Extracorporeal photopheresis as second-line treatment for acute graft-*versus*-host disease: impact on six-month freedom from treatment failure

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ABSTRACT

Second-line therapy for corticosteroid-refractory or -dependent acute graft-*versus*-host disease remains ill-defined, due to limited efficacy of drugs and evolving clinical trial endpoints. Six-month freedom from treatment failure has been proposed as a novel clinical trial endpoint and is defined by the absence of death, malignancy relapse/progression, or addition of a next line of systemic immunosuppressive therapy within 6 months of intervention and prior to diagnosis of chronic graft-*versus*-host disease. We analyzed the 6-month freedom from treatment failure endpoint in 128 patients enrolled from three centers who were treated with extracorporeal photopheresis as second-line therapy for acute graft-*versus*-host disease. The incidence of 6-month freedom from treatment failure was 77.3% with a 2-year survival rate of 56%. Corticosteroid dose or response status at onset of second-line therapy did not influence outcome. Higher grade of acute graft-*versus*-host disease (grade 2 *versus* grades 3-4) at onset of photopheresis predicted for poor outcome as measured by survival (hazard ratio 2.78, $P<0.001$), non-relapse mortality (hazard ratio 2.78, $P=0.001$) and 6-month freedom from treatment failure (hazard ratio 3.05, $P<0.001$). For the 91 patients who achieved 6-month freedom from treatment failure, 1-year, 2-year and 3-year survival rates were 78.9%, 70.8% and 69.5%, respectively. Six-month freedom from treatment failure is a reasonable early surrogate for outcome and should be considered as a clinical trial endpoint. This study demonstrates the durable effect of photopheresis as second-line therapy for corticosteroid-refractory or -dependent acute graft-*versus*-host disease using 6-month freedom from treatment failure as the primary endpoint.

Introduction

Acute graft-*versus*-host disease (GVHD) remains a serious complication of allogeneic hematopoietic stem cell transplantation. Despite prophylaxis, acute GVHD of grade B-D according to the International Bone Marrow Transplantation Registry severity index occurs in 39% to 59% of patients receiving a T-replete related or unrelated donor allogeneic stem cell transplant.[1] The incidence and outcome of acute GVHD are influenced by a variety of risk factors.[1,2] First-line and salvage therapy remain corticosteroid-based, with clinical response and overall survival assessed at various time points after therapy being the primary endpoint of most clinical trials and retrospective studies.[3-5] Response parameters are prone to be confounded by various clinical etiologies and inter-observer variability. Corticosteroid-based initial therapy for patients with ≥grade 2 or B-D acute GVHD[6-8] reportedly leads to a complete response in 25% to 69% of patients.[6,9,10] A recent randomized study failed to show an improvement in outcome with addition of mycophenolate mofetil to corticosteroids for primary therapy of acute GVHD.[11]

Patients not responding to corticosteroids have a dismal survival.[2,4,6,7] Given the limited efficacy of corticosteroid-based therapy, second-line therapy for corticosteroid-refractory (SR) or corticosteroid-dependent (SD) acute GVHD remains an active area of clinical investigation. Multiple agents have been studied for SR acute GVHD.[4,12-14] Augmenting immunosuppressive therapy may lead to clinical responses but has been associated with increased risk of relapse, due to a decrease in the graft-*versus*-tumor effect and non-relapse-related complications, especially serious opportunistic infections. The clinical response of acute GVHD in isolation can, therefore, be misleading for patients' overall outcome and is problematic when used as the main study endpoint for second-line therapy of acute GVHD. The American Society for Blood and Marrow Transplantation (ASBMT) has recently proposed 6-month freedom from treatment failure (FFTF) as a clinical trial endpoint. The ASBMT 6-month FFTF is defined by the absence of death, malignancy relapse/progression, or addition of systemic immunosuppressive therapy within 6 months of intervention and prior to the diagnosis of chronic GVHD.[4,15] In a recent prospective study, the day 28 response and 6-month FFTF after primary therapy for acute GVHD were reported as 86% and 64%, respectively.[16]

Single center studies suggest that extracorporeal photophere-

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sis (ECP) using ultraviolet-A irradiation of peripheral blood mononuclear cells after incubation with 8-methoxypsoralen is an effective treatment for SR acute GVHD.[17-19] Here, we present the results from three centers administering ECP as second-line therapy for SR and SD acute GVHD using 6-month FFTF as an endpoint. The goals of this retrospective study were: (i) to describe the incidence of 6-month FFTF when ECP is used as second-line therapy of SR or SD acute GVHD and to identify causes of treatment failure; (ii) to identify the pre-transplant and acute GVHD characteristics associated with a higher incidence of 6-month FFTF; and (iii) to show that 6-month FFTF is a reasonable surrogate endpoint to predict overall survival and non-relapse mortality (NRM).

