortality since the initiation of ECP was estimated considering death from progression of underlying malignancy as a competing risk. Predictors of nonrelapse mortality were evaluated using the Cox proportional hazards model. Overall survival since initiation of therapy was estimated using the Kaplan-Meier method. Statistical significance was determined at P value of .05. Analysis was performed using STATA 7.0 (Stata Corp, College Station, TX).

Results

Demographics

Patient characteristics are summarized in Table 1. The median age was 39 years (range, 5-70 years), with a 1.1:1 male-to-female ratio. The majority of patients underwent transplantation for myeloid (n = 50, 71%) and lymphoid (n = 17, 24%) malignancies. Other indications for allogeneic stem cell transplantation included aplastic anemia (n = 2), sickle cell anemia (n = 1), and breast cancer (n = 1). Most patients had human leukocyte antigen (HLA)–identical sibling grafts (n = 43, 60%), followed by matched unrelated donor (n = 19, 27%) and mismatched related donor (n = 9, 13%) grafts. The highest fraction of patients had relapsing (n = 30, 48%) chronic GVHD.

All patients received methylprednisolone as initial treatment of chronic GVHD. At the time of initiation of ECP 59 (83%) of 71 patients were still on steroids, and 58 were also receiving a calcineurin inhibitor. Six (8%) patients achieved an initial CR or PR prior to initiation of ECP. Thirty-one (44%) patients received more than 2 lines of immunosuppression, including steroids and tacrolimus, prior to ECP. Other immunosuppressants included mycophenolate mofetil (n = 16), infliximab (n = 10), daclizumab (n = 5), sirolimus (n = 3), PUVA (n = 1), hydroxychloroquine (n = 1), thalidomide (n = 1), and ethanercept (n = 1).

Patients received a median of 32 ECP procedures (range, 1-259 procedures) over a median of 14.5 weeks (range, 1-333 weeks). Three patients received 1, 2, or 3 ECP procedures, respectively, and were considered nonresponders because of early death (n = 1) or the addition of other immunosuppression lines for severe chronic GVHD manifestations (n = 2). Once discontinued, ECP was not restarted as salvage therapy in any of these patients.

Chronic cutaneous GVHD was the leading indication for ECP (n = 56, 79%), often with sclerodermal changes (n = 21 of 56, 38%). The second most common indication was GVHD of the liver (n = 21, 30%), followed by pulmonary GVHD in the form of bronchiolitis obliterans (n = 11, 15%) and oral (n = 9, 13%), ocular (n = 6, 8%), and GI (n = 3, 4%) GVHD.

Response to treatment

The overall response rate was 61% (n = 43), and complete responses were seen in 14 patients. The cumulative incidence of CR/PR at 1 year since initiation of ECP was 83% (SE, 9%). The best responses were observed in GVHD of the skin, liver, oral mucosa, and eye. A total of 33 (59%) patients with skin GVHD responded to ECP therapy, and about half of these responses were seen in patients with sclerodermal forms (n = 14, 42%). Indeed, most patients with scleroderma (n = 14 of 21, 67%) had objective responses to ECP. Responses were also seen in liver (n = 15, 71%), oral mucosa (n = 7, 77%), eye (n = 4, 67%), and BO (n = 6, 54%). Among the 6 patients with BO who responded, 1 had a CR with resolution of all respiratory symptoms and return of FEV1 levels to baseline, even after discontinuation of all immunosuppression. The other 5 patients had a partial response. Three of them had corticosteroids tapered off, 1 with stable pulmonary function and the other 2 with improvement in absolute FEV1 levels of 10% and 20%, respectively. The remaining 2 patients had stable FEV1 levels after more than 80% taper in the corticosteroid dose. There were a total of 2 cases of colonic GVHD, and both responded to ECP. One patient with upper GI GVHD showed no response.

