



**HAL**  
open science

## Extracorporeal photopheresis as first line strategy in the treatment of acute graftversus-host disease after haematopoietic stem cell transplantation: a single centre experience

Simona Sestili, Sandra Eder, Ramdane Belhocine, Rémy Duléry, Giorgia Battipaglia, Eolia Brissot, Clemence Mediavilla, Anne Banet, Zoé van de Wyngaert, Annalisa Paviglianiti, et al.

### ► To cite this version:

Simona Sestili, Sandra Eder, Ramdane Belhocine, Rémy Duléry, Giorgia Battipaglia, et al.. Extracorporeal photopheresis as first line strategy in the treatment of acute graftversus-host disease after haematopoietic stem cell transplantation: a single centre experience. *Cytotherapy*, 2020, 22 (8), pp.445-449. 10.1016/j.jcyt.2020.03.003 . hal-03145941

**HAL Id: hal-03145941**

**<https://hal.sorbonne-universite.fr/hal-03145941v1>**

Submitted on 18 Feb 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## **Extracorporeal photopheresis as first line strategy in the treatment of acute graft-versus-host disease after haematopoietic stem cell transplantation: a single centre experience**

Simona Sestili<sup>1</sup>, Sandra Eder<sup>1</sup>, Ramdane Belhocine<sup>1</sup>, Remy Dulery<sup>1</sup>, Giorgia Battipaglia<sup>1</sup>, Eolia Brissot<sup>1,2</sup>, Clemence Mediavilla<sup>1</sup>, Anne Banet<sup>1</sup>, Zoe Van de Wyngaert<sup>1</sup>, Annalisa Paviglianiti<sup>1</sup>, Tounes Ledraa<sup>1</sup>, Agnes Bonin<sup>1</sup>, Mohamad Mohty<sup>1,2</sup>, Florent Malard<sup>1,2</sup>

<sup>1</sup> APHP, Hôpital Saint Antoine, Service d'Hématologie Clinique et de Thérapie cellulaire, Paris, France

<sup>2</sup> Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine (CRSA), F-75012 Paris, France

**Running title:** Front-line ECP for aGVHD

**Keywords:** photopheresis, hematopoietic stem cell transplantation, acute GVHD

### **Correspondence and reprint requests:**

Florent Malard MD, PhD, Department of Clinical Hematology and Cellular Therapy, Saint-Antoine Hospital, 75012 Paris, France.

E-mail address: [florent.malard@inserm.fr](mailto:florent.malard@inserm.fr)

## **Abstract**

Corticosteroids are the standard first line treatment for acute graft-versus-host disease (aGVHD). However, corticosteroids are associated with many complications and less than half of the patients have durable response. In order to improve outcomes, we performed a retrospective study to analyze the efficacy of the addition of extracorporeal photopheresis (ECP) to low dose corticosteroids in 37 adult patients (median age, 57 years) with skin predominant aGVHD (grade I, n=17; grade II, n=18 and grade III, n=2). All patients received ECP in combination with 1 mg/kg prednisone (n=26) or topical steroids (n=11). Overall response rate (ORR) was 81% after a median of 3 ECP procedures (range, 2-8), including 22 complete responses (CR, 59%) and 8 very good partial responses (VGPR, 22%). The 11 patients treated with topical corticosteroids achieved CR. Furthermore 16 (62%) patients reached prednisone withdrawal at a median of 100 days (range, 42-174 days) after its initiation. Eighteen patients developed chronic GVHD (cGVHD), 11 of them (who were in CR of aGvHD) had a new onset cGVHD and 7 experienced progressive cGVHD (5 non-responding and 2 VGPR patients). A second line immunosuppressive treatment was initiated in only 5 (14%) non-responding patients. With a median follow-up of 31 months (range, 6-57 months) two-year overall survival and non-relapse mortality were 74% and 11%, respectively. Overall, the combination of low-dose corticosteroids and ECP appear to be safe and effective for first-line treatment of skin predominant aGVHD.