Methods

All patients receiving ECP for second-line therapy for SR or SD acute GVHD from November 1995 to May 2011 were included in this study. Three centers (Nashville, USA; Nottingham, UK; and Vienna, AT) contributed to the study. The study protocol was reviewed and approved by the Human Subject Institutional Review Board (IRB) at Vanderbilt University Medical Center, Nashville, USA. All patients were transplanted on standard of care or Institutional Review Board-approved protocols and consented to data release.

Acute GVHD was diagnosed clinically and was confirmed by biopsy at the discretion of the treating physician. The clinical severity of acute GVHD was determined by the organ specific stage (0-4) and composite grade (0-4) as defined by the 1994 consensus conference criteria.[20] All patients were treated with corticosteroids at a dose of at least 1 mg/kg/day alone as first-line therapy of acute GVHD with continuation of calcineurin inhibitors. SR acute GVHD was defined as progressive acute GVHD within 3 days or no response within 7 days of starting systemic corticosteroids (1 - 2 mg/kg). SD acute GVHD was defined as recurrence of acute GVHD during corticosteroid tapering. Patients developing GVHD after donor lymphocyte infusion were excluded (n=11).

ECP was initiated at a frequency of two or three treatments per week on a weekly basis for the first 4-6 weeks followed by every other week. ECP was stopped after achieving maximal response (Vienna, Nottingham) or was gradually tapered after achieving a response (Vanderbilt). The severity of acute GVHD was assessed weekly by the treating physician. A complete response was defined as complete resolution of all symptoms and signs (including laboratory abnormalities). A partial response was defined as some improvement. The timing of response assessment after ECP was not standardized and varied among the participating centers. Tapering of corticosteroids and other immunosuppressive therapy was at the discretion of the treating physician. All patients received supportive care according to institutional criteria.

Statistics

Descriptive statistics were calculated and groups were compared using the chi-square test (nominal variables) and Wilcoxon rank-sum test (continuous variables). Two proportion tests were used to compare stage of GVHD before and after therapy. Overall survival was measured from the initiation of ECP using Kaplan-Meier survival curves and compared using the log-rank test.[21] NRM was defined as death due to any cause, with death due to relapse as a competing risk. For the 6-month FFTF analysis, an event was defined as a relapse death or addition of new systemic immunosuppressive therapy within 6 months of initiating ECP and prior to a diagnosis of chronic GVHD. Multivariable analyses were performed using logistic regression or Cox proportional hazard regression. The analyses were conducted using SPSS version 20 (SPSS Inc., Chicago, IL, USA) or R version 2.7.0 (Free Software Foundation, Boston, MA, USA).

Results

Table 1 provides the demographics, pre-transplant and GVHD characteristics of the 128 patients, stratified by SR (78 patients) or SD (50 patients) status. Ten (8%), 27 (21%) and 91 (71%) patients were from the centers in Nottingham (UK), Nashville (USA) and Vienna (Austria), respectively. In the SR subgroup, these centers contributed 11%, 17% and 72% of the patients. In the SD subgroup, the centers contributed 2%, 28%, and 70% of the patients. Three-organ involvement at onset of ECP was seen in 22% and 20% of patients with SR and SD acute GVHD, respectively. Among patients with grades 3-4 acute GVHD, involvement of three organs was seen in 58% (14 of 24) and 64% (9 of 14) of patients within the SR and SD subgroups, respectively.