The median time from the onset of ECP to CR was 27 (range, 13-238 days), and to CR or PR was 46 days (range, 10-280 days). The median time to CR/PR was 26 days in skin (range, 9-238 days), 48.5 days in liver (range, 11-91 days), 116 days in eye (range, 17-280 days), 42 days in mouth (range, 11-231 days), and 36.5 days in lung GVHD (range, 17-280 days).

A total of 4 (29%) of 14 patients who originally achieved a CR after ECP and 18 (62%) of 29 with a PR required additional immunosuppressive therapy. Of 43 patients who initially responded, 13 (32%) progressed after a median of 23 days (range, 16-188 days). The remaining 30 of 43 patients maintained their responses for a median duration of 18 months (range, 0.4-65 months), and the cumulative incidence of progression after initial response was 40% (± 8%). At 6 months, a total of 28 of 44 patients who were alive continued to have a sustained response (CR, 5 [11%] of 44; and PR, 23 [52%] of 44) and 12 (27%) patients were able to discontinue corticosteroids.

Toxicity

Only 4 patients developed toxicity, and this was mild, reversible, and did not require discontinuing therapy. One patient developed abdominal pain, 2 had variations in blood pressure (hyper- and hypotension, respectively) and another 1 developed fever. A total of 22 patients (35%) required a median of 4 packed red blood cell transfusions (range, 1-42 transfusions) while on ECP. Fourteen (22%) patients had a median of 4.5 platelet transfusions (range, 1-26 transfusions).

Mortality

A total of 42 (59%) patients died, with a median follow up of 34 months (range, 4-66 months) among survivors. At 5 years after initiation of ECP, the overall survival was 19% (range, 2%-49%), and the cumulative incidence of NRM was 46% (SE 7%) (Figure 1). The primary cause of death was GVHD plus infection (n = 28, 67%), followed by relapse (n = 12, 29%), infection outside the setting of GVHD or its treatment (n = 1, 2%), and hemorrhage (n = 1, 2%).

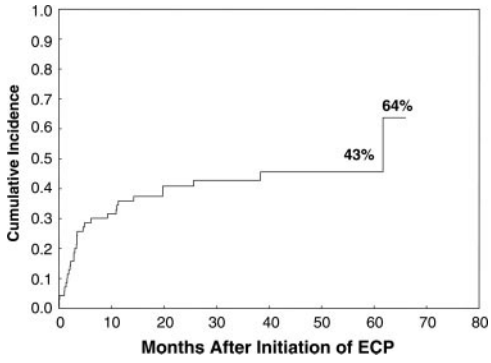

Figure 1. Cumulative incidence of nonrelapse mortality at 60 months. CR indicates complete response; PR, partial response; and PLT, platelets.

