

PREDICTORS OF RESPONSE AND SURVIVAL IN PATIENTS OF CHRONIC GRAFT VERSUS HOST DISEASE TREATED WITH EXTRACORPOREAL PHOTOPHERESIS:A SINGLE CENTRE EXPERIENCE

A. Garg ,R. Whittle, F. Hammerton, A. Alfred, P. Taylor

PHOTOPHERESIS UNIT, ROTHERHAM GENERAL HOSPITAL, ROTHERHAM, YORKSHIRE, UK

Introduction

Chronic graft versus host disease (cGVHD) remains a major cause of late non relapse mortality and morbidity after allogeneic hematopoietic stem cell transplantation. It results in functional impairment and prolonged duration of immunosuppression with a negative impact on quality of life and survival(1). Corticosteroids either alone or in combination with the calcineurin inhibitors is the recommended first line therapy for cGVHD. The median duration of immunosuppressive treatment is about three years which contributes to increased risk of infections and other treatment related morbidities .Despite many immunosuppressive and immunomodulatory treatments available , none of them have shown a durable steroid sparing effect. Extracorporeal photopheresis (ECP) has been widely used as a second line therapy for treatment of cGVHD with recognized efficacy as a steroid sparing intervention(2,3).It is a cell based immunomodulatory therapy , which induces apoptosis in activated T cells and modulated cytokine production. Few studies have reported progressive steroid reduction with increase in duration of ECP(4).The factors influencing the outcome of patients treated by ECP are still under investigation.

Aim

In this study, we evaluated the efficacy of ECP in affected organs and attempted to identify variables associated with improved response rates and survival.

Materials and Methods

We evaluated a total of 219 consecutive patients who started ECP (1996-2012) for cGVHD after allogeneic stem cell transplantation. Patients were referred from other transplant centers in at the discretion of the transplant physicians. All the patients were steroid dependent, steroid refractory or intolerant of steroids. Data was collected from the retrospective analysis of the medical records and from the local ECP database.

Baseline features including gender, age, type of transplant, sex of the donor, performance status, steroid dose, bilirubin level, platelet count, ECP duration, number of immunosuppressive agents, type of cGVHD and overall severity of GVHD were recorded.

Skin was assessed using modified Rodnan's scoring system . Other organs including oral mucosa, eyes, liver ,lungs and gut were retrospectively scored using NIH (National Institute of Health) score.

The response was measured at 14 weeks, 28 weeks, 56 weeks and 112 weeks. Patients who showed improvement in NIH organ score($\geq 25\%$ for Rodnan's skin score) and/or $\geq 50\%$ reduction in steroid dose were classified as responders. All the others were in the non responder group.

Patient baseline characteristics

Variable	Category	Data
Gender	Male	134
	Female	85
Age	<18 yrs	33
	18-50 yrs	138
	>50 yrs	48
Donor sex	f/m	40
	m/m	43
	m/f or f/f	85
	Not known	51
Prior Acute GVHD	Yes	127
	No	92
Bilirubin score	≤ 2 mg/dl	198
	> 2 mg/dl	21
Platelet count	$\leq 100 \times 10^9/L$	36
	$> 100 \times 10^9/L$	183
Steroid at the time of ECP	Yes	188
	No	31
Steroid dose(mg/kg)	> 0.5	47
	≤ 0.5	141
Type of cGVHD	Overlap	94
	Classic	125
NIH severity	Mild	37
	Moderate	101
	Severe	81

- Median time from transplant to start of ECP:527 days (Range 69-1247 days)
- Median duration of ECP:57 weeks (Range 1-585 weeks)
- Median number of treatments received:31(Range 1-137)
- Median dose of steroids at the start of ECP:0.25(Range 0.01-10.1mg/kg)
- Total mortality in study group:86(39%)
- Median follow up amongst survivors after stopping ECP:42.7 months (Range 5-177 months)

Organ responses

Organs	Pre ECP n=178	Response at 14 wks n (%)	Response at 28 wks n (%)	Response at 56 wks n (%)	Response at 112 wks n (%)
Skin	134	91/134 (68)	81/117 (69)	69/87 (79)	23/33 (69)
Ocular	73	29/73 (39)	26/71 (36)	21/43 (39)	11/24 (46)
Oral	63	42/63 (67)	45/54 (65)	30/47 (53)	21/28 (78)
Lung	86	6/86 (7)	10/81 (12)	9/77 (13)	4/25 (16)
Liver	51	27/51 (53)	19/46 (41)	18/23 (56)	9/12 (75)
Gut	40	21/40 (53)	21/38 (55)	22/31 (70)	5/9 (56)

