Bone Marrow Transplantation (2021) 56:1316–1324
https://doi.org/10.1038/s41409-020-01188-4

ARTICLE

Randomized phase II trial of extracorporeal phototherapy and steroids vs. steroids alone for newly diagnosed acute GVHD

Rohtesh S. Mehta[1] · Roland Bassett[2] · Gabriela Rondon[1] · Bethany J. Overman[1] · Uday R. Popat[1] · Chitra M. Hosing[1] · Katy Rezvani[1] · Muzaffar H. Qazilbash[1] · Paolo Anderlini[1] · Roy B. Jones[1] · Partow Kebriaei[1] · David Marin[1] · Issa F. Khouri[1] · Betul Oran[1] · Stefan O. Ciurea[1] · Kayo Kondo[1] · Daniel R. Couriel[3] · Elizabeth J. Shpall[1] · Richard E. Champlin[1] · Amin M. Alousi[1]

Received: 22 August 2020 / Revised: 1 October 2020 / Accepted: 2 December 2020 / Published online: 4 January 2021

Abstract

Steroids remain the initial therapy for acute graft-vs.-host disease (AGVHD). Strategies to improve response and minimize steroid exposure are needed. We report results of a randomized, adaptive, Bayesian-designed, phase II trial of prednisone with or without extracorporeal photopheresis (ECP) as an initial therapy for patients with newly diagnosed AGVHD. The primary endpoint was success at day 56 defined as: alive, in remission, achieving AGVHD response without additional therapy, and on <1 mg/kg at day 28 and <0.5 mg/kg on day 56 of steroids. Eighty-one patients were randomized to the ECP arm ($n = 51$) or steroids alone ($n = 30$). Median age was 54 years (range: 17–75); 90% had grade II AGVHD and 10% had grades III and IV AGVHD, with skin (85%), upper (22%)/lower (22%) gastrointestinal, and liver (10%) involvement. The ECP arm had a higher probability of success (0.815) and exceeded the predefined threshold for determining the investigational arm promising. ECP was potentially more beneficial than steroids-alone in skin-only AGVHD (response rate: 72% vs. 57%, respectively) than for visceral-organ AGVHD (47% vs. 43%, respectively). The addition of ECP to steroids may result in higher GVHD response as initial therapy for AGVHD, especially for patients with skin-only involvement.

Introduction

Acute graft-vs.-host disease (AGVHD) is a major limitation of allogeneic hematopoietic cell transplantation (AHCT). Prednisone (or methylprednisolone, MP) at a dose of 2 mg/kg/day remains the standard initial therapy with 40–70% of patients achieving a response by day 28 [1–5]. Efforts to improve outcomes through the addition of a second agent have proven unsuccessful in randomized control trials [6–11]. As steroids are associated with considerable toxicity [12], therapies that can improve GVHD response, facilitate steroid tapering, and are themselves limited in side-effects are needed.

Extracorporeal photopheresis (ECP) is an immunomodulatory therapy Food and Drug Administration approved for the treatment of patients with cutaneous T-cell lymphoma [13]. ECP results in apoptosis of leukocytes and infusion of these cells are believed to result in a tolerogenic response and modulation of cytokine production [14–18]. The procedure involves separation of leukocyte-rich plasma followed by ex vivo administration of a photosensitizer (8-methoxypsoralen) and exposure to ultraviolet A-irradiation before reinfusion. ECP is widely used for the treatment of patients with chronic GVHD with a randomized trial demonstrating improvement in the non-blinded investigator assessment of skin responses [19, 20]. Additionally, retrospective reports with ECP for the treatment of steroid-refractory AGVHD have demonstrated response rates from

Supplementary information The online version of this article (https://doi.org/10.1038/s41409-020-01188-4) contains supplementary material, which is available to authorized users.

✉ Amin M. Alousi
aalousi@mdanderson.org

[1] Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas Cancer Center, Houston, TX, USA

[2] Department of Biostatistics, The University of Texas Cancer Center, Houston, TX, USA

[3] Huntsman Cancer Center, University of Utah, Salt Lake City, UT, USA

44 to 58% with a favorable safety profile and limited overlapping toxicity with steroids [21–26]. However, to date, there have been no prospective trials in patients with AGVHD.

Based on the reported efficacy of ECP in acute and chronic GVHD, we started a phase II trial of ECP plus high-dose steroids vs. steroids alone in patients with newly diagnosed AGVHD, to obtain preliminary signals about potential efficacy of ECP, with a goal of pursuing a larger phase III trial if such an effect was noted.