Table 2. Factors affecting response to ECP

	No.	(%)	CR/PR	OR	95% CI	*P*
Age, y						
50 or younger	48	(76)	27	—	—	—
Older than 50	15	(24)	10	1.6	0.5-5.2	.5
Sex						
Female	30	(48)	17	—	—	—
Male	33	(52)	20	1.2	0.4-3.2	.7
Donor type						
Matched sibling	38	(60)	22	—	—	—
Other	21	(33)	12	1	0.35-3.0	.9
Diagnosis						
ALL	2	(3)	1	—	—	—
AML/MDS	23	(37)	12	1.8	0.2-1.5	.2
CML/MPD	21	(33)	14	2	0.5-6.2	.3
Lymphoma	13	(21)	9	0.5	0.5-8.6	.3
Aplastic anemia	2	(3)	0	—	—	—
Sickle-cell anemia	1	(2)	1	—	—	—
Breast cancer	1	(2)	0	—	—	—
GVHD prophylaxis						
Tacrolimus/MTX	57	(90)	28	—	—	—
Tacrolimus/steroids	5	(8)	4	—	—	—
Cyclosporine/MTX	1	(2)	0	—	—	—
Acute GVHD						
Grades 2-4	33	(54)	15	1.05	0.35-3.1	.9
Grades 0-1	30	(46)	21	—	—	—
Steroids at ECP						
No	11	(17)	6	—	—	—
Yes	52	(82)	31	1	0.3-3.7	.9
No. prior treatments*						
2	40	(63)	26	—	—	—
3	23	(37)	11	0.5	0.2-1.4	.2
Type of chronic GVHD						
De novo	17	(27)	13	—	—	—
Progressive	16	(25)	7	0.2	0.05-1.1	.06
Relapsing	30	(48)	17	0.4	0.1-1.5	.2
Organ involvement						
No skin	13	(21)	9	2.25	0.5-10.05	.3
Skin only	30	(48)	18	1.5	0.5-4.9	.5
Skin and visceral	18	(29)	9	—	—	—
Skin and eyes/mouth	2	(3)	1	—	—	—
Scleroderma†	21	(33)	14	2.1	0.7-6.9	.2
Response to first-line immunosuppression						
CR/PR	7	(11)	5	1.9	0.3-10.5	.5
Other	56	(89)	32	—	—	—
Platelet count						
Less than 100 000/mm^3‡	24	(38)	10	0.3	0.1-0.95	.04
100 000/mm^3 or more	38	(60)	26	—	—	—
Unknown	1	(2)		—	—	—
LDH						
1000 IU/L or less	41	(65)	27	—	—	—
More than 1000 IU/L	20	(32)	8	0.3	0.1-1.04	.06
Unknown	2	(3)		—	—	—

ALL indicates acute lymphoblastic leukemia; AML/MDS, acute myelogenous leukemia/myelodysplastic syndrome; CML/MPD, chronic myelogenous leukemia/myeloproliferative disorders; MTX, methotrexate; OR, odds ratio; and —, not applicable.

*Including tacrolimus or cyclosporine.

†When skin was the only organ involved.

‡100 000 mm^3 is equal to 100 × 10^9/L.

Prior therapy and outcomes

We stratified patients in 2 groups according to number of therapies preceding ECP to better understand the effects of ECP without the confounding influence of multiple lines of immunosuppression.

Patients who received more than 3 lines of immunosuppression (n = 8 of 71) were considered to be heavily pretreated, and were compared with those who received up to 3 lines of immunosuppression, including calcineurin inhibitors and steroids (n = 63 of 71). The cumulative incidence of response was similar in both groups (87% versus 84%, respectively). However, the cumulative incidence of progression after responding to ECP was 100% in the more heavily pretreated group compared with 22% in patients who received up to 3 lines of immunosuppression. Only 1 of 8 heavily pretreated patients could taper off all immunosuppression, including steroids. In the less pretreated group, the cumulative incidence of complete immunosuppression discontinuation at 1 year after initiation of ECP was 10% (n = 6), and that of steroid discontinuation was 22% (n = 13). Nonrelapse mortality in the heavily

Table 3. Factors affecting nonrelapse mortality

	No.	Nonrelapse deaths, no. (%)	HR	95% CI	*P*
Age					
50 y or younger	48	19 (40)	—	—	—
Older than 50 y	15	7 (47)	1.2	0.5-2.9	.7
Sex					
Female	30	14 (47)	—	—	—
Male	33	12 (36)	0.7	0.3-1.4	.3
Donor type					
Matched sibling	38	15 (39)	0.8	0.4-1.8	.6
Other	21	11 (52)	—	—	—
Acute GVHD					
Grades 2-4	33	15 (45)	1.9	0.8-4.6	.1
All other	30	8 (33)	—	—	—
No. prior treatments*					
2	40	12 (30)	—	—	—
3	23	14 (61)	2.8	1.25-6.1	.01
Steroids at ECP					
Yes	11	4 (36)	—	—	—
No	52	22 (42)	1.5	0.5-4.3	.5
Chronic GVHD					
De novo	17	6 (35)	—	—	—
Progressive	16	8 (50)	3	1.0-8.9	.04
Relapsing	30	12 (40)	1.6	0.5-3.8	.5
Scleroderma†					
Yes	21	6 (29)	0.4	0.1-0.99	.05
No	29	14 (48)	—	—	—
Response to tacrolimus/MP					
CR/PR	7	4 (57)	1.9	0.6-5.9	.2
All other	56	22 (39)	—	—	—
Response to ECP‡					
CR/PR	37	9 (24)	0.2	0.1-0.5	< .001
All others	25	17 (65)	—	—	—
Platelets at ECP					
Fewer than 100 000/mm^3§	24	16 (67)	7.25	3.1-16.9	< .001
100 000/mm^3 or more	38	10 (26)	—	—	—
Unknown	1	2 (—)	—	—	—
LDH					
1000 IU/L or less	41	14 (35)	—	—	—
More than 1000 IU/L	20	12 (60)	3.1	1.4-6.9	.005
Unknown	2	— (—)	—	—	—

