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Effects of extracorporeal photopheresis on survival in chronic graft versus host disease

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ABSTRACT

Objective: Chronic graft versus host disease (cGVHD) develops after allogeneic hematopoietic cell transplantation, when immune cells from a non-identical donor initiate an immune reaction against the transplant recipient. Extracorporeal photopheresis (ECP) can be used in combination with prednisone in steroid-resistant cGVHD. In this study, the effect of ECP use on survival in cGVHD was examined.

Patients and Methods: Twenty-six patients who were followed up in the adult Hematology Clinic of Inonu University Turgut Ozal Medical Center for cGVHD were included in the study. Stem cell transplantation and ECP application parameters that may affect the survival of the patients were examined.

Results: The degree of involvement in cGVHD affects survival. Involvements with clinical and laboratory scores of 2 and above according to the National Institutes of Health consensus criteria, significantly reduced survival. The development time of cGVHD was found to be associated with survival, and that it had a positive impact on survival, especially when the disease developed after 220 days after the transplantation. It was observed that steroid dose taken during ECP, patient age and cGVHD prophylaxis used affected survival.

Conclusion: The use of ECP may be effective in survival, especially, in patients who develop cGVHD, 220 days after allogeneic transplantation. Concurrent use of steroids with ECP affects survival.

Keywords: Graft versus host disease, Allogeneic hematopoietic cell transplantation, Extracorporeal photopheresis, Survival

1. INTRODUCTION

Graft versus host disease (GVHD) can develop after allogeneic hematopoietic cell transplantation (HCT) when T cells from the donor initiate an immune reaction against the transplant recipient. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) can be differentiated by clinical manifestations. The National Institutes of Health (NIH) consensus criteria are the criteria accepted by many bone marrow transplant centers in the definition and follow-up of cGVHD. GVHD may sometimes be encountered by the clinician as an overlapping syndrome where acute and chronic features are intertwined [1].

The onset of cGVHD is typically ≥3 months after transplant. Nearly all cases occur within the first year after transplant, but in some cases, cGVHD can occur months or even years after HCT. Previously, the distinction between aGVHD and cGVHD was based on baseline <100 days and ≥100 days after transplantation, respectively. However, these conditions are no longer defined by the onset time after transplantation, but by their clinical and pathological features, both syndromes may occur outside of these time periods [2].

Chronic graft versus host disease is a clinical entity that mimics rheumatologic disorders (eg, scleroderma, Sjögren's disease, primary biliary cirrhosis, bronchiolitis obliterans). It may affect many systems of the body and may have a limited involvement. It is manifested by skin lesions, mucositis, increased liver function tests, dry mouth and respiratory complaints [3]. Higher degree of human leukocyte antigen incompatibility, older donor or recipient, transplantation from a female donor to a male recipient, history of pregnancy or transfusion in the donor, use of peripheral blood stem cell grafts, application of non-irradiated donor buffy coat transfusions, splenectomy

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of the recipient, cytomegalovirus (CMV), Epstein-Barr virus (EBV) seropositivity in the donor or recipient are major risk factors for the development of cGVHD [4,5].

There are more than 100 synthetic derivatives of psoralen used in extracorporeal photopheresis (ECP) [6]. When psoralen is exposed to UVA rays at a wavelength of 320-400nm, it forms the C4 psoralen-thymine compound, which binds to DNA pyrimidine bases [7]. In addition to blocking DNA synthesis, its reactivity to lipid membranes and cell elements contributes to cellular cytotoxicity [8].

Extracorporeal photopheresis occurs by collecting peripheral lymphocyte cells with an apheresis device, adding 8-methoxypsoralen to the product and transferring the new product formed as a result of exposure to ultraviolet rays [9]. ECP is an effective method in the treatment of patients with steroid-refractory cGVHD. In one third of the patients using steroids, steroid use is considerably reduced.