Methods

Patients

Patients with new onset biopsy-proven AGVHD grades II–IV following an AHCT from any graft source or donor were eligible. Patients could not have received previous systemic immunosuppressive therapy for the treatment of AGVHD except for a maximum of 72 h of steroids (2 mg/kg/day prednisone or MP equivalent). Patients could have late AGVHD; however, those with chronic GVHD were excluded. The initial weight requirement of 40 kg was later reduced to 15 kg when the UVAR XTS was replaced by the CELLEX system (Therakos, Inc.). Patients were required to have an absolute white blood cell count of >1500/mL and be able to sustain (in the clinical judgment of the provider) a platelet count of ≥20,000/mL and hematocrit ≥ 27% with or without transfusion support. Patients were excluded if they were felt to be unable to tolerate the volume shifts associated with ECP due to an uncompensated medical condition, active bleeding, an international normalized ratio > 2 or uncontrolled, persistent hypertriglyceridemia with levels > 800 mg%. Patients with a known photosensitive disease, allergy, or hypersensitivity to psoralen, citrate, or heparin were excluded. The protocol (clinicaltrials.gov: NCT00609609) was approved by the Institutional Review Board of the University of Texas, MD Anderson Cancer Center. All patients or their surrogates signed informed consent in accordance with the Declaration of Helsinki.

Study design

This was a single-center, open-label, phase II, adaptively randomized Bayesian design. Randomization probabilities were based on the probability of treatment success (defined below) at day 56 post enrollment in each arm, stratified by skin only (protocol-defined standard risk) vs. visceral involvement (high risk). The Bayesian adaptive design called for the first 20 patients to be randomized fairly, after which the probability of assignment to an arm was based on the probability of success in each arm, so that successive patients were more likely to receive the treatment showing better results. Therakos, Inc. had no role in the design of the trial, collection or interpretation of the data, or authorship of the paper.

Treatment of AGVHD

Patients were randomized to either high-dose steroids alone or ECP plus high-dose steroids. ECP was initiated within 72 h of randomization using the UVAR (up until September 2012) or the CELLEX ECP systems (Therakos, Inc.). All patients in the ECP arm required the placement of a new central venous catheter (generally a non-tunneled Quinton catheter), which would support the apheresis procedure. The frequency of ECP was eight to nine sessions though day 14 post randomization, six sessions between days 15 and 28, eight sessions between days 29 and 56 (two sessions per week). After day 56, patients could continue ECP at the discretion of the patient's primary physician; however, therapy was neither mandated nor was it performed under the context of the trial.

Patients on both arms received steroids at a starting dose of prednisone 2 mg/kg/day (or MP equivalent), which could not be tapered below 1 mg/kg/day of prednisone before day 14, but otherwise decisions regarding the pace of tapering were at the discretion of the treating providers. Supportive care was identical between the arms and followed institutional practice. Patients on a calcineurin inhibitor for GVHD prophylaxis were continued with doses adjusted based on trough levels.

GVHD scoring, definition of response, and treatment success

Acute GVHD was scored as per the consensus criteria [27]. Complete remission required resolution of all signs and symptoms of GVHD in all organs without intervening salvage therapies. Partial response was an improvement of one stage in one or more organs without progression in any organ. No response was defined as absence of improvement within 14 days of therapy initiation for skin, 7 days for GI, and 21 days for liver. Progression was defined as worsening by one or more organ stages after a minimum of 72 h of high-dose steroids or receipt of second-line therapy at any time. Treatment success on day 56 (the primary endpoint) was defined as meeting all of the following criteria: be alive, in remission from malignancy, achieved AGVHD response without the need for additional therapy, be on <1 mg/kg of prednisone (or MP equivalent) on day 28 and <0.5 mg/kg of prednisone (or MP equivalent) on day 56. Patients who did not meet all criteria were considered treatment failures regardless of AGVHD response.

Statistical analysis

The main purpose of the trial was to study if ECP had potential merits, and to pursue a future larger clinical trial if a statistical signal in favor of ECP was noted in this phase II trial, rather than establishing definitive efficacy in this small phase II trial. The primary analysis was to calculate the Bayesian predictive probability that ECP had a higher success than steroids alone. Denoting the treatment failure rates for the ECP and steroids alone groups as f_{ECP} and f_S, respectively, and denoting the posterior probability that treatment with ECP had a lower failure rate as p_{ECP} (data) = $Pr(f_{ECP} < f_S)$ (response data assessed to date), the trial would have been stopped in favor of ECP if at any time p_{ECP}(data) > 0.95 and stopped in favor of steroids alone if at any time p_{ECP}(data) < 0.05. If no decision was made early to select either treatment as superior, the selection criterion at the end of the trial was to declare ECP superior if p_{ECP}(data) > 0.80 and steroids alone superior if p_{ECP}(data) < 0.20. Note that during the trial, the randomization probabilities were also based upon p_{ECP}(data) and p_S(data) following the initial 20 patients who were equally randomized between the groups.

The incidence of grade ≥ 3 toxicities or infections through 6 months and ECP-specific adverse events through day 56 were collected. The cumulative incidence of chronic GVHD, non-relapse mortality (NRM), and relapse was estimated using competing risks methods and compared between arms using the Gray test, with relapse as the competing risk for NRM, relapse and death in remission competing risks for chronic GVHD, and NRM as a competing risk for relapse. In addition, regression models were fit to the cumulative incidence data using the method of Fine and Gray. Overall survival (OS) was estimated using the Kaplan–Meier method and compared using between arms using the log-rank test. Cox proportional hazards regression models were also fit for OS. Adherence to ECP was determined calculating the percent of completed ECP sessions per calendar week through day 56 or the point of treatment failure.