The median time to start of ECP after hematopoietic stem cell transplantation was 42 days (range, 17-121 days). The median duration of ECP therapy was 60 days (range, 2-324 days). The median number of ECP treatments was 11 (range, 2-42). Only five patients started ECP beyond day 100 after hematopoietic stem cell transplantation, and in only 20% of these did the duration of ECP exceed 120 days for ECP maintenance or for chronic GVHD. The median dose of corticosteroids at the onset of ECP was 2 mg/kg (range, 0.5 to 10 mg/kg) with no difference between the SR (median of 2 mg/kg; range, 0.5 to 10 mg/kg) and SD (median of 2 mg/kg; range, 0.5 to 4 mg/kg) groups. There was no significant difference in steroid dosing among the three centers.

Overall survival and non-relapse mortality

The overall response rate was 77% (99 of 128 patients). There was no difference between response rate in patients with SR or SD acute GVHD (72% *versus* 86%, P=0.061). Further analyses of predictors of response and association of response with overall survival, NRM and 6-month FFTF were not undertaken, given lack of standardized time points of response assessments at the three centers.

The median follow-up of the cohort was 23.3 months (range, 0.6 to 194.1 months). Sixty-three (49.2%) patients died with a 2-year overall survival of 56% and a median survival of 41.4 months (95% CI, 0-125). GVHD accounted for 46%, 49% and 43% of the deaths in entire group, and the SR and SD subgroups respectively. Relapse of underlying disease led to death in 25%, 14% and 39% in these groups. The 2-year cumulative incidence of relapse was 12.9%. The causes of death did not differ between the SR and SD subgroups. The 2-year cumulative incidence of chronic GVHD was 34.2% (Figure 1) for the entire cohort.

In univariate analyses (Table 2), regimen intensity, stage of liver involvement, overall grade of acute GVHD and number of organs involved were associated with overall survival. There was no difference in 2-year overall survival between the SR and SD subgroups (62.5% *versus* 48.2%, P=0.283). As the grade of GVHD encompasses the stage and number of organs involved, only grade of acute GVHD was used in the multivariable model. Adjusted for donor status, steroid dose (≤1 mg/kg *versus* >1 mg/kg), steroid responsiveness (SR *versus* SD), and regimen intensity, acute GVHD (grade 2 *versus* 3-4) (HR 2.78, 95% CI 1.67-4.62, P<0.001) remained an inde-

pendent predictor of overall survival.

The 2-year cumulative incidence of NRM was 33.8% (Figure 2). NRM was similar in the subgroups with SR or SD acute GVHD (P=0.70). NRM was influenced by regimen intensity, stage of gastrointestinal and liver involvement, overall grade of acute GVHD and number of organs involved (Table 2). In multivariate analyses, both acute GVHD grade (grade 2 *versus* 3-4) (HR 2.78, 95% CI 1.46-5.28, P=0.001) and liver stage (stage 2 or less *versus* stage 3-4) (HR 2.27, 95% CI 1.06-4.83, P=0.033) predicted for higher NRM.

Six-month freedom from treatment failure

The incidence of remaining free of treatment failure at 6 months after initiation of ECP was 77.3% (Figure 3, panel A). Chronic GVHD developed in 25 patients (19.5%) within 6 months of initiating ECP and was not counted as a failure of ECP. The causes of failure (n=37) were addition of third-line systemic therapy (17 patients, 13.3%), death from relapse (6 patients, 4.7%) and NRM (14 patients, 10.9%). Sixty-six patients (51.6%) remained free of treatment failure without development of chronic GVHD at 6 months after the onset of ECP. In univariate analyses (Table 2), only grade of acute GVHD was associated with 6-month FFTF. In multivariable analyses, grade of acute GVHD (grade 2 *versus* 3-4) (HR 3.05, 95% CI 1.59-5.86, P<0.001) remained an independent predictor of treatment failure. The 2-year NRM and 2-year overall survival of the 17 patients who required third-line therapy was 57.9% and 40.3%, respectively.

For the 91 patients who achieved 6-month FFTF after ECP, 1-year, 2-year and 3-year overall survival rates were 78.9%, 70.8% and 69.5%, respectively (Figure 3, panel B). In these patients, causes of death after meeting the initial 6-month FFTF (Table 3) included GVHD (14 patients, 15.4%), relapse (9 patients, 9.9%), infections (6 patients, 6.6%) and other causes (3 patients, 3.3%). The 2-year cumulative incidence of NRM for patients achieving 6-month FFTF was 22.4% (Figure 3, panel C). Pre-ECP steroid response status (SR *versus* SD: 12.6% *versus* 31.1%, P=0.059) and grade of acute GVHD (grade 2 *versus* grade 3-4: 17.2% *versus* 31.2%, P=0.031) (Figure 3, panel D) influenced NRM. The 2-year overall survival for patients achieving 6-month FFTF was not affected by steroid response status (SR *versus* SD: 78.3% *versus* 45.3%; P=0.086) or grade of acute GVHD (grade 2 *versus* grades 3-4: 71.3% *versus* 63.1%; P=0.207).

