52

CHARACTERIZATION OF OUTCOMES AFTER SECONDARY SYSTEMIC TREATMENT OF CHRONIC GRAFT-VERSUS-HOST DISEASE

Inamoto, Y., Storer, B.E., Lee, S.J., Carpenter, P.A., Flowers, M.E.D., Martin, P.J. Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Nearly 50% of patients with chronic graft-versus-host disease (GVHD) require secondary systemic treatment to control the disease. Outcomes after secondary treatment and the associated prognostic factors have not been examined well. This retrospective study had 3 goals; (1) to establish a benchmark that could be used to evaluate the efficacy of secondary treatment in future trials, (2) to elucidate prognostic factors associated with outcomes, and (3) to test the hypothesis that a composite of response and steroid dose at 6 months correlates with long-term outcomes, similar to results observed in a trial of primary treatment for chronic GVHD (BBMT 2011;17:124).

Methods: The study included 289 consecutive relapse-free patients who had high-intensity conditioning and required secondary treatment for chronic GVHD due to worsening or persistence of GVHD. Failure was defined as third-line systemic treatment or death, with recurrent malignancy considered a competing risk. Platelet count, serum bilirubin concentration and prednisone dose were assessed at start of secondary treatment. Response was assessed at 6 months among 174 patients without prior failure or relapse, and was defined as complete response in any organ, prednisone dose <0.25 mg/kg, or the combination. Cox regressions were used to evaluate potential risk factors for failure at the beginning of secondary treatment, and to evaluate the risk of subsequent failure associated with the 3 response definitions at 6 months.

Results: Median age of the patients was 44 (1-70) years. The single agents most commonly used for secondary treatment included MMF (n = 83), tacrolimus (n = 73) and sirolimus (n = 51); 16 received multiple new agents at start of secondary treatment. The cumulative incidence of failure was 48% (95% CI, 42-53%) at 1 year. Cox models revealed that the risk of failure was increased in patients treated with multiple agents and in those with thrombocytopenia, hyperbilirubinemia or oral involvement at the beginning of secondary treatment. None of the 3 response definitions showed strong correlation with the risk of subsequent failure (Table).

Table. Correlation of response after secondary treatment with subsequent failure

Response definition	Response at 6 months	N	Cumulative incidence of failure*	P
CR in any organ	Y	103	37%	0.66
	N	65	43%	
Prednisone dose <0.25 mg/kg/day	Y	104	35%	0.05
	N	66	47%	
CR in any organ and prednisone dose <0.25 mg/kg/day	Y	64	34%	0.25
	N	103	43%	

*At 2 years after the beginning of secondary treatment.

Conclusion: Secondary treatment for chronic GVHD is associated with a 48% failure rate at one year, with failure predicted by thrombocytopenia, hyperbilirubinemia or oral involvement. Unlike the results reported for primary treatment, a composite of response and steroid dose would not perform well as a surrogate endpoint in secondary treatment studies.

53

EXTRACORPOREAL PHOTOPHERESIS: EFFECTIVE THERAPY FOR STEROID DEPENDENT AND REFRACTORY ACUTE GRAFT-VERSUS-HOST DISEASE

Jacobs, R.W.[1], Jagasia, M.H.[2], Savani, B.N.[2], Neff, A.T.[2], Engelhardt, B.G.[2], Goodman, S.[2], Greer, J.P.[2], Proctor, K.[2], Schuening, F.[3], Russell, N.H.[4], Das-Gupta, E.[4] [1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN; [3]St. Louis University, St. Louis, MO; [4]Nottingham University Hospital, Nottingham, United Kingdom

Outcome of patients (pts) with steroid refractory (SR) acute graft-versus-host disease (aGVHD) remains poor. We studied the efficacy and outcome of extracorporeal photopheresis (ECP) used as salvage therapy for pts with SR (progression of aGVHD after 3 days or no response after 7 days of ≥ 1mg/kg of prednisone equivalent) or steroid dependent (SD) aGVHD (recurrence of aGVHD during steroid taper) at Vanderbilt University, USA (n = 29) and Nottingham, UK (n = 23). Responses to ECP were determined at completion of ECP. **Results:** 52 pts were treated for SD (29%) or SR (63%) grade 2-4 aGVHD. Indication for ECP was missing for 5 pts. Grade 3-4 aGVHD was present at onset in 29 (57%) pts with 3 organ involvement in 9 (17%) pts. Median duration of ECP was 55 days. At the end of ECP treatment, grade 3-4 aGVHD was present in 17 pts (33%). The median steroid dose at end of ECP in responders and non-responders was 0.15 mg/kg (range, 0-0.75) and 2 mg/kg (range, 0.15-2.3) (P<0.001). Donor type, stem cell source, GVHD prophylaxis, aGVHD grade at onset, and organ specific stage did not impact response. ECP response was superior for aGVHD developing after ablative regimen (76%) compared with other regimens (48%) (P = 0.05). Pts with response at 7 days after initial steroid treatment and subsequent steroid dependent aGVHD had a better response with ECP (80% vs. 50%, P = 0.042). In logistic regression analyses, adjusted for regimen intensity, response after 7 days of initial steroid therapy showed a trend for predicting ECP response (OR = 4.22, 95% CI 0.95-18.7, P = 0.058). 2-yr overall survival in all patients and in ECP responders was 42% and 65%, respectively. Median survival after ECP onset was superior for pts receiving an ablative compared to other regimens (not reached vs. 44 days, P = 0.05), and grade 1-2 aGVHD compared to grade 3-4 aGVHD at onset (not reached vs. 79 days, P = 0.028). SD or SR status did not impact survival. Pts with ECP response had a superior survival (measured from end of ECP) compared to non-responders (median survival, not reached vs. 14 days, P<0.001). In Cox proportional analyses, response to ECP was an independent predictor of survival (HR 0.091, 95% CI 0.034-0.263, P<0.001), adjusted for regimen intensity and aGVHD grade at onset.

Conclusion: ECP is an effective steroid-sparing salvage therapy for pts with SD/SR aGVHD. It is reasonable to undertake a prospective randomized study of ECP versus other agents, in pts with SD/SR aGVHD.

Table. GVHD, ECP and Response Characteristics of Patients (N = 52)

Variable	N (%)
aGVHD (steroid dependent/refractory) Characteristics	
After first transplant	44 (85)
After second transplant	1 (2)
After donor lymphocyte infusion	7 (13)
Skin involvement (stage 3 or 4) at ECP onset	28 (37)
Gastrointestinal involvement at ECP onset	15 (29)
Liver involvement at ECP onset	9 (18)
Steroid therapy for aGVHD	
Duration of steroids prior to ECP, median, days (range)	18 (10-91)
Steroid dose 1 mg/kg	24 (46)
Steroid dose 2 mg/kg	26 (50)
ECP Characteristics	
Time to onset of ECP, median, days (range)	59 (12-99)
ECP treatments, median (range)	12 (2-45)
ECP response	
Complete response	26 (50)
Partial response	6 (12)
Skin involvement (stage 3 or 4) at end of ECP	4 (8)
Gastrointestinal involvement at end of ECP	10 (20)
Liver involvement at end of ECP	10 (20)
Survival Characteristics	
Follow-up, median, days (range)	309 (12-1657)
Alive/Deceased	24 (46)/28 (54)
Median survival (measured from ECP onset), days (95% CI)	442 (0-993)