Correlative studies

A subset of patients submitted whole-blood samples at baseline and posttreatment (between 2 and 6 months) for T-cell subset analysis (details in Supplementary 1).

Results

Patient characteristics

A total of 81 patients were adaptively randomized to either ECP ($n = 51$) or steroids alone ($n = 30$) between February 2008 and September 2014 (Fig. 1). The median age was 54 years (range: 17–75), and acute myeloid leukemia/myelodysplastic syndrome was the most common indication for transplant. A majority received myeloablative conditioning (69%) and had an unrelated donor (63%). The graft was peripheral blood (75%), marrow (19%), or umbilical cord blood (UCB, 6%). At enrollment 90% had grade II and 10% had grades III and IV AGVHD; with stages 1–4 skin (86%), stages 1–3 lower gastrointestinal (22%), upper gastrointestinal (22%), and stage 1 liver (10%) involvement. The median time posttransplant to enrollment was 35 days (range: 12–112). The arms were well balanced (Table 1), except patients on the ECP arm were more likely to have received an UCB (5 vs. 0) and a trend for more grades III and IV AGVHD cases at enrollment (14 vs. 3%, $p = 0.25$). There was also a trend for higher-risk patients (for relapse of underlying malignancy) on the ECP arm based on a disease risk index (DRI) of high/very high (37 vs. 17%, $p = 0.08$).

Adherence to ECP

Administering ECP early posttransplant was feasible. An average of 88.9% of the total planned ECP treatments were delivered (median 100%, range: 8.3–100%) and 69% of patients received ≥ 90% of planned sessions. The reasons for missed sessions (which were generally low) were not numerically captured, but were mainly related to scheduling conflicts or access issues.

Treatment success

Treatment success at day 56 post enrollment was the primary composite endpoint that consisted of patients being alive, in remission, achieving AGVHD response and meeting days 28 and 56 steroid dose requirements as mentioned above. After 81 patients were enrolled, the a priori defined statistical threshold was met in favor of the ECP arm with a probability of 0.815. Treatment success was noted in 36/51 (65%) patients in the ECP arm vs. 16/30 (53%) in steroids only arm. Although the study was not powered for subgroup analyses, the response appeared to be more dramatic in patients with skin-only AGVHD, with treatment success in 72% (26/36) vs. 57% (13/23), respectively. In comparison, among patients with visceral AGVHD, treatment success was noted in 47% (7/15) vs. 43% (3/7 patients), respectively (Table 2). Patients with treatment success (regardless of arm assignment) had a markedly lower risk for NRM when compared to those with treatment failure (hazard ratio (HR): 0.32; 95% confidence interval (CI): 0.15–0.68, $p = 0.003$) (Fig. 2).

There were a total of 32 treatment failures—18 in the ECP arm and 14 in the SOC arm. No failure occurred due to