HR indicates hazard ratio; —, not applicable.
*Including tacrolimus or cyclosporine.
†When skin was the only organ involved.
‡Evaluated since time of response to ECP.
§100 000/mm^3 is equal to 100 × 10^9/L.

pretreated group was 50% (n = 4) and not significantly different compared with the less immunosuppressed group (41% [n = 26]) (hazard ratio [HR] 0.7, $P = .4$). The median survival since ECP was 6 months for the heavily pretreated group, compared with 18 months in the less immunosuppressed group.

Factors affecting response and survival

Patients receiving multiple lines of immunosuppression had a mortality rate of 87% at 19 months since initiation of ECP, and only 1 patient was alive beyond 19 months. The high mortality rate prevented an accurate assessment of the individual prognostic factors that would influence

Table 4. Characteristics according to type of chronic GVHD

	De novo	Relapsing	Progressive	*P*
No. patients	17	30	16	—
Response (CR/PR), no. (%)	13 (76)	17 (57)	7 (44)	.07
More than 2 prior treatments, no. (%)*	3 (18)	13 (48)	7 (44)	.05
Platelet count below 100 000/mm^3 at ECP, no. (%)†	5 (29)	8 (27)	11 (69)	.3
Scleroderma, no. (%)‡	11/14 (79)§	9/27 (33)	1/9 (11)	.002
Time from chronic GVHD to ECP, median (range)	512 (23-1537)	263 (1-1205)	90 (4-1351)	.02

— indicates not applicable.
*Including tacrolimus or cyclosporine.
†100 000/mm^3 is equal to 100 × 10^9/L.
‡When skin was the only organ involved.
§Eleven out of 14 patients with scleroderma.

Table 5. Factors affecting nonrelapse mortality in patients without de novo chronic GVHD

	No.	HR	95% CI	*P*
Response to ECP*				
CR/PR	23	0.3	0.1-0.8	.01
All others	21	—	—	—
Platelets at ECP†				
Fewer than 100,000/mm^3	19	29	6.2-142	< .001
100,000/mm^3 or more	25	—	—	—
LDH				
1000 IU/L or lower	30	—	—	—
More than 1000 IU/L	15	3.1	1.4-6.9	.005
No. prior treatments‡				
2	25	2.4	0.9-6.1	.06
3	20	—	—	—

— indicates not applicable.
*Including tacrolimus or cyclosporine.
†100 000/mm^3 is equal to 100 × 10^9/L.
‡Evaluated since time of response. Two patients who died on the day the response was evaluated are excluded.

those effects. In addition, the potentially shorter median survival of these patients could preclude the analysis of effects that occur over long time periods, such as immunosuppression withdrawal. Thus, our analysis of factors affecting response and mortality was done on the 63 patients receiving up to 3 lines of immunosuppression. A platelet count of less than 100 000/mm^3 at time of initiation of ECP was associated with a lower response rate (HR = 0.3, 95% confidence interval [95% CI] 0.1-0.95, $P = .04$). There was a trend toward a higher response rate in patients with lactose dehydrogenase (LDH) levels lower than 1000 IU/L, and in patients with de novo chronic GVHD when compared with progressive and relapsing forms (HR = 2.8, 95% CI 0.8-10.1, $P = .1$). Age, sex, number of prior treatments, scleroderma versus other skin disease, and HLA compatibility did not significantly impact the response rate (Table 2).