Extracorporeal photopheresis effectiveness is reduced if the patient has extensive involvement of cGVHD, thrombocytopenia, and if aGVHD has developed beforehand [10]. Contraindications for ECP are as follows: Psoralen sensitivity, photosensitivity, pregnancy, lactation, low complete blood count parameters (WBC<1.000mm3 / Platelet <20.000mm3 / Htc<28%), uncontrolled systemic infection, absence of lens (aphakia), history of heparin-induced thrombocytopenia, hemodynamic disorder. ECP administration should be avoided in patients with severe cardiovascular or renal impairment [11]. In this study, it was aimed to examine the parameters affecting survival in bone marrow transplant patients with cGVHD.

2. PATIENTS and METHODS

Study design

Adult patients (over 18 years of age) who had allogeneic bone marrow transplantation and developed post transplant cGVHD between January 2009-February 2022 were included in this study after institutional ethical approval.

Parameters that may affect survival, such as demographic data, donor characteristics, stem cell source, how long after a bone marrow transplant, cGVHD develops, preparation for transplantation, organs involved in cGVHD, cGVHD degree, ECP administration, steroid administration, cGVHD response assessment, patient follow-up time were examined. Data were analyzed retrospectively.

Response evaluation after ECP

National Institutes of Health (NIH) consensus criteria were used to evaluate patients' response [12]. For each organ or site (the skin, nails, scalp and body hair, mouth, eyes, genitalia, gastro intestinal tract, liver, lung, muscles/fascia/joints, hematopoietic and Immune) disease severity was graded with the degree of involvement between 0-3. Mild cGVHD (1 or 2 organs involved with no more than score 1 plus, Lung score 0), Moderate cGVHD (3 or more organs involved with no more than score 1 or at least 1 organ (not lung) with a score of 2 or Lung score 1), Severe cGVHD (At least 1 organ with a score of 3 or Lung score of 2 or 3). The response rate of the patients (complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), progression of disease (PD) was decided by examining differences between the grades.

Extracorporeal photopheresis procedure details

Extracorporeal photopheresis procedure was applied after the jugular or femoral catheters were inserted. The treated patients were using steroids (1-2 mg/kg/day). After collecting an average of 100 ml of mononuclear cells from the patient with the Spectra Optica Apheresis System (terumobct serial no: ip 07554 Atasehir/Istanbul), the collected product was placed in macrogenic sets (Macogenic Set, Mouvaux, France) and saline was added as much as the collected product. The amount of methoxypsoralen (micrograms) was calculated (amount of product collected X 0.017) and added to the collected product set. The product, which came to the final stage, was infused into the patient in minutes after being processed in the macogenic extracorporeal photopheresis device (Macopharma, Mouvaux, France) for an average of 8-10 minutes. The procedure was repeated once a week for an average of at least 4 weeks for each patient.

GVHD prophylaxis regimens

a.Methotrexate plus calcineurin inhibitor in transplants involving an HLA-matched sibling/relative donor. Antithymocyte globulin was added to methotrexate plus a calcinin inhibitor in transplants using a matched unrelated donor (i.e. ≥9/10 or ≥7/8 HLA alleles). **b**.Calcineurin inhibitor plus mycophenolate mofetile in haploidentical transplants. Post transplant cyclophosphamide was added. GVHD prophylaxis was performed using myeloablative conditioning calcineurin inhibitor plus methotrexate. **c**.Non-myeloablative conditioning regimens. In non-myeloablative or reduced-intensity conditioning (RIC), calcineurin inhibitor plus mycophenolate mofetil was administered.

Bone marrow conditioning regimens

In our center, busulfan/cyclophosphamide (Bu/Cy) for acute myeloid leukemia (AML), Bu/Cy for all or Cy/total body irradiation (TBI) preparation regimen was used in young patients under 40 years of age without comorbidities. Fludarabine (Flu)/Cy plus antithymocyte globulin (ATG) was used for apilastic anemia. BEAM for lymphomas and Bu/Cy/etoposide (E) regimens for non-hodgin lymphomas were applied. Bu/Flu/ATG was frequently used in the reduced-intensity conditioning (RIC) protocol.