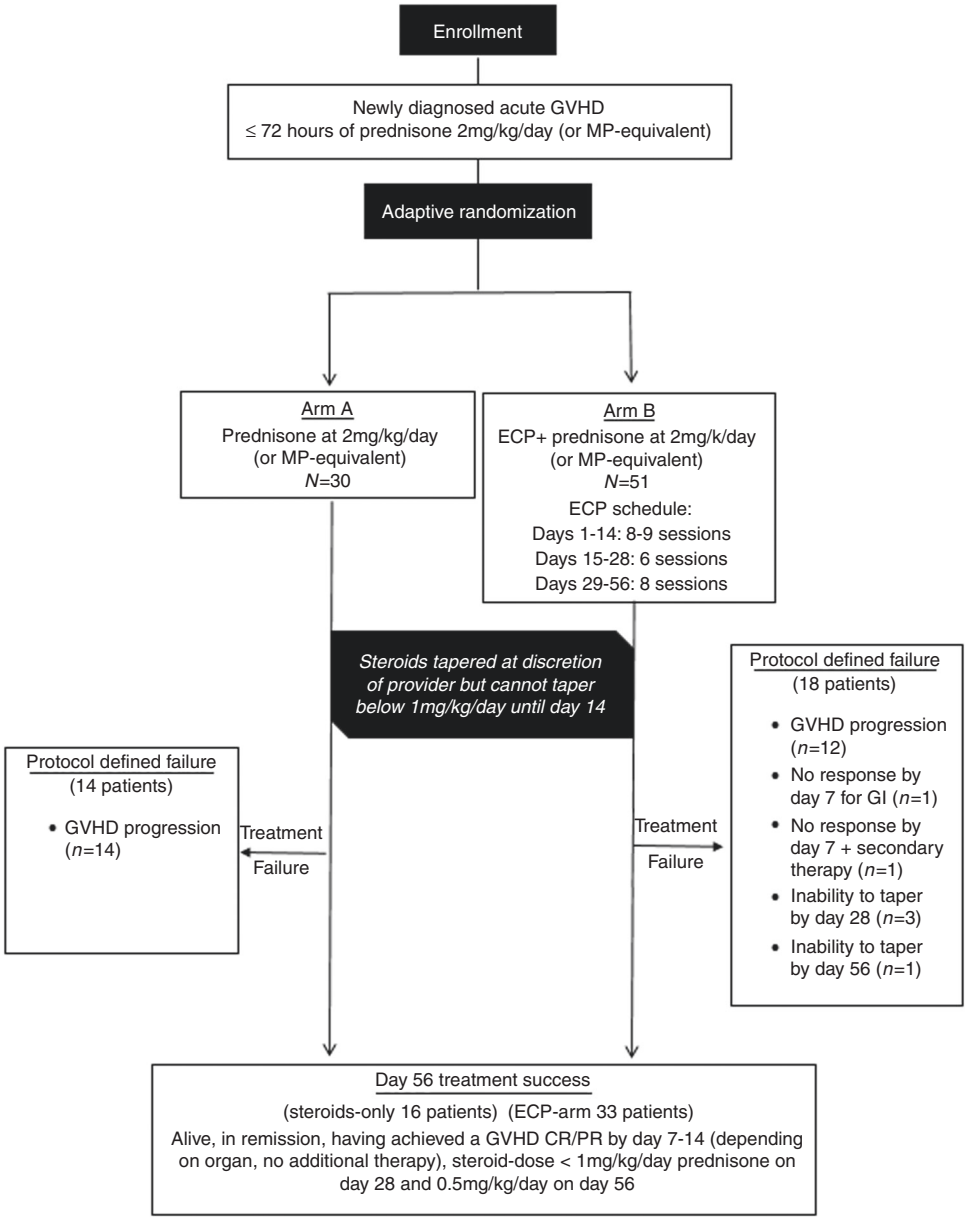

Fig. 1 Patient consort diagram. Study arm assignment as well as day 56 treatment success or failure (and reason for failure) for the 81 patients enrolled.

death or relapse of the underlying malignancy. All failure events in the SOC arm were related to not achieving AGVHD response without the need for additional therapy, which accounted for 14/18 (77.8%) events in the ECP arm (Table 3). Therefore, conversely, more treatment success events in the ECP arm were related to attaining GVHD response.

Acute GVHD response, toxicity, and infections

The day 28 AGVHD response rate was 74.5% (38/51) vs. 56.7% (17/30) in the ECP and steroids alone, respectively, $p = 0.14$, while day 56 response rates were 66.7% (34/51 patients) vs. 50% (15/30), respectively, $p = 0.16$ (Table 3).

Cumulative incidence of grade ≥ 3 toxicities through 6 months (regardless of attribution) was similar (ECP: 41.2%; 95% CI: 27.5–54.9 vs. steroids alone 43.3%; 95% CI: 25.2–61.5; $p = 0.68$) (Fig. 3a). Likewise, the cumulative incidence for grade ≥ 3 infections through 6 months did not differ between the arms, $p = 0.93$ (Fig. 3b). Adverse events possibly related to ECP were uncommon ($n = 14$ vs. 3 in steroids alone); were grades 2 and 3 in severity included 7 catheter-associated blood-stream infections (vs. 2 in steroid only), 5 catheter-associated thrombus events (vs. 1 in steroid alone), and hemorrhage (1 gastrointestinal bleed and 1 hematoma) (vs. 0 in steroids-alone). The median number of packed red blood cells (RBC) units transfused through day 56 in the ECP arm was 4 (interquartile range

Table 1 Patient characteristics.

Characteristic	Treatment arm		*p* value
	ECP + steroids	Steroids alone	
	n = 51	*n* = 30	
Gender (female)	20 (39)	11 (37)	1.0
Age in years, median (range)	54 (17–75)	53 (24–70)	0.94
Time from transplant, median days (range)	35 (12–112)	32.5 (17–85)	0.83
Diagnosis, *n* (%)			0.42
AML/MDS	23 (45)	11 (37)	
ALL	6 (11)	4 (13)	
CML	2 (4)	6 (20)	
Lymphoma	10 (20)	4 (13)	
Other	10 (20)	5 (17)	
Disease risk index, *n* (%)			0.08
Low/intermediate	32 (63)	25 (83)	
High/very high	19 (37)	5 (17)	
Myeloablative conditioning, *n* (%)	33 (65)	23 (77)	0.32
Donor relation, *n* (%)			0.81
Related	18 (35)	12 (40)	
Unrelated	33 (65)	18 (60)	
Donor match, *n* (%)			0.65
Matched	41 (82)	24 (80)	
Mismatched	10 (18)	6 (20)	
Graft source, *n* (%)			0.21
Peripheral blood	36 (71)	25 (83)	
Bone marrow	10 (19)	5 (17)	
Umbilical cord	5 (10)	0	
GVHD prophylaxis, *n* (%)			0.15
Tacrolimus/methotrexate	44 (86)	28 (93)	
Tacrolimus/ mycophenolate	2 (4)	0	
Other	5 (10)	2 (7)	
Acute GVHD grade at enrollment, *n* (%)			0.37
Grade II	44 (86)	29 (97)	
Grade III	5 (10)	1 (3)	
Grade IV	2 (4)	0	
Organ and stage at enrollment, *n* (%)			
Skin			0.89
Stage 0	7 (14)	4 (13)	
Stages 1 and 2	5 (10)	3 (10)	
Stage 3	37 (73)	23 (77)	
Stage 4	2 (4)	0	
Upper GI tract			0.79
Stage 0	39 (77)	24 (80)	
Stage 1	12 (23)	6 (20)	
Lower GI tract			0.57
Stage 0	38 (74)	25 (84)	
Stages 1 and 2	11 (22)	4 (13)	
Stages 3 and 4	2 (4)	1 (3)	
Liver			0.46
Stage 0	47 (92)	26 (87)	
Stage 1	4 (8)	4 (13)	

AML acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *CML* chronic myeloid leukemia, *GVHD* graft-vs.-host disease, *MDS* myelodysplastic syndrome.

