The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease

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Acute graft-versus-host disease (GVHD) is a major cause of mortality after allogeneic hematopoietic stem cell transplantation. We performed a phase II study on patients with acute steroid-refractory GVHD grades II to IV given extracorporeal photochemotherapy (ECP) weekly and analyzed response and long-term survival. Complete resolution of GVHD was achieved in 82% of patients with cutaneous involvement, 61% with liver involvement, and 61% with gut involvement. The probability of survival was 59% among patients who responded completely to ECP compared to 11% in patients not responding completely. We conclude that intensified ECP is highly effective in acute GVHD and that sustained responses are associated with over 50% long-term survival.

Key words: acute graft-versus-host disease, extracorporeal photochemotherapy.

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Acute graft-versus-host disease (GVHD) is a major impediment to the cure of patients with blood disorders after allogeneic hematopoietic stem cell transplantation (HSCT).[1,2] Durable complete responses to corticosteroids were reported in only 24% to 40% of patients with acute GVHD and no standard effective treatments for steroid-refractory GVHD are available.[1-4] Extracorporeal photochemotherapy (ECP) is based on the infusion of autologous blood mononuclear cells collected by apheresis, incubated with the DNA-intercalating agent 8-methoxypsoralen (8-MOP) and then irradiated with UVA. ECP has demonstrated efficacy in selected T-cell diseases, including chronic extensive GVHD.[5-8] So far, only a few patients with acute GVHD treated with ECP have been reported.[9-14]

Based on the promising results of our pilot study we performed a prospective phase II study to evaluate the efficacy of ECP as second-line therapy in a larger cohort of patients and to analyze variables associated with treatment response and post-transplant survival.

Design and Methods

Patients

We studied 59 patients with post-transplant acute GVHD. The first 21 patients have been previously reported.[9] The patients' characteristics are shown in Table 1. All patients gave written informed consent and the use of ECP was approved by the medical ethics committee of the Medical University of Vienna.

Evaluation criteria

From 1996 onwards, patients with a clinicopathologic diagnosis of acute GVHD[15] who were refractory to steroids were treated with ECP. Until 1999, due to the limited capacity for ECP at our institution, not all consecutive patients eligible could receive ECP. Thereafter, ECP was the second-line therapy for all consecutive patients with steroid-refractory and steroid-dependent acute GVHD. The definitions of response criteria have already been published.[9]

Extracorporeal photochemotherapy and treatment protocol

ECP was performed using the UVAR photopheresis system (Therakos, West Chester, PA, USA), as described previously.[9] Initially patients were treated on two consecutive days (one cycle) at 1 to 2-week intervals until improvement and thereafter every 2 to 4 weeks until maximal response. The treatment was then tapered off individually over 0.5 to 25 months. Due to the lack of GVHD flare-ups and stability of ECP responses observed in the pilot study, in the phase II study ECP was given on two consecutive days at weekly intervals and ECP was stopped immediately after achieving maximal response. At the start of ECP all patients were receiving immunosuppressive therapy with prednisone and cyclosporine A.

Statistical methods

Overall survival and disease-free survival were estimated using the Kaplan-Meier method, whereas cumulative incidences were calculated for relapse, transplant-related mortality, and chronic GVHD in order to

Table 1. Overall patients' characteristics.

	All	*Steroid-Refractory**	*Steroid-Dependent°*
No. of patients	59	37	22
Pilot study	21	13	8
Phase II study	38	24	14
Median age (years)	40	42	39
Range	21-60	27-60	21-60
Male/Female	29/30	15/22	14/8
Disease stage			
Standard risk#	37	23	14
High risk	22	14	8
Median day of onset of acute GVHD	17	20	16
Range	8-42	8-37	8-42
Grade of acute GVHD at ECP			
II	36	21	15
III	13	10	3
IV	10	6	4
Organ involvement at ECP			
Skin alone	31	18	13
Skin and liver	13	9	4
Skin, liver and gut	8	5	3
Skin and gut	5	4	1
Liver and gut	2	1	1
Med. days of steroids prior to ECP	17	13	23
Range	4-49	4-43	13-49
Med.cum.steroid dose prior to ECP (mg/kg bw)	2.8	2.7	2.9
Range	2-10.4	2-10.4	2-10
Median interval day 0 to ECP(d)	37	35	40
Range	14-70	14-62	22-70
Med.dose of steroids at ECP (mg/kg bw)	2.1	2.2	2.0
Range	0.7-10.4	2-10.4	0.7-4
Best response after cycle (median)	4	4	4
Range	1-13	1-13	1-8
Best response after month (median)	1.3	1.4	1.4
Range	0.5-6	0.5-6	0.5-4.5
Med.days to discontinuation of steroids after the start of ECP	55	51	65
Range	17-284	17-284	18-156

*No: number; GVHD: graft-versus-host disease; med: median; cum: cumulative; bw: body weight; d days; *steroid-refractory GVHD was defined as progression or no improvement of acute GVHD after a minimum of 4 days of prednisone ≥2 mg/kg bw; °steroid-dependent GVHD was defined as a flare-up of acute GVHD during tapering of prednisone; #standard risk was defined as chronic phase of chronic myeloid leukemic, first and second complete remission of acute leukemia and first partial remission of lymphoma and myeloma.*

adjust the analysis for competing risks. Cumulative incidences in the different groups were compared using the k-sample Gray test. Log-rank test statistics were used to evaluate the univariate effects of variables on outcome. Multivariate analyses were carried out using Cox proportional hazards regression modeling. The median follow-up of surviving patients was 52 months (range, 10 to 108).