Discussion

Our study shows that ECP can effectively salvage patients with SR or SD acute GVHD when used as second-line therapy with a 2-year overall survival of 56%. As far as we know, this is the numerically largest study on the efficacy of ECP as second-line therapy of SR and SD acute GVHD. First, we found that the incidence of 6-month FFTF using ECP as second-line therapy was 77.3%. Second, the grade of acute GVHD (grade 2 *versus* 3-4) at the onset of second-line therapy remained an important determinant of outcome and influenced overall survival, NRM and 6-month FFTF. Interestingly, steroid dose at the onset of second-line therapy or SR/SD status did not affect overall survival, NRM, or 6-month FFTF. Thus, initiation of second-line ECP prior to progression of acute GVHD to grades 3-4 could have substantial benefits for this cohort of patients. Patients who had grade 2 acute GVHD at onset of second-line therapy and achieved 6-month FFTF had 2-year NRM and 2-year overall survival rates of 17.2% and 71.3%, respectively, suggesting that earlier intervention with ECP in the disease course can improve survival. Third, our study demonstrated that patients who

Table 1. Pre-transplant, acute GVHD characteristics, and response to ECP stratified by corticosteroid-refractory and -dependent status.

Variable	All patients (n=128) N (%)	Steroid-refractory (n=78) N (%)	Steroid-dependent (n=50) N (%)
Pre-transplant characteristics			
Age, median (years) (range)	41.9 (17-66.8)	42 (17-66.8)	41 (21-66.2)
Gender, recipient			
Male	66 (52)	40 (51)	26 (52)
Female	62 (48)	38 (49)	24(48)
Donor type			
Related	29 (23)	22 (28)	7 (14)
Unrelated	99 (77)	56 (72)	43 (86)
Stem cell source			
Marrow	44 (34)	23 (30)	21 (42)
Peripheral blood	77 (60)	52 (67)	25 (50)
Umbilical cord	7 (6)	3 (3)	4 (8)
Regimen intensity			
Ablative	99 (77)	55 (71)	44 (88)
RIC/NMA	29 (23)	23 (30)	6 (12)
HLA match			
10/10	88 (69)	55 (71)	33 (66)
Other	40 (31)	23 (29)	17 (34)
In-vivo T-cell depletion			
None	117 (91)	71 (91)	46 (92)
ATG/alemtuzumab	11 (9)	7 (9)	4 (8)
Acute GVHD grade/stage at onset of ECP			
Skin			
≤ stage 2	101 (79)	61 (78)	40 (80)
Stage 3-4	27 (21)	17 (22)	10 (20)
Gastrointestinal			
≤ stage 2	81 (63)	44 (56)	37 (74)
Stage 3-4	47 (37)	34 (44)	13 (26)
Liver			
≤ stage 2	108 (84)	61 (78)	47 (94)
Stage 3-4	20 (16)	17 (22)	3 (6)
Overall grade			
Grade 2	90 (70)	54 (69)	36 (72)
Grades 3-4	38 (30)	24 (31)	14 (28)
Number of organs involved			
< 3 organs involved	101 (79)	61 (78)	40 (80)
3 organs involved	27 (21)	17 (22)	10 (20)
Steroid dose (mg/kg) at onset of ECP			
≤1mg/kg	27 (21)	10 (13)	18 (36)
>1 mg/kg	100 (78)	68 (87)	32 (64)
Days of steroid prior to onset of ECP, median (range)	19 (2-91)	13 (4-82)	24 (2-91)
Response to ECP			
No response	29 (23)	22 (28)	7 (14)
Overall response (CR+PR)	99 (77)	56 (72)	43 (86)
Complete response	86 (87)	48 (86)	38 (88)
Partial response	13 (13)	8 (14)	5 (12)

CR: complete response; PR: partial response; RIC: reduced intensity conditioning; NMA: non-myeloablative; HLA: human leukocyte antigen; ATG: anti-thymocyte globulin; DLI: donor lymphocyte infusion.