Table 2 Primary outcome: day 56 treatment success[a].

Treatment Arm	Risk group	Success	Failure	Total
Steroids alone	All patients	16 (53%)	14 (47%)	30
	Visceral	3 (43%)	4 (57%)	7
	Skin only	13 (57%)	10 (43%)	23
ECP + steroids	All patients	33 (65%)	18 (35%)	51
	Visceral	7 (47%)	8 (53%)	15
	Skin only	26 (72%)	10 (28%)	36

[a]Defined as being alive, in a remission, achieving a GVHD response (CR or PR) without additional therapy and on a prednisone (MP equivalent) dose of <1 mg/kg/day on day 28 and <0.5 mg/kg/day by day 56. The probability the ECP + steroids arm has a higher success rate compared to steroids alone for day 56 treatment success was 81.5%.

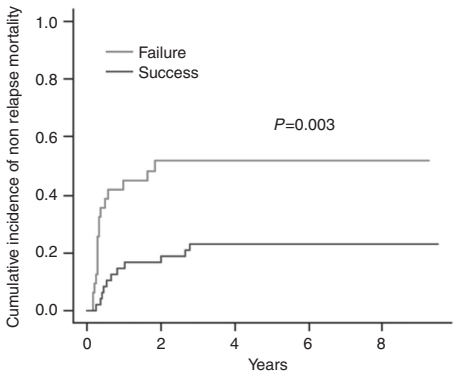

Fig. 2 Non-relapse mortality by success or failure. A landmark analysis starting at day 56 by whether the patient was a success or failure for the primary (composite) endpoint. Patients experiencing relapse or death before day 56 were excluded from this analysis with a total of two patients excluded.

Table 3 Causes of failure and secondary outcomes.

	ECP + steroids	Steroids alone	
Failure events	18	14	
Death	0	0	
Relapse of the underlying malignancy	0	0	
Did not achieve AGVHD response without the need for additional therapy	14 (77.8%)[a]	14 (100%)[b]	
Not on <1 mg/kg of prednisone (or MP equivalent) on day 28	3 (16.7%)	0	
Not on <0.5 mg/kg of prednisone (or MP equivalent) on day 56	1 (5.5%)	0	
Outcome			*p* value
Acute GVHD day 28 response	74.5%	56.7%	0.14
Acute GVHD day 56 response	66.7%	50%	0.16
Incidence of chronic GVHD	40%	47%	0.95
	Hazard ratio	95% confidence interval	*p* value
Relapse	1.54	0.60–3.97	0.37
Non-relapse mortality	1.28	0.55–3.01	0.57
Overall survival	1.44	076–2.76	0.27

[a]Three secondary therapy, nine progressive AGVHD, one increase in AGVHD stage by 72 h, and one no response GI AGVHD by day 7.

[b]Eight secondary therapy, four progressive AGVHD, one new organ AGVHD, and one increase in AGVHD stage by 72 h.

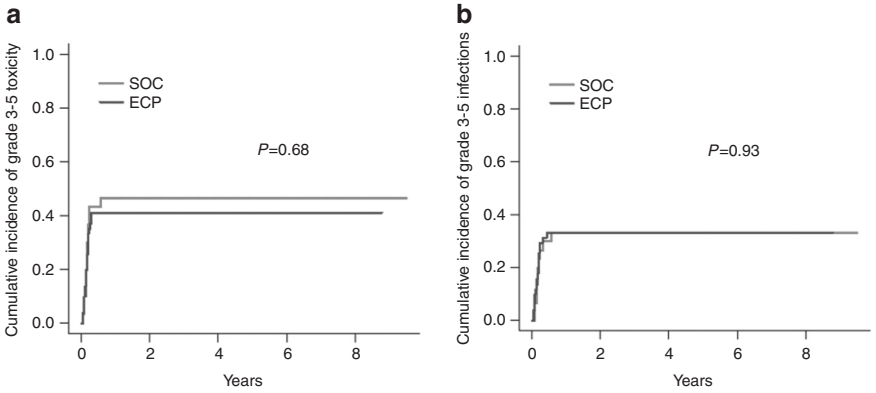

Fig. 3 Adverse events. a Cumulative incidence of grades 3–5 toxicity by treatment arm. **b** Cumulative incidence of grades 3–5 infections by treatment arm.