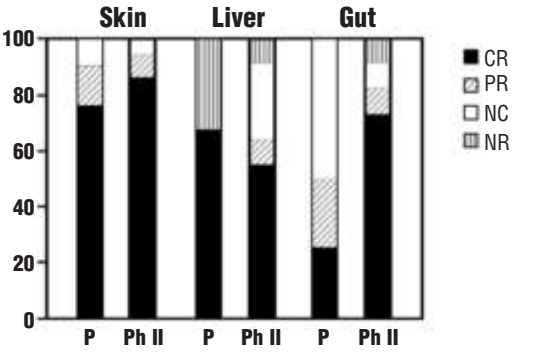

Figure 1. Response of patients with acute steroid-refractory and steroid-dependent GVHD to ECP according to organ manifestations. The left columns show the responses in the pilot study patients (P) and the right columns the responses of patients in the phase II study (Ph II) in relation to organ involvement (skin, liver or gut) at the start of ECP. CR: complete resolution of GVHD defined as resolution of all organ manifestations; PR: partial resolution of GVHD defined as a greater than 50% response in organ involvement; NC: no change of GVHD defined as stable organ involvement despite tapering down at least 50% of the dosage of other immunosuppressive agents; NR: no response of GVHD defined as progressive worsening of GVHD and the inability to taper other medications.

Results and Discussion

Patients in the pilot study had had significantly longer steroid pretreatment (median of 21 versus 15 days, p=0.03) and longer intervals from day 0 of HSCT until the start of ECP (median of 41 versus 34 days, p=0.002). Both the cumulative steroid dose prior to ECP (median 3.9 versus 2.1 mg/kg b.w., p=0.001) and the steroid dose at the start of ECP (median 2.6 versus 1.8 mg/kg b.w., p=0.01) were significantly higher in the patients included in the pilot study than in those in the phase II study.

Response of acute GVHD to ECP

Complete resolution of GVHD was documented in 82% of patients with cutaneous involvement, 61% with liver involvement, and 61% with gut involvement. Whereas 87% and 62% of patients with exclusively skin or skin and liver involvement had a complete response to ECP, only 25% of patients with skin, liver and gut and 40% of patients with skin and gut involvement obtained complete resolution of their acute GVHD in response to ECP. Complete responses were obtained in 86% of patients with grade II acute GVHD, 55% of patients with grade III, and 30% of patients with grade IV disease. Compared with responses in the pilot study, markedly higher complete resolution rates were obtained in phase II study patients with gut involvement (25% versus 73%, Figure 1) and grade IV acute GVHD (12% versus 60%).

In univariate analysis, fewer organs involved and a lower grade of acute GVHD both during first-line therapy and at the start of ECP, later start of steroid medication after HSCT, and lower cumulative steroid dose for first line therapy of GVHD significantly increased the probability of ECP producing complete resolution. However, in logistic regression analysis, only a lower

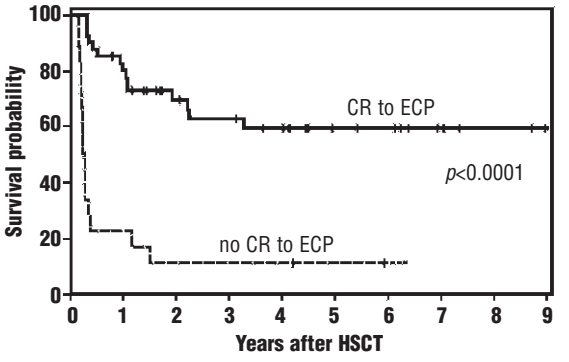

Figure 2. Kaplan-Meier probability of overall survival among patients with acute steroid-refractory and steroid-dependent GVHD. Overall survival is shown for patients achieving a complete response (CR) or not to ECP. The difference between the two groups is statistically significant (p<0.0001).

grade of GVHD at the start of ECP, and later onset of steroid medication after HSCT were factors significantly favoring the achievement of complete resolution by ECP.