## **Introduction**

Acute graft-versus-host disease (aGVHD) is a severe complication of allogeneic hematopoietic stem cell transplantation (allo-HCT) and one of the leading causes of early non-relapse mortality (NRM) and long-term complications<sup>1</sup>. Despite improved immunosuppressive prophylaxis, aGVHD still occurs in approximately 30% to 50% of patients, with 14% to 36% of them developing severe aGVHD<sup>2,3</sup>. Corticosteroids are the standard first-line therapy for aGVHD and despite initial responses in up to 70% of patients<sup>4</sup>, less than 50% of these responses are durable<sup>5</sup>. There is currently no consensual second-line treatment<sup>6,7</sup> and patients who fail to respond have a poor prognosis, with high NRM<sup>4</sup> due to GVHD itself but also to its treatment complications, in particular opportunistic infections or other dose-related steroid side effects. In order to improve outcomes, several prospective randomized clinical trials have evaluated the combination of corticosteroids with an additional agent for aGVHD first-line treatment<sup>8-12</sup>. However, none of them have demonstrated a benefit compared to corticosteroids alone.

In the last decade, extracorporeal photopheresis (ECP) has shown some encouraging results in steroid-refractory acute and chronic GVHD, particularly in the case of skin involvement<sup>13-15</sup>. Treatment with ECP involves harvesting peripheral white blood cells from patients receiving 8-methoxypsoralen, exposing cells to UV-A light and reinfusing the cells after treatment has been completed. This procedure induces an apoptotic cellular cascade in all leukocytes treated within 24–48 hours. The exact mechanism by which ECP exerts its therapeutic effect is still under investigation, however murine models have shown that ECP may work through the induction of immune tolerance, including reduced dendritic cell activation and increased regulatory T-cell numbers<sup>16,17</sup>. Therefore, ECP is expected to have limited side effects, with no increased risk of infectious complications, no metabolic or organic impairment and potential preservation of the graft-versus-leukemia effect<sup>18</sup>. Furthermore, its immunomodulatory effects, primarily based on the generation of active immune cells, may lead to a sustained response without severe flare-up of GVHD<sup>19</sup>. In a phase II study, second line-treatment with ECP for grade II-IV steroid refractory aGVHD was associated with a high response rate, being 61%, 61% and 82%, in patients with gut, liver and skin involvement respectively<sup>19</sup>. Overall, all these data suggest that addition of ECP to corticosteroids for first-line treatment of skin aGVHD, may be an effective strategy to improve response rate while reducing steroid exposure.

Here, we report our single-center experience on 37 transplanted patients treated for skin predominant aGVHD with ECP as first-line therapy in combination with topical steroids or low-dose systemic steroids.

## **Patients and methods**

### *Patients*

This retrospective single-center study included 37 consecutive patients that received ECP in combination with topical steroids or systemic low-dose steroids for first line-treatment of skin predominant aGVHD after allo-HCT between 2013 and 2019. All patients gave written informed consent. This study was approved by the hospital's institutional review board and the local ethics committee. Patient with a first episode of skin predominant acute GVHD and treated with ECP in combination with topical steroids or systemic low-dose steroids (1 mg/kg) were eligible. Skin predominant acute GVHD was defined as isolated skin acute GVHD or skin acute GVHD with skin stage > liver and/or gut acute GVHD stage and liver and/or gut acute GVHD stage ≤2. Patients with grade I aGVHD, or grade II aGVHD with high-risk underlying malignancies received topical steroids, while others received 1 mg/kg oral prednisone or equivalent. In responding patients, steroids were tapered quickly with an objective of a 50% reduction of the dose at day 28, thereafter, steroids were reduced by 5-10 mg every 7-10 days. In addition, patients with gut involvement received topical steroids (budesonide). Acute GVHD grading was performed according to the revised Glucksberg-criteria<sup>20</sup>. Patients were excluded if they had overlap syndrome with hallmarks of chronic GVHD (cGVHD) or had received prior or concomitant additional systemic immunosuppressive therapy for aGVHD. Ongoing GVHD prophylaxis with cyclosporine A (CsA) and/or mycophenolate mofetil (MMF) was allowed. Antimicrobial prophylaxis consisted of valacyclovir and trimethoprim-sulfamethoxazole or atovaquone, starting after neutrophil recovery for one year and pursued beyond if CD4+ T cells remained below  $0.2 \times 10^9/L$ . In addition, patient treated systemic corticosteroids (>10 mg equivalent prednisone) received antifungal prophylaxis with posaconazole.