(IQR): 1–9.5) vs. 2 (IQR: 0–5.75) for the steroid-alone arm, $p = 0.14$.

Tapering of immunosuppressive therapies, chronic GVHD, relapse, non-relapse mortality, and overall survival

The median dose of steroids at days 28 and 56 post randomization did not differ between the arms (Fig. 4), nor did the cumulative incidence of discontinuation of steroids or other immunosuppressive therapy (data not shown). At 2 years, the cumulative incidence of chronic GVHD was 40% in the ECP arm (95% CI: 22–58) vs. 47% for steroids alone (95% CI: 33–61); $p = 0.95$. In multivariate, analysis adjusted for covariates, relapse (HR: 1.54; 95% CI: 0.6–3.96, $p = 0.37$), NRM (HR: 1.28; 95% CI: 0.57–3.01, $p = 0.57$), and OS (HR: 1.44; 95% CI: 0.76–2.76, $p = 0.2$) did not differ between the arms (Fig. 5).

Immunologic response: T-cell subsets

Immune subsets (Tcon and Tregs) were analyzed at baseline and post-therapy in four patients treated with ECP + steroids and five patients treated with steroids alone. Cell counts did not differ between the two arms (data not shown).

Discussion

The goal of this current trial was to examine an upfront strategy, which aimed to maintain AGVHD response, and allowed for the tapering of steroids, without the need for additional therapy, and without increasing the risk of relapse of the underlying malignancy through the addition of ECP. As these isolated outcomes, although significant, do not reflect a complete picture of "success," we designed this trial based on a composite endpoint that accounted for all of these factors together. The threshold for declaring an arm superior was set a priori at a probability of 80% in this relatively small, single-center randomized phase 2 trial, with the aim of confirming in a larger phase 3 trial should ECP be noted to have some indications of potential benefit. Indeed, more patients in the ECP arm attained "treatment success" at day 56 post randomization based on this composite primary endpoint than those treated with steroids alone (65% vs. 53%, respectively). Realizing the limitation that the trial was not powered for subgroup analysis, patients with skin-only AGVHD appeared to benefit the most—with 15% absolute improvement in treatment success with ECP than those treated with steroids alone (72% vs. 47%, respectively), while those with visceral disease appeared to have roughly similar success (47% vs. 43%, respectively). Nonetheless, skin-only AGVHD represents the largest proportion of patients who present with newly diagnosed acute with just over half of all AGVHD cases presenting in this manner [3, 6]. Treatment success for this composite endpoint (irrespective of arm assignment) resulted in significantly lower NRM.

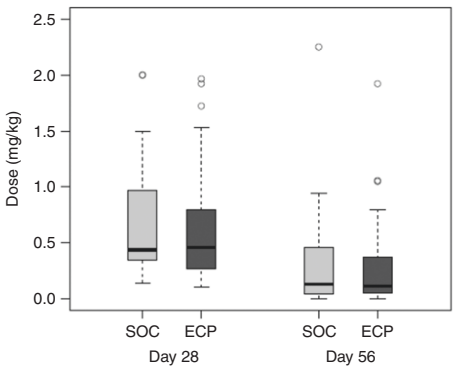

Fig. 4 Days 28 and 56 steroid doses by treatment arm. Box plots for the days 28 and 56 doses of steroids (prednisone equivalent in mg/kg) in patients randomized to steroids only (standard of care; SOC) or ECP + steroids.

Furthermore, despite the fact that more patients in the ECP arm had grades III and IV AGVHD at enrollment than in the steroid-alone arm (14% vs. 3%, respectively), we noted about 18% absolute improvement in the AGVHD response rate at day 28 (74.5% vs. 56.7%, respectively), and about 17% absolute improvement at day 56 (66.7% vs. 50%, respectively). Yet, our results did not reach statistical significance likely due to small numbers. The administration of ECP over the course of 56 days following the development of AGVHD did not appear to reduce the rate of chronic GVHD. Whether continuation of this therapy for a longer period would have reduced this risk remains unknown. Similarly, NRM did not differ either; however, it should be noted that 6-month NRM was relatively low for the study population, again restricting the ability to demonstrate any statistical significance. More importantly, with the addition of ECP, we did not observe any increased risk of relapse of the underlying malignancy, which is always a concern with additional immunosuppression. Again, although the independent endpoints did not differ statistically (some due to small numbers), the composite endpoint that includes these endpoints favored the ECP arm.