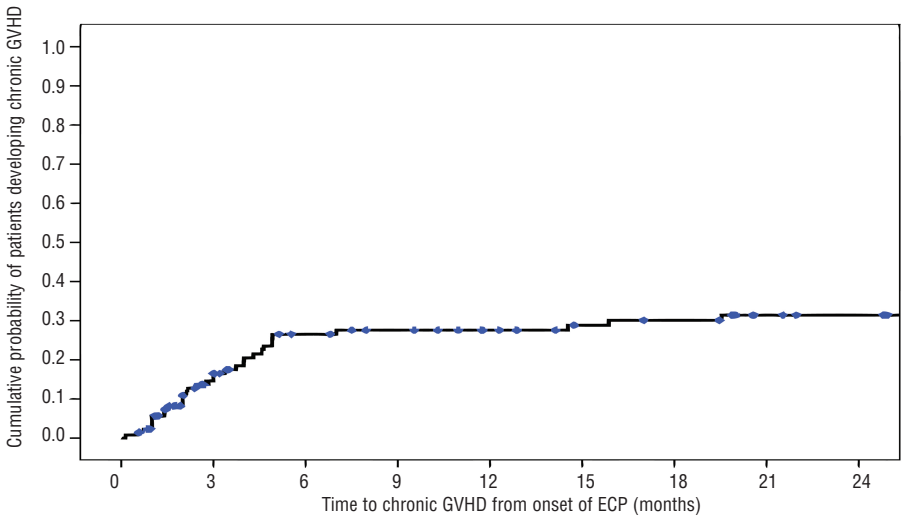

Figure 1. Two-year cumulative incidence of developing chronic graft-*versus*-host disease for all patients.

achieve 6-month FFTF maintained an excellent outcome with 1-year, 2-year and 3-year overall survival rates of 78.9%, 70.8% and 69.5%, respectively.

Traditionally, acute GVHD clinical trials have focused on clinical response rates and overall survival, without accounting for salvage therapy required after occurrence of an initial response. Thus, responses at day 28 and day 56, although excellent surrogates for 2-year survival after first-line therapy, may not be as valid for second-line therapy.[3] These time-dependent response assessments are still important in the conduct of clinical trials, to guide schedules for tapering immunosuppressive therapy and to define progression of acute GVHD. Unfortunately, therapy for SR and SD acute GVHD has not improved despite multiple clinical trials.[4,12,13] It has become obvious that augmenting systemic immunosuppression does not necessarily lead to meaningful improvements in patients' outcome, as shown by the lack of efficacy of the addition of anti-thymocyte globulin to corticosteroids or further escalation of corticosteroid doses.[22,23] Studying response as a sole indicator of success is not valid for second-line therapy, as deaths from relapse/progression due to abrogation of the graft-*versus*-tumor effect, infections, and other non-relapse causes of death can complicate second-line therapy. Additionally, it is unclear whether the Food and Drug Administration or the European Medicines Agency would approve a new drug based on response endpoints alone. The ASBMT recommended 6-month FFTF as a composite endpoint that is objective and not dependent on response criteria that are prone to inter-observer variability. The 6-month FFTF is analogous to progression-free survival in medical oncology. Data support the use of progression-free survival as a surrogate for overall survival.[24-26] Our study validates the hypothesis that achieving 6-month FFTF is associated with excellent survival and can be used as a primary endpoint for clinical trials. The 2-year NRM of this group of patients still remains high at 22.4%, suggesting subsequent GVHD progression and secondary late effects of therapy remain important barriers.

Recent data suggest that in patients receiving corticosteroids as initial therapy for grades 2-4 acute GVHD, response rates can be high, but only 64% of the patients met the 6-month FFTF endpoint.[16] In our study of second-line therapy, the likelihood of achieving 6-month FFTF was 77.3%. Current generation anti-cytokine therapy has shown minimal impact on the outcome of patients with SR acute GVHD with responses in the 30% range and a 2-year overall survival rate of 30%[12]. In our study, 66.7% of SR patients achieved the 6-month FFTF endpoint with a 2-year overall survival rate of 62.5%. A multicenter retrospective study in patients with SR acute GVHD showed a higher response rate to ECP than to anti-cytokine therapy, which translated into an overall survival benefit.[27] The cumulative 2-year NRM rate in patients who achieved 6-month FFTF was 22.4%, with infections accounting for 6.6% of the deaths. This suggests that ECP does not cause generalized immunosuppression leading to an increased risk of severe opportunistic infections. This should be an important consideration when planning prospective randomized studies for SR/SD acute GVHD patients incorporating ECP as an efficient treatment modality.