Ethical consent

The study carried out by the adult Hematology Clinic of the Turgut Ozal Medical Center was approved by the Non-interventional Clinical Research Ethics Committee of Inonu University, Faculty of Medicine (date: 26.04.2022, approval number 2022/3326).

Statistical evaluation

Statistical analysis was performed using the SPSS (Windows software version 26.0 (IBM Corp., Armonk, NY, USA). Mann-Whitney U test and Pearson's chi-square test were used in the comparison of groups. Chi-square test and Fisher's exact test were used in the analysis of categorical variables. Categorical data were given as percentage. Quantitative variables were given as mean, standard deviation, median. Hazard ratio was calculated by Cox regression analysis. Follow-up period of the patients was determined as the time from bone marrow transplantation to the death of the patient. P values less than 5% were accepted as positive in the tests.

3. RESULTS

The data of 26 patients who developed cGVHD after allogeneic stem cell transplantation were evaluated. The mean age was 36.27 (± 13.82) years (10 (38.5%) women, 16 (61.5%) men). The descriptive and demographic data of the patients are shown in Table I.

Table I. ***Chronic graft versus host disease demographic data***

		Event				P
		Alive		Dead		
		n (%)	Median (Min-Max)	n (%)	Median (Min-Max)	
Sex	Female	5 (38.46)		5 (38.46)		1
	Male	8 (61.53)		8 (61.53)		
Age			26 (20-64)		45 (23-57)	0.044*

*Min-Max: Minimum-Maximum, * Statistical significance*

In the survival analysis of the patients, two groups were defined as alive (n=13) and deceased (n=13) (total=26). The mean survival time of the patients was 31.96±7.33 months, the 1-year survival rate was 53.6% and the 2-year survival rate was 47.6%. Figure 1 shows the survival curve of the patients.

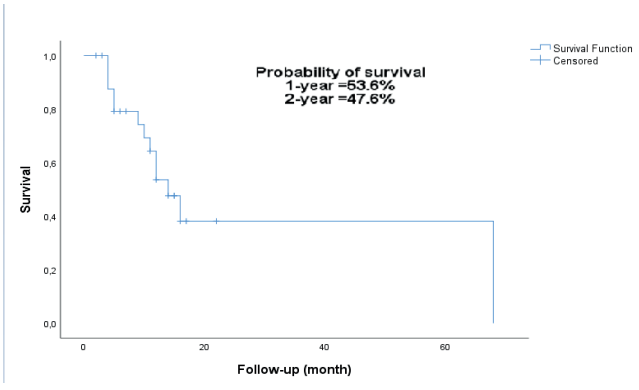

Figure 1. *Survival curve for cGVHD patients*

A statistically significant difference was found in cGVHD in terms of donor proximity (p=0.047), duration of cGVHD after transplantation (p= 0.006), ECP 1st month response (p= 0.03), and the last follow-up of the patient after ECP. The degree of involvement in cGVHD affected survival (p=0.097).

The degree of involvement in cGVHD was found to be 84.61% of patients with Grade ≤2 and 15.38% of patients with Grade >2. The survival of cGVHD patients with grade 2 and higher involvement was significantly reduced.

The duration of cGVHD development after transplantation was found to affect survival, and cGVHDs that developed after 220 days were found to have a positive effect on survival. Survival of the patients who developed cGVHD after 220 days or more was calculated as 84.61%. The percentage of mortality was 23.07.

No statistically significant correlation was found between the first week and 1st month response evaluation of ECP use and cGVHD (Table II).

Table II. *Statistical analysis of descriptive data in chronic graft versus host disease*