### *ECP and treatment protocol*

ECP was performed using the Therakos UVAR photopheresis system<sup>21</sup>. The mean treatment time for the photopheresis procedure was 1.5 hours. Peripheral vein catheters were exclusively used. ACD-A (Anticoagulant Citrate Dextrose Solution, Solution A) was used as an anticoagulant. Methoxalen (Uvadex, Therakos) was injected into the collection bag at a dose of 0.017 mL per 1 mL of the apheresis product before photoactivation. Before each ECP procedure, patients had to be hemodynamically stable, without signs of acute infection (fever, signs of acute respiratory disease...) and have a white blood cell count of at least  $1 \times 10^9/L$ . When necessary, patients were transfused with red blood cells or platelets to maintain a hematocrit level of at least 27% and a platelet count of at least  $20 \times 10^9/L$ .

Patients received 1-week cycles with 2 ECP, however, based on physician decision and patient tolerability (difficult venous access), some patients received 1-week cycle with one ECP, until achievement of a VGPR and thereafter every 2 to 4 weeks until CR. ECP was then quickly tapered, no maintenance was administered. All adverse effects occurring during the treatments were recorded.

#### *Statistical methods*

The primary endpoint of the study was to evaluate the overall response rate (ORR) at any time and the cumulative incidence of NRM. Complete response (CR) was defined as complete resolution of all manifestations of GVHD, irrespective of pursuing or terminating CsA/MMF or steroids. Very good partial response (VGPR) was defined for skin as no rash, or residual erythematous rash involving <25% of the body surface, without bullae, for liver total serum bilirubin concentration <2 mg/dL and for gut as tolerating food or enteral feeding with predominantly formed stools according to Martin et al.<sup>22</sup> and cGVHD was assessed according to the NIH grading system<sup>23</sup>. CR and VGPR were evaluated at day 28 and day 56. Treatment failure was defined as absence of VGPR at day 56 or any increase of baseline immunosuppressive treatment or addition of any additional treatment before day 56.

Overall survival (OS) was calculated from the date of allo-HCT until the time of death or the last observation if a patient remained alive. Probability of OS was estimated using the Kaplan–Meier method with a landmark analysis at day 56 and groups were compared using the log-rank test. NRM was calculated using the cumulative incidence procedure

and relapse was considered as the competing event and groups were compared using Gray's test.

## **Results**

### *Patient, donor and transplant characteristics*

Patient and donor characteristics are summarized in Table 1. The median age was 57 years (range, 22-66 years). All donor/recipient pairs were typed at the allelic level for HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ. Thirty-five (95%) patients received in vivo T-cell depletion using antithymocyte globulin. GVHD prophylaxis, consisted of either cyclosporine A alone (CsA) for patients with matched sibling donors (n=9; 24%) or CsA and mycophenolate mofetil (MMF) for patients with an unrelated or an haploidentical donor (n=28; 76%). In addition, patients with an haploidentical donor received post-transplant cyclophosphamide.

### *Baseline acute GVHD characteristics*

Acute GVHD assessment at baseline is summarized in Table 2. All patients had skin involvement, which was associated with gut and/or liver GVHD in only 8 patients.. Acute GVHD appeared at a median of 28 days (range, 11-333) after allo-HCT. Three patients were diagnosed as having late onset aGVHD (beyond day +100). In one of them, late onset aGVHD developed after donor lymphocyte infusion (DLI).