Our study raises several unanswered questions regarding second-line therapy for acute GVHD. First, the timing of second-line therapy for patients with SR acute GVHD is not well defined. Patients can meet the definition of SR acute GVHD as early as 3-7 days after the start of initial therapy. The addition of anti-thymocyte globulin as early as day 5 in non-responders to initial therapy, or escalation of corticosteroids to a higher dose has not been able to salvage patients effectively.[6,22] Recent recommendations suggest that it is reasonable to consider starting second-line therapy in progressive acute GVHD after 3 days of corticosteroids and lack of improvement after 7 days (grades 3-4 acute GVHD) or 14 days (grade 2 acute GVHD).[4] Earlier intervention should be considered to avoid multi-organ involvement and higher grade of acute GVHD, which was associated with worse overall survival in our study. A significantly lower transplant-related mortality in patients with shorter interval from day 0 until start of ECP was previously reported.[18] Second, the optimal frequency, duration and tapering schedule of ECP in SR/SD acute GVHD remain important unanswered issues. Although ECP requires multiple treatments, most patients are in the vicinity of the transplant center during the first 3-4 months after hematopoietic stem cell transplantation, thus logistics should not be a barrier to considering ECP. The median number of ECP treatments was 12, suggesting that prolonged courses of ECP may not be neces-

sary.[18] Intensified weekly ECP is suggested to improve responses in gut and grade 4 acute GVHD.

Our study has some limitations. First, the study cohort consisted of 128 patients from three centers over a 16-year period. We analyzed for center effect in both univariate and multivariate analyses but did not detect any statistically significant differences. Although all patients who received ECP for second-line therapy for SR or SD acute GVHD were included in the study, the choice of ECP *versus* other agents was at the discretion of the treating physician. Biopsy confirmation of acute GVHD prior to starting ECP was physician-dependent. Supportive care standards could have contributed to differences in outcome and were not analyzed in this study. Second, although both SR and SD patients were included, the dose and duration of corticosteroid exposure, the frequency, schedule, and duration of ECP, and the tapering of immunosuppressive therapy varied and could have influenced treatment outcome. Third, our study does not include detailed analyses of chronic GVHD subtypes, as the assessment of chronic GVHD has changed significantly over the last decade. It would be important to study the impact of ECP used for second-line therapy for acute GVHD on incidence, organ manifestations and severity of chronic GVHD using the National Institutes of Health criteria and classification in future studies. Fourth, 6-month FFTF as a clinical trial endpoint does have some limitations as well. It does not include quality of life metrics. Given the low morbidity of ECP, and its corticosteroid-sparing effect as well as the low risk of infections, it is likely that quality of life may be favorably affected by ECP, as has been reported in patients with chronic GVHD.[28-30] Six-month FFTF in a prospective study can be confounded by treatment biases, as

Table 2. Univariate analyses: overall survival, non-response mortality and 6-month freedom from treatment failure.