		Event		P
		Survived	Deceased	
		n (%)		
PRIMARY DISEASE	AML	6 (46.2)	8 (61.5)	0.48
	ALL	3 (23.1)	2 (15.4)	
	HODGKIN'S LYMPHOMA	0 (0)	0 (0)	
	NON-HODGKIN'S LYMPHOMA	0 (0)	1 (7.7)	
	APLASTIC ANEMIA	0 (0)	0 (0)	
	MDS	2 (15.4)	0 (0)	
	MULTIPLE MYELOMA	0 (0)	0 (0)	
	OTHERS	2 (15.4)	2 (15.4)	
DONOR FEATURE	MATCH (8/8)	12 (92.3)	13 (100)	1
	MISMATCH (7/8)	0 (0)	0 (0)	
	MISMATCH (≤6/8)	1 (7.7)	0 (0)	
DONOR KINSHIP	RELATIVE	10 (76.9)	5 (38.5)	0.047*
	NON RELATED	3 (23.1)	8 (61.5)	
STEM CELL SOURCE	PERIPHERAL	13 (100)	13 (100)	-
	HARVEST	0 (0)	0 (0)	
PRE-RANSPLANTATION-DISEASE REMISSION	NOT REMISSION	0 (0)	0 (0)	-
	REMISSION	13 (100)	13 (100)	
TBI USED	NO	13 (100)	13 (100)	-
	YES	0 (0)	0 (0)	
PREPARATION REGIME	MYELOABLATIF	13 (100)	13 (100)	-
	REDUCED INTENSITY	0 (0)	0 (0)	

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GVHD PROPHYLAXIS	Cyclosporine (2x1.5 mg/kg)-methotrexate (10 mg/m2)	0 (0)	0 (0)	1
	Cyclosporine (2x1.5 mg/kg)-methotrexate (10 mg/m2)- post TX cyclosporine (2 x3 mg/kg-PO	13 (100)	12 (92.3)	
	Cyclosporine (2x1.5 mg/kg)-methotrexate (10 mg/m2) – ATG-(2.5 mg/kg/day)-post TX cyclosporine (2 3 mg/kg-PO	0 (0)	1 (7.7)	
	DİĞER	0 (0)	0 (0)	
GRADE	≤2	11 (84.61)	6 (46.15)	0.097
	>2	2 (15.38)	7 (53.84)	
POST TRANSPLANT cGVHD OCCURRENCE	≤220 day	2 (15.38)	10 (76.92)	0.006*
	>220 day	11 (84.61)	3 (23.07)	
cGVHD ORGAN INVOLVEMENT	SKIN	2 (15.4)	2 (15.4)	0.075
	LIVER	5 (38.5)	1 (7.7)	
	GUT	1 (7.7)	2 (15.4)	
	LUNG	3 (23.1)	0 (0)	
	SKIN and GUT	0 (0)	2 (15.4)	
	SKIN and LıVER	2 (15.4)	6 (46.2)	
	GUT and LIVER	0 (0)	0 (0)	
	OTHERS	0 (0)	0 (0)	
ECP 1 WEEK RESPONSE	CR	0 (0)	0 (0)	0.16
	VGPR	3 (23.1)	2 (15.4)	
	PR	3 (23.1)	1 (7.7)	
	SD	6 (46.2)	4 (30.8)	
	PD	1 (7.70)	6 (46.2)	
ECP 1 MONTH RESPONSE	CR	0 (0)	0 (0)	0.03*
	VGPR	7 (53.8)[a]	2 (15.4)[b]	
	PR	3 (23.1)[a]	3 (23.1)[a]	
	SD	3 (23.1)[a]	2 (15.4)[a]	
	PD	0 (0)[a]	6 (46.2)[b]	
ECP LAST SEEN	CR	8 (61.5)[a]	0 (0)[b]	0.002*
	VGPR	3 (23.1)[a]	1 (7.7)[a]	
	PR	0 (0)[a]	2 (15.4)[a]	
	SD	0 (0)[a]	2 (15.4)[a]	
	PD	2 (15.4)[a]	8 (61.5)[b]	
ECP SIDE EFFECTS	Not Happened	13 (100)	13 (100)	-
	Happened	0 (0)	0 (0)	

*AML: Acute myelocytic leukemia, ALL: Acute lymphoblastic leukemia, CR:Complete remission, ECP: Extracorporeal photopheresis, cGVHD: Chronic graft versus host disease, MDS: Myelodysplastic syndrome, PD: Progressive disease, PO: Peri oral, PR: Partial remission, SD: Stable disease, TBI: Total body irradiation, TX: Stem cell transplant, VGPR: Very good partial remission. Different superscript letters in each row show a statistically significant difference (P ≤ .05), *Statistically significant*