Several factors that significantly impacted on NRM are summarized in Table 3. Response to ECP and platelet count at initiation of therapy were the strongest predictors of NRM on univariate analysis. Less immunosuppressive therapy (2 versus 3 lines, including tacrolimus and steroids), a lower LDH, sclerodermal GVHD, and de novo chronic GVHD (versus progressive forms) were also significantly associated to a lower NRM. Of note, de novo chronic GVHD was associated with several factors conferring a more favorable prognosis, including better response to ECP, less immunosuppressive therapy prior to ECP, sclerodermal forms, and a trend to higher platelet counts and lower LDH (Table 4).

Patients with de novo chronic GVHD also had a significantly longer median time from diagnosis of chronic GVHD to initiation of ECP, possibly reflecting milder forms of disease with a delayed need for immediate intervention. Since the small sample size precluded multivariate analysis, we evaluated the independent effects of these factors in the subset of patients without de novo chronic GVHD (n = 46). In this group, response to therapy, platelet count and LDH maintained a significant effect (Table 5). Less immunosuppressive therapy prior to ECP was favorable but did not reach statistical significance ($P = .06$). The clinical significance of LDH as a prognostic factor is unclear, but values higher than 1000 IU/L were highly correlated with thrombocytopenia ($P = .004$). Thus, we only evaluated the individual effects of platelet count and response to ECP as shown in Figure 2. In patients with a CR or PR to ECP, thrombocytopenia was associated with a significant increase in the risk of NRM ($P < .001$). Conversely, patients with thrombocytopenia who achieved a CR or PR with ECP had a lower NRM, although this was not statistically significant ($P = .4$).

Discussion

Chronic GVHD is one of the major limitations to successful allogeneic transplantation, with a substantial impact not only on survival but also on the quality of life of otherwise cancer-free patients.

Chronic GVHD is a multifaceted disease, and its diagnosis, definition, staging, and therefore criteria to evaluate response to therapy are particularly challenging. Furthermore, almost every study on chronic GVHD has defined chronic GVHD chronologically (ie, GVHD beyond day 100), which can result in the misclassification of patients with clinical features of acute GVHD occurring after day 100 as having chronic GVHD.[4] This further complicates evaluation of interventions like ECP,[18] where factors like technical issues, dose (ie, number of weekly or biweekly treatments), total duration of therapy, and criteria for additional salvage immunosuppression after initiation of ECP usually varies from one transplantation physician to the next. All these differences need to be taken into account when assessing and comparing the efficacy of this and any therapy for chronic GVHD.

Several retrospective and prospective studies have shown activity of ECP in controlling the manifestations of chronic GVHD. Greinix et al[11] treated 15 patients with extensive chronic GVHD failing corticosteroids and reported responses of up to 80% in skin, 70% in liver, and all of the patients with involvement of the oral mucosa. Cases with skin GVHD included sclerodermatous forms with improvement in contractures. Responses in ulcerative chronic GVHD of the oral mucosa showed resolution in 100% of patients. The procedure was well tolerated, and no major toxicities were reported in this study. Apisarnthanarax et al[15] reported on 32 heavily pretreated patients with chronic GVHD of the skin, with responses in both lichenoid and sclerodermal forms in about half of the patients (CR 22%, PR 34%). The procedure was also well tolerated in this group of patients.[15] There are several other reports on the efficacy of ECP for the treatment of chronic GVHD in small groups of patients, with overall response rates of 50% and higher in skin, oral, eye, liver, GI, and also lung GVHD.[12,13,16] A similar response rate and tolerability was observed in children with skin and visceral GVHD.[14,19] All of these reports included patients who had received at least 1 line of therapy, in most cases steroids, prior to initiation of ECP. The interpretation of these results is complicated by different factors, including the small number and heterogeneity of patients treated in all of these reports, the diversity of schedules and duration of treatment, the possibility of "delayed" responses to concurrent immunosuppression (eg, steroids), or spontaneous improvement over time. Finally, although a variety of different mechanisms have been proposed to explain the efficacy of ECP and ultraviolet (UV) light in the treatment of GVHD,[20-27] we are still in the