	2-year overall survival		2-year NRM		6-month FFTF	
Pre-transplant characteristics	**(%)**	***P***	**(%)**	***P***	**(%)**	***P***
Donor type						
Related	58.6	0.886	36.4	0.548	62.1	0.177
Unrelated	56.3		31.2		73.7	
Stem cell source						
Peripheral blood	59.1	0.902	34.7	0.287	75.3	0.247
Other	53.7		28.8		64.7	
Regimen intensity						
Ablative	59.6	0.034	29	0.04	73.7	0.123
Other	48		43.9		62.1	
HLA match						
10/10	56	0.912	34.7	0.387	69.3	0.46
Other	59.4		26.5		75	
In-vivo T-cell depletion						
None	57.4	0.934	31.8	0.691	71.8	0.541
ATG/alemtuzumab	53		37.9		63.6	
Acute GVHD characteristics at onset of ECP						
Skin						
≤ stage 2	57.7	0.834	29.5	0.334	73.3	0.307
Stages 3-4	53.8		42.5		73	
Gastrointestinal						
≤ stage 2	58.2	0.323	28.7	0.063	71.6	0.867
Stages 3-4	52.5		38.7		70.2	
Liver						
≤ stage 2	61.2	0.005	27.3	<0.001	73.1	0.224
Stages 3-4	33.3		61.7		60	
Overall grade						
Grade 2	65.7	<0.001	23	<0.001	79	0.002
Grades 3-4	36.2		53.3		52.6	
Number of organs involved						
< 3 organs	60.5	0.007	27.4	0.002	74.3	0.148
3 organs	39.9		50.6		59.3	
Variable						
Steroid dose (mg/kg) at onset of ECP						
≤1 mg/kg	61.4	0.379	31.2	0.587	74.1	0.699
>1 mg/kg	56.3		31.9		70	
Steroid status						
Refractory	62.5	0.283	32.6	0.701	66.7	0.148
Dependent	48.2		32		78	

ATG: anti-thymocyte globulin.

escalation or tapering of corticosteroid doses, or introduction of additional immunosuppressive therapy is physician-dependent. Prospective clinical trials could mandate a minimal duration of initial corticosteroid doses and *a priori* defined benchmarks of corticosteroid dose at certain time-points after enrollment. Failure to reach these benchmarks could constitute treatment failure. The feasibility of implementing such benchmarks in multicenter clinical trials needs to be tested.

In summary, ECP is an effective intervention for SR and SD acute GVHD as second-line therapy and is associated with a high incidence of 6-month FFTF. This study along with other ongoing efforts exploring the role of ECP in acute GVHD will allow clinical investigators to design prospective, risk-stratified clinical trials targeting ECP as an intervention for front-line or second-line therapy. Additionally, the 6-month FFTF reported in this study could be used as a historical comparator for future phase 2 clinical trials exploring novel immunosuppressive agents. Given the encouraging results of ECP in SR/SD acute GVHD, it is reasonable to consider a prospective, randomized, phase 3 second-line study of corticosteroids plus ECP *versus* an accepted institutional standard of care using 6-month FFTF as the primary endpoint. Furthermore, front-line treatment with ECP plus corticos-

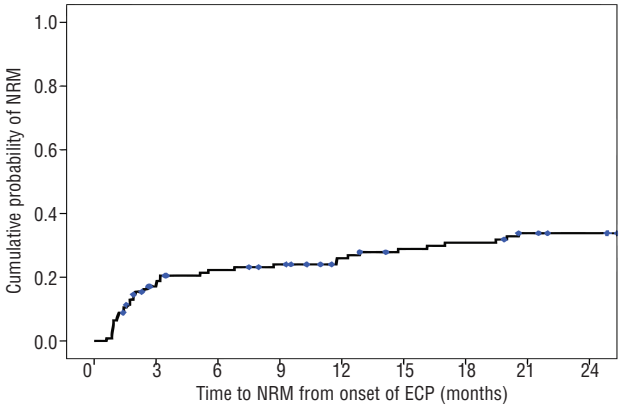

Figure 2. Two-year cumulative incidence of non-relapse mortality (NRM) for all patients.