Steroid response

Time point	No. of patients	$\geq 50\%$ reduction n(%)	Steroids stopped n(%)
14 weeks	150	80(53)	12(8)
28 weeks	132	92(69)	27(20)
56 weeks	105	80(76)	39(37)
112 weeks	77	65(84)	40(52)

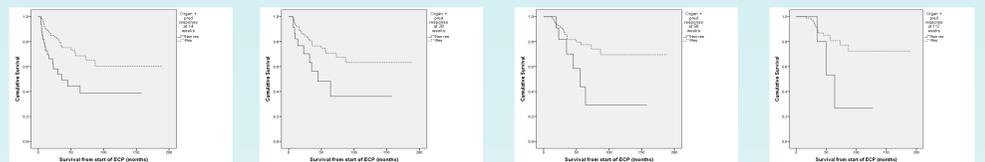
Predictors of Survival

Variable	Category	No. of patients	HR(95% CI)	p value
Gender	Female vs Male	219	0.650(0.408-1.036)	0.068
Age	18-50 vs >50	186	1.006(0.591-1.712)	0.984
Adult/Paediatric	Adult vs Paediatric	219	1.015(0.441-2.338)	0.972
Type of Donor	MUD vs Non MUD	218	0.993(0.634-1.556)	0.977
DLI	DLI vs Non DLI	219	1.654(0.828-3.303)	0.150
Sex of donor	F/M vs M/M	83	1.680(0.827-3.412)	0.147
Prior Acute GVHD	No vs Yes	219	1.138(0.745-1.738)	0.550
Bilirubin score	≤ 2 mg/dl vs > 2 mg/dl	219	0.345(0.190-0.626)	<0.001
Karnofski score	≤ 70 vs > 70	219	1.116(0.691-1.802)	0.653
Platelet count	≤ 100 vs > 100	219	2.671(1.653-4.315)	<0.001
Steroid use	No vs Yes	219	0.492(0.237-1.020)	0.056
Steroid dose	≤ 0.5 mg/kg vs > 0.5 mg/kg	188	0.464(0.289-0.745)	0.001
Type of GVHD	Classic vs Overlap	219	1.052(0.681-1.626)	0.819
NIH Score	Not severe vs Severe	219	0.890(0.574-1.380)	0.603
ECP Duration	Increase per week	219	0.979(0.973-0.985)	<0.001
Number of sites involved	0-2 vs ≥ 3	219	1.204(0.786-1.843)	0.393
Number of ISAs	0-2 vs ≥ 3	219	0.724(0.457-1.149)	0.170
Cyclosporin at start of ECP	No vs Yes	219	1.271(0.831-1.943)	0.268
Skin Score	≤ 150 vs > 150	168	1.504(0.599-3.776)	0.382
Lung Score	0/1 vs 2/3	119	0.620(0.285-1.347)	0.222
Liver Score	0/1 vs 2/3	204	0.708(0.360-1.393)	0.318

Effect of response on survival

Time point	Category	No. of patients	HR(95% CI)	P value
14 weeks	Res vs Non res	150	0.408(0.223-0.746)	0.003
28 weeks	Res vs Non res	138	0.412(0.199-0.856)	0.014
56 weeks	Res vs Non res	112	0.345(0.137-0.886)	0.018
112 weeks	Res vs Non res	88	0.383(0.109-1.344)	0.120

Kaplan Meier Survival curves



Conclusion

- Response rates to ECP were maximum in skin followed by oral mucosa, gut, liver, eyes and lungs.
- High bilirubin(> 2 mg/dl),Thrombocytopenia($< 100 \times 10^9 /L$), steroid dose (> 0.5 mg/kg) at the onset of ECP were predictors of poor survival.
- Response to ECP is an important predictor of improved survival.
- Duration of ECP is a predictor of response with improvement in response rates with increasing duration of ECP.
- There are no reliable patient characteristics predicting the response to ECP which could help in patient selection at the start.

References

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