Table III. *Univariate and multivariate Cox regression analyses for chronic graft versus host disease, n=26*

Variables in the Equation	Univariate		Multivariate	
	HR [95% CI]	P	HR [95% CI]	P
Age	**1.038 [0.999-1.079]**	**0.049**		
Sex [male]	0.754 [0.235-2.416]	0.63		
PRIMARY DISEASE (ALL)	0.155 [0.019-1.273]	0.082		
PRIMARY DISEASE (NON HODGKIN)	9.925 [0.854-115.352]	0.066		
PRIMERY DISEASE [MDS]	1.519 [0.307-7.513]	0.6		
PRIMARY DISEASE (OTHER)	0.69 [0.165-2.885]	0.69		
DONOR FEATURE	0.846 [0.255-2.68]	0.75		
DONOR KINSHIP	**4.927 [1.288-18.847]**	**0.019**	**15.4 [1.456-162.96]**	**0.023**
GVHD PROPHYLAXY	**11.503 [1.043-126.84]**	**0.046**		
POST TRANSPLANT GVHD OCCURRENCE >220	**0.093 [0.02-0.434]**	**0.003**	**0.076 [0.006-0.947]**	**0.045**
GVHD ORGAN INVOLVEMENT (LIVER)	0.333 [0.03-3.722]	0.37		
GVHD ORGAN INVOLVEMENT (GUT)	0.566 [0.05-6.389]	0.64		
GVHD ORGAN INVOLVEMENT (LUNG)	0 [0-0]	0.98		
GVHD ORGAN INVOLVEMENT (SKIN and GUT)	4.848 [0.623-37.707]	0.13		
GVHD ORGAN INVOLVEMENT (SKIN and LIVER)	1.715 [0.34-8.642]	0.51		
STEROID DURATION (DAYS)	0.998 [0.995-1.002]	0.45		
ECP USAGE TIME (DAYS)	1.0002 [0.995-1.005]	0.93		
CYCLE OF ECP USE	1.005 [0.925-1.093]	0.88		
STEROID DOSE DURING ECP	**1.02 [1.0007-1.041]**	**0.042**		
ECP 1 WEEK RESPONSE [VGPR]	1.113 [0.069-17.941]	0.93		
ECP 1 WEEK RESPONSE [PR]	3.112 [0.343-28.246]	0.31		
ECP 1 WEEK RESPONSE [SD]	6.996 [0.826-59.259]	0.07		
ECP 1 MONTH RESPONSE [VGPR]	6.297 [0.65-61.014]	0.11		
ECP 1MONTH RESPONSE [PR]	4.589 [0.409-51.441]	0.21		
ECP 1 MONTH RESPONSE [SD]	**16.394 [1.934-138.963]**	**0.01**	**16.36 [1.659-161.49]**	**0.016**
ECP LAST SEEN [CR]	1.118 [0.075-17.989]	0.966		
ECP LAST SEEN [VGPR]	0.178 [0.022-1.44]	0.100		
ECP LAST SEEN [PR]	0.295 [0.036-2.41]	0.255		
ECP LAST SEEN [SD]	2.64 [0.474-14.75]	0.267		
GVHD GRADE >2	**4.003 [1.227-13.053]**	**0.021**	**4.85 [1.344-17.5]**	**0.015**
APPLYING ECP AFTER GVHD (DAYS)	1 [0.996-1.003]	0.82		

HR: Hazard ratio, CI: Confidence Interval ECP: Extracorporeal Photopheresis, TBI: Total body irradiation, CR: Complete remission VGPR: Very good partial remission, SD: Stable disease, PD: Progressive disease, GVHD: graft versus host disease

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In univariate Cox regression analysis; Age, donor proximity, cGVHD prophylaxis, time to reccurrence of cGVHD after transplantation, steroid dose during ECP, ECP 1st month response and cGVHD grade had significant HR p values (Post transplant GVHD time-0.045/ ECP 1 month response-0.016/ GVHD grade-0.015). A multivariate Cox regression model was created with these parameters with significant p values. Obtained results; for cGVH, donor proximity, duration of cGVHD after transplantation, ECP 1st month response and cGVHD grade were found to be significant; HR p value <0.05 (Table III).