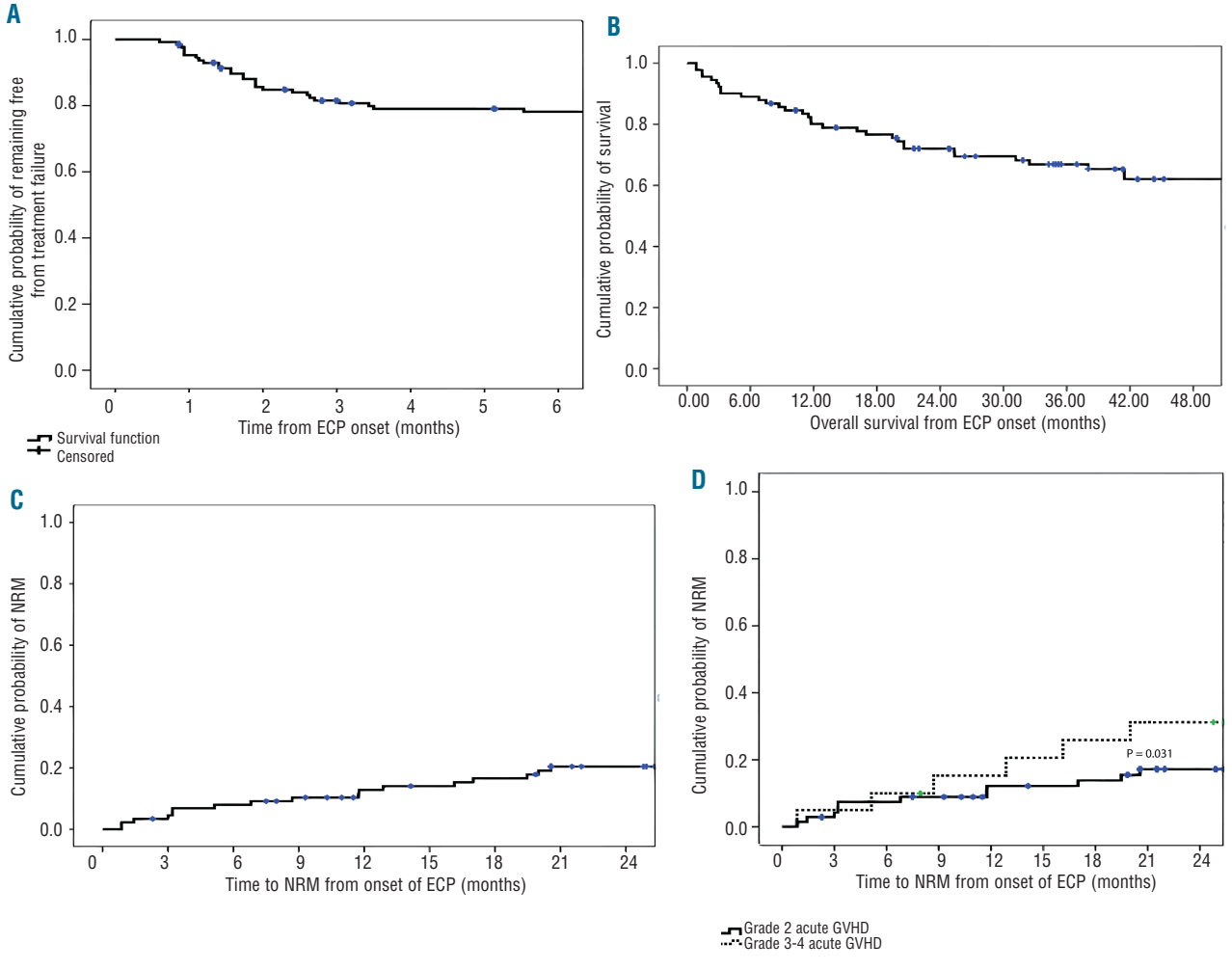

Figure 3. (A) Six-month freedom from treatment failure survival for all patients. (B) Overall survival from onset of extracorporeal photopheresis for patients achieving 6-month freedom from treatment failure. (C) Two-year cumulative incidence of non-relapse mortality for patients achieving 6-month freedom from treatment failure. (D) Two-year cumulative incidence of non-relapse mortality for patients achieving 6-month freedom from treatment failure stratified by grade 2 *versus* grades 3-4 acute graft-*versus*-host disease.

Table 3. Causes of death: all patients, patients achieving 6-month freedom from treatment failure, patients not achieving 6-month freedom from treatment failure.

Variable	Entire cohort# Total deaths (n=63) (%)	6 m FFTF Achieving end-point* and subsequently deceased Total deaths (n=32) (%)	6 m FFTF Not achieving end-point## Total deaths (n=31) (%)
Acute GVHD	17 (27)	11 (34)	6 (19)
Chronic GVHD	12 (19)	3 (9)	9 (29)
Relapse	16 (25)	9 (29)	7 (23)
Infection	13 (21)	6 (19)	7 (23)
Other	5 (8)	3 (9)	2 (6)

*# Entire cohort =128; * Achieving endpoint=91 patients; ## Not achieving endpoint=37 patients.*

teroids *versus* corticosteroids alone should be evaluated in patients with acute GVHD in a prospective, randomized trial.

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Authorship and Disclosures

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