Among all the 37 patients receiving ECP, 26 patients received concomitant systemic steroid at 1 mg/kg prednisone equivalent dose, while in the remaining 11 patients only topical steroids were used. Systemic steroid therapy was initiated at a median of 0 day (range, 0-47) after onset of acute GVHD. Patients treated with topical steroids alone were those with isolated stage 1 skin GVHD or patients with stage 2 skin GVHD considered to be at high risk of relapse (high or very-high DRI)<sup>24</sup>. ECP was performed once weekly in 23 (62%) and twice a week in 14 (38%) patients. Median time between diagnosis of aGVHD and start of ECP treatment was 9 days (range 0-54) and ECP was aimed to be initiated within the first week following systemic steroids initiation in the majority of patients (median 7 days, range 0-14).

Treatment with CsA was continued in all patients except one who had already discontinued CsA at that time (aGVHD post DLI at day 333 after allo-HCT). In addition, 19 patients were still receiving GVHD prophylaxis with MMF.

### *Response*

The ORR was 81%, including 22 (59%) CR and 8 (22%) VGPR. Median times for ORR and CR achievement after ECP initiation were 15.5 days (range, 6-56) and 52 days (range, 15-144) respectively. ORR at day 28 and day 56 were 65% and 81% respectively, CR rates at day 28 and day 56 were 11% and 46% respectively. ORR at day 56 were 100% and 65% for grade I and grade II-III acute GVHD respectively (Figure 1A). The 11 patients treated with topical corticosteroids achieved CR. In the 26 patients treated with ECP and systemic corticosteroids, 19 achieved a response, including 11 (42%) CR and 8 (31%) VGPR. In patients with gut and/or liver involvement ORR and CR rates at day 56 were 75% and 50% respectively. Seven patients were in treatment failure, including 3 patients with acute GVHD worsening during the first 56 days and 4 patients with stable disease at day 56. A second immunosuppressive line was initiated in only 5 (14%) non-responding patients, consisting of methotrexate (n=2), rituximab (n=2) and imatinib (n=1).

Median number of ECP require to achieve CR was 8 (range, 2-26) and patients received a median of 1 additional ECP (range 0-2) after CR achievement. There was no difference in the median number of ECP performed before CR between patients treated with topical steroids alone or with systemic steroids [7 (range, 2-26) versus 7 (range, 3-15) respectively, p=0.9]. Finally, 16 (62%) patients reached complete systemic steroid withdrawal at a median of 100 days (range, 42-174 days) after their initiation (Figure 1).

Eighteen patients developed cGVHD, including 11 new onset cGVHD in patients in CR of their aGVHD, and 7 progressive cGVHD in non-responding patients (n=5) or in patients with VGPR (n=2). The two patients in VGPR were still receiving ECP. In patients in CR, median cGVHD onset was 130 days (range, 62-203) after last ECP. Chronic GVHD was mild in 6 patients, moderate in 11 and severe in only one patient. In the subgroup of 11 patients treated without systemic steroids, only 3 developed new onset cGVHD.

### *Safety assessment*



The median number of ECP procedures was 13 (range, 3-36). Reasons for ECP discontinuation were complete resolution of aGVHD (n=17), venous access issue (n=3), relapse of underlying disease (n=7), absence of response (n=2) and patient choice (n=1). No serious adverse events related to the procedure were reported.