Efforts to reduce steroid exposure are considered a top priority for ~75–85% of patients with newly diagnosed AGVHD who will have low/standard risk AGVHD based on validated clinical and/or biomarker prognostic tools. Although patients in the ECP arm who met the primary endpoint were able to taper steroids successfully (<1 mg/kg/

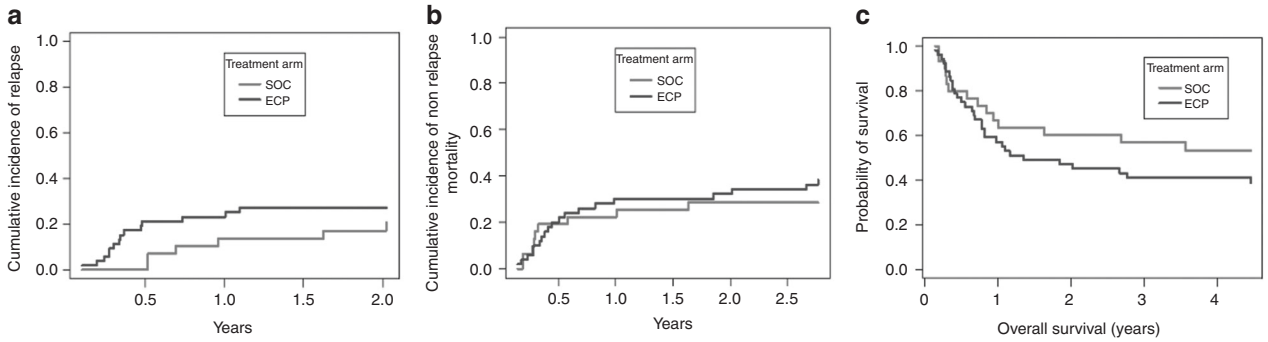

Fig. 5 Long-term outcomes. a Cumulative incidence of relapse by treatment arm adjusted by disease risk index (DRI, high/ very high vs. low/intermediate), conditioning (myeloablative vs. non-myeloablative), age (>60 vs. ≤60 years), and CMV status (CMV negative patient/donor vs. other). **b** Cumulative incidence of non-relapse mortality by treatment arm adjusted by DRI, conditioning, age, and comorbidity index. **c** Kaplan–Meier plot of overall survival by treatment arm adjusted by DRI, conditioning, age, and CMV status.

day by day 28 and <0.5 mg/kg/day of prednisone (or MP equivalent) by day 56), the median steroid dose at days 28 and 56 did not differ between the arms. This is likely because the protocol did not dictate a steroid-taper schedule, and center-specific practices were often employed. Future trials of ECP with a built-in abbreviated course of steroids would be important to truly test the efficacy of this therapy.

The frequency of ECP in patients with AGVHD has not been studied. In one retrospective study, an ORR of 57% was noted patients with AGVHD with ECP using a less intensive schedule, which included 2 days per week for the first 2 weeks, then 1 day per week for 2 weeks, followed by 1 day every 2 weeks for a minimum of 16 ECP procedures [26]. In this trial, we elected to use a rather intensive schedule consisting of roughly 15 treatments over the 1st month and 8 over the 2nd month (two sessions per week). While significant coordination of care was required to maintain this schedule, the average adherence approached 90% and two-thirds of the patients assigned to the ECP arm completed ≥90% of the planned therapies. In large part, ECP was well tolerated; however, patients receiving ECP had a trend for requiring more RBC transfusions over the treatment period. Whether this reflected transfusions for symptomatic anemia vs. simply the need to maintain a higher hematocrit as mandated for performing ECP is unknown. The frequency of catheter-related thrombotic events was also higher in the ECP arm perhaps due to the need for placement of a larger apheresis catheter. The rationale for adding ECP to steroids was the lack of overlapping toxicities with steroids. The similar incidences of grades 3–5 infections between the study arms would seem to support this approach when compared to agents currently being studied.

We were unable to examine the effect of ECP on Treg and Tcon as the correlative studies could only be performed on a handful of patients. Another limitation of the trial includes the lack of biomarker-based risk stratification. Nevertheless, the breakdown of patients based on the Revised Minnesota Criteria is reflective of prior upfront trials with the vast majority of patients having standard risk AGVHD (85%); primarily, skin-only GVHD [6].

In conclusion, in this randomized phase 2 trial, the addition of ECP to steroids resulted in a higher probability of treatment success. Future trials, incorporating an abbreviated steroid course, are needed to confirm the efficacy of this approach.

Acknowledgements This physician-initiated trial was supported by a grant from Therakos, Inc., a Mallinckrodt Pharmaceuticals company. Additional support was provided through the Cancer Center Support Grant (NCI Grant P30 CA016672).

Author contributions RSM contributed patient enrollment, paper writing, and interpretation of results; RB contributed to trial design, interpretation of results, and statistical analysis; GR contributed data collection and interpretation of results; BJO contributed data collection; URP, CMH, MQ, PA, IFK, BO, SOC, and EJS contributed patient enrollment and interpretation of results; KR contributed patient enrollment, laboratory analysis, and interpretation of results; DM and KK contributed laboratory analysis and interpretation of results; DRC contributed study design; REC contributed to study design, patient enrollment, and interpretation of results; and AMA contributed to study design, enrollment of patients on study, interpretation of results, and wrote the paper. All authors reviewed and approved the paper.