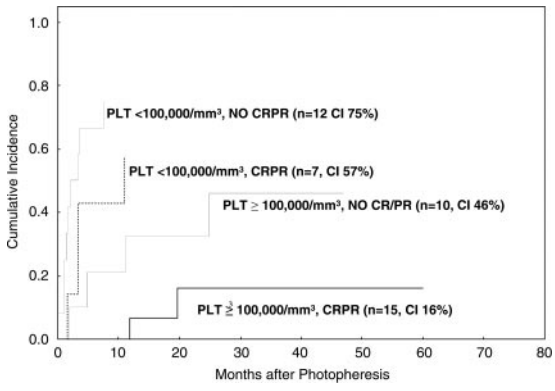

Figure 2. Cumulative incidence of nonrelapse mortality according to response to photopheresis and platelet count. 100 000/mm^3 is equal to 100 × 10^9/L.

process of understanding the fundamental pathophysiology underlying chronic GVHD as well as the biologic effects of ECP on this process. Massive induction of lymphocyte apoptosis,[20,24] changes in dendritic cell (DC) differentiation and function,[21] induction of regulatory T-cell subsets synthesizing interleukin-10 (IL-10),[28] and, in the long term, restoration of the DC1/DC2 and T helper 1 (Th1)/Th2 balance in favor of DC2/Th2[21,25] in the course of the disease are some of the proposed mechanisms of action of ECP.

In this retrospective experience, patients were assessed by defined criteria for the diagnosis of chronic GVHD and response to therapy. All patients were diagnosed with chronic GVHD based on a clinical definition and were treated with at least 2 prior lines of immunosuppressive therapy, which included corticosteroids. Responses were not only seen in chronic GVHD of the skin, but in cases of visceral involvement as well. Most patients with skin GVHD had sclerodermatous involvement, and the majority of these had responses manifested by improved skin scores and/or range of motion in affected joints. Of note, challenging situations such as liver and lung GVHD showed objective responses in more than half of the patients.

Response to ECP, along with thrombocytopenia, were the most important prognostic factors affecting NRM. High LDH levels were correlated with both NRM and platelet count, and its significance and value as an independent predictor of survival is unclear. Less immunosuppressive therapy prior to ECP was associated with a trend to a lower NRM as well.

In the small subset of patients who received more than 3 lines of immunosuppression prior to ECP (n = 8), the response rate also was high, but every responder had progression of their chronic GVHD. This group of patients had a relatively short 18-month median survival after initiation of ECP.

Definitive evaluation of novel therapies for chronic GVHD requires prospective, controlled studies. With some interventions, the benefit of clinical responses was offset by an increase in infectious complications related to immunosuppressive treatment.[29] ECP has activity to improve the symptomatic manifestations of chronic GVHD. Unfortunately, its prospective evaluation been complicated by a variety of factors, including accessibility to the technique, health insurance coverage, the need for intravenous access, and controversies surrounding assessment of chronic GVHD.

Our results warrant further evaluation of ECP in prospective, controlled clinical trials to document its effect on response, survival, immune function, infections, and relapse of the underlying disease.

ECP has objective activity in the treatment of chronic GVHD, including in cases of liver and lung GVHD, where more objective response parameters were available. The procedure was well tolerated overall, with no fatal toxicities. These results support previous reports of objective responses of skin and visceral GVHD to ECP. Patients who responded to ECP and those with higher platelet counts had a significantly lower NRM, which warrants further studies in earlier stages of chronic GVHD.

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