Transplant-related mortality

The cumulative incidence of transplant-related mortality at 4 years was, overall, 36% (95% confidence interval (CI), 25-50%), whereas it was 14% (95% CI, 10-31%) and 73% (95% CI, 56-94%) in patients achieving or not complete resolution of GVHD during ECP (p<0.0001). On univariate analysis, a shorter interval between day 0 of HSCT and the start of ECP (HR 0.9; 95% CI 0.8-0.9), a shorter duration of ECP (HR 0.7; 95% CI 0.5-0.99), a steroid dose below 1 mg/kg b.w. at 4 weeks (HR 0.4; 95% CI 0.1-0.9) and below 0.5 mg/kg b.w. at 8 weeks after the start of ECP (HR 0.2; 95% CI 0.1-0.7) were associated with lower transplant-related mortality whereas higher grade of acute GVHD during first-line therapy (HR 2.3; 95% 1.4-3.7) and at the start of ECP (HR 1.8; 95% CI 1.1-2.9), more organs involved at the start of ECP (HR 1.6, 95% CI 1.2-2.7), higher steroid dose at the start of ECP (HR 1.3; 95% CI 1.05-1.6), and failure to achieve complete resolution 3 months after the start of ECP (HR 6.5; 95% CI 2.7-16) were associated with higher transplant-related mortality.

Survival and long-term outcome

The Kaplan-Meier estimates for overall survival at 4 years were 47% for all patients, 59% for patients achieving a complete resolution of acute GVHD and 11% for those who did not achieve complete resolution in response to ECP (p=<0.0001, Figure 2). On univariate analysis, a steroid dose below 1 mg/kg b.w. at 4 weeks (HR 0.4; 95% CI 0.2-0.8) and below 0.5 mg/kg b.w. at 8 weeks after the start of ECP (HR 0.3; 95% CI 0.1-0.8) were associated with improved survival whereas a higher grade of acute GVHD during first-line therapy (HR 1.9; 95% CI 1.3-3.0) and at the start of ECP (HR 1.7; 95% CI 1.1-2.6), more organs affected by GVHD at the start of ECP (HR 1.9; 95% CI 1.2-2.8), a higher steroid dose at the start of ECP (HR 1.3; 95% CI, 1.1-1.6), and failure to achieve complete resolution by 3 months after the start of ECP (HR 3.7; 95% CI 1.8-7.5) were associated with worse survival. At the end of both studies 14 patients (24%) had experienced relapse including eight (22%) with standard- risk and six (27%) with high-risk disease prior to HSCT. The cumulative incidence of relapse for both studies at 4 years was 28% (95% CI, 19-43%). The current analysis of 59 patients treated with ECP as second-line therapy represents the numerically, largest study so far of patients with acute steroid-refractory and steroid-dependent GVHD. After a median of four cycles of ECP, ever a median of 1.3 months of therapy, 69.5% of patients had achieved complete resolution of GVHD and another 10% had had a partial resolution. Complete resolution of GVHD was documented in 82% of patients with cutaneous involvement, 61% with liver involvement, and 61% with gut involvement. Compared with response rates in the pilot study,[9] higher response rates were seen in patients with cutaneous and gut involvement and in patients with grade IV acute GVHD. Since a lower grade of GVHD at the start of ECP was highly significant in logistic regression analysis for achieving complete resolution, the higher number of patients with grade II acute GVHD in the phase II study (68% versus 48%) should be taken into account. Prompt initiation of ECP in patients in need of second-line therapy for acute GVHD led to improved response rates in the phase II study and also resulted in a significantly lower transplant-related mortality of 14% in patients with complete response to ECP compared to the 73% in patients without a complete response. Response to ECP, a shorter interval from day 0 of HSCT until the start of ECP and a shorter duration of ECP all had significantly favorable impacts on transplant-related mortality.

We confirm in a larger population of patients that ECP allows accelerated tapering of corticosteroids, which had a significantly favorable impact on transplant-related mortality. Despite abrupt discontinuation of ECP after maximal response in the phase II study, the durability of response was not compromised. Recently, Garban *et al.,* reported promising response rates to an intensified ECP schedule.[14] Since we applied weekly therapy with ECP in our phase II study, we can confirm, in a larger number of patients, the importance of intensive treatment for achieving resolution of GVHD. The overall survival rate of 47% after a median observation of 52 months after HSCT in our study compares favorably with published results on second-line therapy of patients with acute steroid-refractory GVHD.[4,16-19] A significantly higher probability of long-term survival (59%) was seen in patients achieving a complete response than in patients not responding to ECP (11%), confirming previous reports on the importance of sustained complete response for long-term survival.[1,2,3] In addition to the pretreatment severity of GVHD, steroid doses during ECP and response to ECP were significant prognostic indicators of survival. In summary, our long-term results in patients with acute steroid-refractory and steroid-dependent GVHD demonstrate durability of responses to ECP with improved overall survival. Improvements in response

rates due to prompt initiation of ECP are promising and support the use of ECP not only as second-line treatment but also upfront in patients with grades II to IV acute GVHD.

HTG: Conception and design, of the study acquisition of data, drafting, revision and final approval of the article; RMK: design of study treatment, critical analysis of data, revision and final approval of the article; NW, PH, WR, AS: acquisition of data, critical revision and final approval of the article; BS: analysis and interpretation of data, critical revision and final approval of the article; AS, MM, PK: interpretation of data, drafting revision and final approval of the article.

All authors approved the manuscript, declare that 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 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. This work was supported by European Commission Grant QLK3-CT-2002-01936 TransEurope.

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