According to the univariate-cox regression analysis in cGVHD patients, an increase in the dose of steroid drug by one unit during ECP was found to be 1.02, and an increase in patient age by one unit increased the risk of deceased by 1.038 times. It was observed that the use of cGVHD prophylaxis (post-transplant oral cyclosporine, methotrexate, antithymocyte globulin) increased the risk of mortality 11,503 times compared to not using the prophylaxis (post-transplant oral cyclosporine, methotrexate).

According to the results of multivariate Cox regression analysis in cGVHD patients; In patients in whom the donor was unrelated, the risk of deceased was 15.4 times higher than that of being a relative. The risk of deceased was 13,157 times higher in patients with cGVHD less than 220 days after transplantation compared to patients with more than 220 days. The risk of deceased was 16.36 times higher in patients with ECP 1st month response SD compared to patients with PD. Patients with higher cGVHD grade levels (> 2) were 4.85 times more likely to die than patients with lower (≤ 2) cGVHD grade levels.

Kaplan-Meier (KM) survival analysis was performed on variables considered as binary in multivariate Cox regression analysis. Table IV shows KM results and Figures 2, 3, 4 and 5 show donor affinity, ECP 1st month response, time to occurrence of cGVHD after transplantation, and survival by grade, respectively. In CM analyzes, survival of patients with low grade (≤ 2) was significantly higher than patients with higher grade (> 2). Patients with a relative of the donor had longer survival than patients who were unrelated. Finally, patients with a longer time to cGVHD after transplantation (>220) and a lower grade (≤2) had significantly higher survival (Table IV).

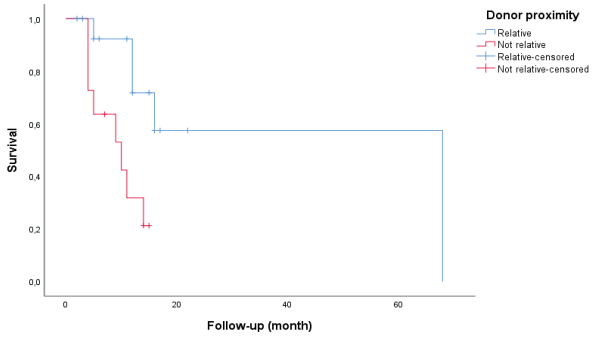

Figure 2. *Survival curve for donor proximity for chronic GVHD (p value-1)*

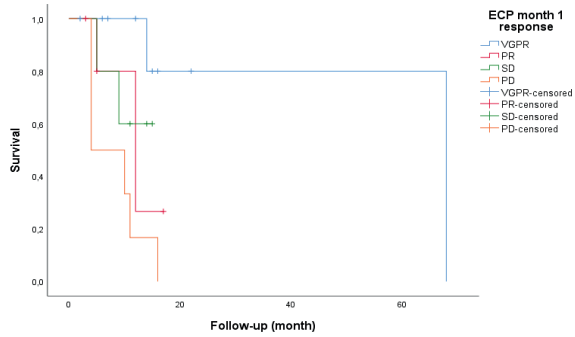

Figure 3. *Survival curve for ECP Month 1 response for chronic GVHD (p value-0.03)*

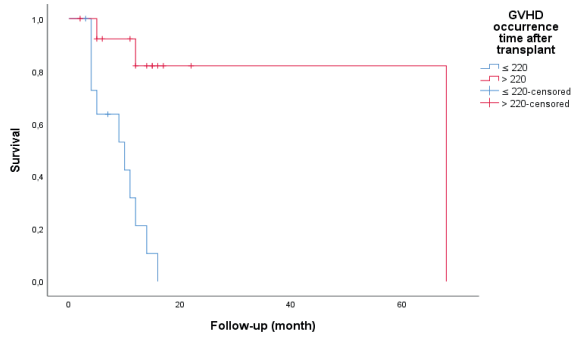

Figure 4. *Survival curve for time to cGVHD after transplantation for chronic GVHD (p value-0.097)*