Compliance with ethical standards

Conflict of interest AMA has served as a speaker for Therakos, Inc. Other authors declare no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. MacMillan ML, DeFor TE, Holtan SG, Rashidi A, Blazar BR, Weisdorf DJ Validation of Minnesota acute graft-versus-host disease risk score. Haematologica. 2020:105:519–24.
2. Levine JE, Braun TM, Harris AC, Holler E, Taylor A, Miller H, et al. A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study. Lancet Haematol. 2015;2: e21–9.
3. MacMillan ML, Robin M, Harris AC, DeFor TE, Martin PJ, Alousi A, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. Biol Blood Marrow Transplant. 2015;21:761–7.
4. Antin JH, Chen AR, Couriel DR, Ho VT, Nash RA, Weisdorf D. Novel approaches to the therapy of steroid-resistant acute graft-versus-host disease. Biol Blood Marrow Transplant. 2004;10:655–68.
5. Weisdorf D, Haake R, Blazar B, Miller W, McGlave P, Ramsay N, et al. Treatment of moderate/severe acute graft-versus-host disease after allogeneic bone marrow transplantation: an analysis of clinical risk features and outcome. Blood. 1990;75:1024–30.
6. Bolanos-Meade J, Logan BR, Alousi AM, Antin JH, Barowski K, Carter SL, et al. Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802. Blood. 2014;124:3221–7.
7. Couriel DR, Saliba R, de Lima M, Giralt S, Andersson B, Khouri I, et al. A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. Biol Blood Marrow Transplant. 2009;15:1555–62.
8. Alousi AM, Weisdorf DJ, Logan BR, Bolanos-Meade J, Carter S, Difronzo N, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood. 2009;114:511–7.
9. Lee SJ, Zahrieh D, Agura E, MacMillan ML, Maziarz RT, McCarthy PL Jr., et al. Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. Blood. 2004;104:1559–64.
10. Cragg L, Blazar BR, Defor T, Kolatker N, Miller W, Kersey J, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. Biol Blood Marrow Transplant. 2000;6:441–7.

11. Cahn JY, Bordigoni P, Tiberghien P, Milpied N, Brion A, Widjenes J, et al. Treatment of acute graft-versus-host disease with methylprednisolone and cyclosporine with or without an anti-interleukin-2 receptor monoclonal antibody. A multicenter phase III study. Transplantation. 1995;60:939–42.
12. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. Expert Opin Drug Saf. 2016;15:457–65.
13. Edelson R, Berger C, Gasparro F, Jegasothy B, Heald P, Wintroub B, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med. 1987;316:297–303.
14. Maeda A, Schwarz A, Bullinger A, Morita A, Peritt D, Schwarz T. Experimental extracorporeal photopheresis inhibits the sensitization and effector phases of contact hypersensitivity via two mechanisms: generation of IL-10 and induction of regulatory T cells. J Immunol. 2008;181:5956–62.
15. Gatza E, Rogers CE, Clouthier SG, Lowler KP, Tawara I, Liu C, et al. Extracorporeal photopheresis reverses experimental graft-versus-host disease through regulatory T cells. Blood. 2008;112:1515–21.
16. Di Renzo M, Sbano P, De Aloe G, Pasqui AL, Rubegni P, Ghezzi A, et al. Extracorporeal photopheresis affects co-stimulatory molecule expression and interleukin-10 production by dendritic cells in graft-versus-host disease patients. Clin Exp Immunol. 2008;151:407–13.
17. Peritt D. Potential mechanisms of photopheresis in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2006;12:7–12.
18. Lamioni A, Parisi F, Isacchi G, Giorda E, Di Cesare S, Landolfo A, et al. The immunological effects of extracorporeal photopheresis unraveled: induction of tolerogenic dendritic cells in vitro and regulatory T cells in vivo. Transplantation. 2005;79:846–50.
19. Greinix HT, van Besien K, Elmaagacli AH, Hillen U, Grigg A, Knobler R, et al. Progressive improvement in cutaneous and extracutaneous chronic graft-versus-host disease after a 24-week course of extracorporeal photopheresis-results of a crossover randomized study. Biol Blood Marrow Transplant. 2011;17:1775–82.
20. Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood. 2008;112:2667–74.
21. Sakellari I, Gavriilaki E, Batsis I, Mallouri D, Panteliadou AK, Lazaridou A, et al. Favorable impact of extracorporeal photopheresis in acute and chronic graft versus host disease: prospective single-center study. J Clin Apher. 2018;33:654–60.
22. Perotti C, Del Fante C, Tinelli C, Viarengo G, Scudeller L, Zecca M, et al. Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. Transfus. 2010;50:1359–69.
23. Greinix HT, Knobler RM, Worel N, Schneider B, Schneeberger A, Hoecker P, et al. The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. Haematologica. 2006;91:405–8.
24. Messina C, Locatelli F, Lanino E, Uderzo C, Zacchello G, Cesaro S, et al. Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. Br J Haematol. 2003;122:118–27.
25. Salvaneschi L, Perotti C, Zecca M, Bernuzzi S, Viarengo G, Giorgiani G, et al. Extracorporeal photochemotherapy for treatment of acute and chronic GVHD in childhood. Transfus. 2001;41:1299–305.
26. Cid J, Carbasse G, Suarez-Lledo M, Moreno DF, Martinez C, Gutierrez-Garcia G, et al. Efficacy and safety of one-day offline extracorporeal photopheresis schedule processing one total blood volume for treating patients with graft-versus-host disease. Transfus. 2019;59:2636–42.
27. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995;15:825–8.