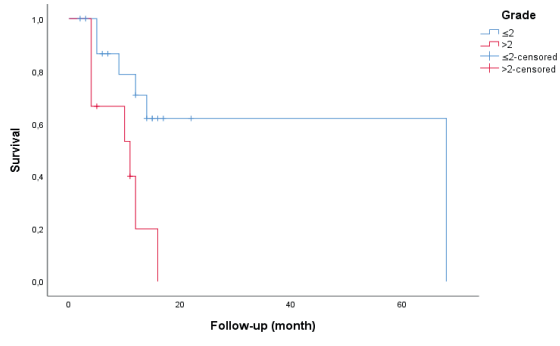

Figure 5. *Effect of the degree of chronic gvhd on survival (p value-0.006)*

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Table IV. *Survival results for variables that were significant in multivariate Cox regression for chronic graft versus host disease*

		Kaplan-Meier Analysis	
		Survival time (month)	Log-Rank
		Mean ± SE	p-value
DONOR KINSHIP	Relative	44.2 ± 10.51	0.009*
	Non Relative	9.39 ± 1.33	
ECP 1 month response	VGPR	57.2 ±13.66	0.007*
	PR	11.93 ± 1.89	
	SD	11.8 ± 1.84	
	PD	8.16 ± 2.03	
GVHD OCCURRENCE AFTER TRANSPLANTATION (≤ 220 DAYS)		9.18 ± 1.35	<0.001*
GVHD OCCURRENCE AFTER TRANSPLANTATION (>220 DAYS)		57.41 ± 8.39	
Grade ≤ 2		45.75 ± 8.71	0.012*
Grade > 2		9.73 ± 7.33	

*ECP: Extracorporeal photopheresis, GVHD: Graft versus host disease, Min-Max: Minimum-Maximum, VGPR: Very good partial response PR:Partial response, SD:Stable disease, PD: Progressive disease. *Statistical significance*

4. DISCUSSION

Our findings show statistically significant differences in cGVHD in terms of donor proximity, time to onset of cGVHD post-transplant, ECP 1st month response and the last follow-up of the patient after ECP and the degree of involvement that affected survival in cGVHD. The survival rate of cGVHD patients with grade 2 and higher involvement was significantly reduced. It was determined that the time to diagnosis of cGVHD after stem cell transplantation affected survival, and especially if the cGVHD developed after 220 days post-transplant, the rate of survival was high.

Many parameters are effective in the development of cGVHD in allogeneic stem cell transplantation. cGVHD treatment strategies are based on previous studies. Some of these studies are focused on transplantation parameters and ECP. ECP stands out as a treatment option that can be easily applied to patients and does not suppress the patient's immune system. In cGVHD, ECP provides effective treatment by causing changes in the function of immune T cells [13,14].

In the study of Sakellari and his colleagues, they reported that ECP must be performed before irreversible systemic damage occurs. Its use in the first phases of cGVHD was found to be more effective. Patients included in this study were those with steroid-refractory cGVHD but without irreversible systemic damage [15].

In the guideline updated by the American Apheresis Committee in 2023, ECP application in both acute and chronic GVHD was evaluated as category 2b. For cGVHD, a course is typically once or twice a week for up to 3 months or until disease stabilization, then tapered to a single course every 2 to 4 weeks (evaluated at 2 – to 3-month intervals) [16].

In this study, the use of ECP in cGVHD patients was more effective, especially in patients with GVHD that developed 220 days after transplantation and in patients with grade 2 and above. ECP application was applied to the patients for at least 4 sessions per week.

The consensus recommendation in the review by Drexler et al., stated that treatment should be administered 2 consecutive days per week or every 2 weeks for at least 8-12 weeks or until a noticeable response was achieved. ECP applications have been shown to be effective, with overall response rates of 57% for aGvHD and 38% for cGvHD [13].

In this study, in patients who developed cGVHD, in a year, overall survival rate was 56.6%, and in two years overall survival rate was 47.6%. ECP use in cGVHD affected the survival response at 1 month, 57.2 % for VGPR, 11.93 % for PR, 11.8 % for SD, and 8.16 % for PD. It was observed that the survival of patients who developed cGVHD after 220 days, was positively affected (57.41 months). Patients with grade 2 and above cGVHD, were adversely affected (9.73 months). NIH consensus criteria were used in the evaluation of patients [12].

In a multicenter study of Dal et al., advanced cGvHD was detected in two-thirds of the patients. Many organs were affected in 50% of the patients. The mean response rate in cGVHD was 46.5%. The overall survival was calculated as 41% at the end of the mean 1-year follow-up of the patients. The rate of mortality due to any reason was observed as 59% in the follow-ups of the patients after stem cell transplantation. It was observed that the overall survival was remarkably high in patients in whom ECP was successful [17].

In the analysis of this study, the mean survival time in patients was approximately 32 months. The 1-year survival rate was approximately 53%, and 2-year survival rate was approximately 47%. The patients who underwent ECP due to cGVHD were given steroids in parallel with the current treatment, and a one unit increase in the steroid dose, increased the risk of mortality by 1.02 times, and an increase in the patient's age by one year increased the risk of mortality 1.038 times. Similarly, patients taking cGVHD prophylaxis (post-transplant oral cyclosporine, methotrexate, antithymocyteglobulin) had a 11.503-fold increased risk of mortality compared to patients receiving cGVHD prophylaxis (post-transplant oral cyclosporine methotrexate). In patients in whom the donor was unrelated, the risk of mortality was 15.4 times higher than the patients with a related donor transplant. The risk of mortality was 13,157 times higher in patients who developed cGVHD in less than 220 days after transplantation when compared to patients who developed cGVHD after 220 days. Patients with ECP 1 month response SD had a 16.36-fold increased risk of mortality compared to patients with PD. Finally, patients with higher cGVHD grade levels (> 2) were 4.85 times more likely to die than patients with lower cGVHD grade levels (≤ 2).

In a review article by Canto et al., ECP application was shown as category 2 level 1b, with an emphasis on the ASFA 2016 guide. They reported a median overall response rate of 75% for cGVHD (median, 76%; IQR, 66% to 84%) in their case series.

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Reducing steroid doses could be achieved without any difference in cGVHD (median, 70%; IQR, 55% to 81%). It is argued that there is consensus regarding the safety and excellent tolerability of ECP [18].

The overall survival rate in our study was 53.6% for the 1st year and 47.6% for the 2nd year. In the response evaluation of ECP use after one month, survival rate was found to be 5.2% in patients with VGPR. Survival was found to be better in patients who developed cGVHD 220 days after transplantation. There was no difference between genders. ECP application was safely applied and no side effects occurred.

Limitation

In case there was no pathological diagnosis, the diagnosis of cGVHD after transplantation was decided according to the patient's post-transplant GVHD development time. GVHD that developed after 100 days was considered chronic. In the evaluation of the response of the patients, patients who could not be fully determined on the scale whether they were grade 1 or 2, were considered to have lower grades.

Conclusion

In steroid-refractory patients who developed cGVHD after allogeneic stem cell transplantation, steroid use during ECP, the type of prophylaxis used for cGVHD in stem cell transplantation, donor kinship, the development time of cGVHD after transplantation (especially in patients who developed cGVHD after 220 days), and the degree of cGVHD disease affected survival.

Compliance with Ethical Standards

Ethics committee approval: The study was approved by the Non-interventional Clinical Research Ethics Committee of Inonu University, (date: 26.04.2022, approval number 2022/3326). The study was conducted in accordance with the Declaration of Helsinki.

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Authors contributions: AK: Conducting the study and writing the article, MAE: Supervising, IK, EK: Collection of the data, IB, SB and SA: Writing the article, FHY: Providing biostatistical support for the study. All authors approved the final version of the article.

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