Bacterial infections upon ECP treatment were reported in 5 patients due to *Clostridium difficile* colitis (n=1), *Pseudomonas aeruginosa* bacteriemia (n=2), *Staphylococcus haemolyticus* bacteriemia (n=1) and an undocumented lung infection. Thirteen patients developed viral reactivation and/or infection, with some patients developing more than one viral complication, including 9 Cytomegalovirus (CMV) reactivations, 8 increases in Epstein-Barr virus (EBV) viral load, one BK virus cystitis, one Rotavirus colitis and one Rhinovirus sinusitis. Only one patient developed a fungal infection (possible pulmonary aspergillosis). Infectious complications were fatal in only one patient. This patient had lung and gastrointestinal colonization with extensively-drug resistant *Pseudomonas aeruginosa* that was responsible for a fatal septic shock. All other infectious complications resolved after adequate treatment. Regarding the subgroup of 11 patients treated without systemic steroids, none of them had bacterial or fungal infection and only three developed viral complications with CMV reactivation in all three and an increase in EBV viral load reactivation in two of them.

### *Outcomes*

The median follow-up among surviving patients was 31 months (range, 6-57 months) and two-year OS was 74%. OS was higher in patients who achieved response at day 56 (VGPR+CR), being 79 % versus 51% in other patients at 2-years (p=0.06) (Figure 2). The 2-year OS of patients with grade I aGVHD was 88% versus 61% in patients with grade II-III aGVHD (p=0.11). Furthermore, 2-year cumulative incidence of NRM was 11%, being 5% in patients who achieved CR, versus 33% in the patients that did not (p=0.06). Causes of NRM were infection in one patient (*Pseudomonas aeruginosa* septic shock already reported), cGVHD in 3 patients and cardiac arrhythmia in one patient. There was no difference in the cumulative incidence of relapse between both groups: 27% versus 40% (p=0.63). Thirteen patients have relapse at a median of 169 (range, 12-585) days after ECP initiation. Relapses occur in patients with acute myeloid leukemia (n=7), myelodysplastic syndrome (n=2), chronic myelomonocytic leukemia (n=1) and acute

lymphoid leukemia (n=3). Disease risk index was low or intermediate in 7 patients and high or very high in 6 patients with relapse.

## **Discussion**

We observed an ORR of 81% with ECP as first-line therapy for skin predominant aGVHD in association with topic or low-dose corticosteroids. Furthermore, in the current retrospective study we showed that it is an effective strategy and can improve response with a CR rate of 59%. This result compares favorably with CR rates reported with standard dose corticosteroids alone, or in combination with dactilizumab, CD5-specific immunotoxin or MMF, ranging from 38%-59.5%<sup>11-13</sup>. It should be pointed out that all patients in our study had skin predominant aGVHD, which was associated with gut or liver involvement in only 8 of them. The majority of them had grade I or II aGVHD, only 5% of patients had grade III and no patients had grade IV. This selection of good prognosis patients could partially explain the excellent results. Nevertheless, Mielcarek et al. found that 53% of patients with grade II skin predominant aGVHD, similar to our patient population, required secondary immunosuppressive treatment when treated with corticosteroids at 1 mg/kg/day compared to only 18% treated with 2 mg/kg/day<sup>25</sup>. With 14% of patients undergoing second line immunosuppressive therapy, our results suggest that addition of ECP to low-dose steroids is as effective as standard corticosteroids at 2 mg/kg/day.

Furthermore, focusing on grade I aGVHD, a prospective study recently randomized observation versus corticosteroid at 1 mg/kg<sup>26</sup>. They reported a cumulative incidence of progression to grade II-IV aGVHD of 50% in the observation arm and 33% in the corticosteroid arm (p=0.005). In contrast, in our cohort, 11 patients with grade I aGVHD received ECP with topical corticosteroid and none of them progressed to grade II-IV aGVHD, suggesting that our ECP based regimen, free of systemic corticoid seems to be particularly effective in this setting.

So far, first-line therapy for aGVHD with ECP has only been reported in a small group of 7 patients who developed aGVHD after haploidentical transplantation<sup>27</sup>. Three patients received ECP alone and 4 patients received ECP in combination with corticosteroids at 1-2 mg/kg/day. Six patients achieved CR and the remaining patient had a PR. These results

confirm that first-line treatment of aGVHD with ECP translates to a high CR rate including in the absence of systemic corticosteroids. More data are available in second or further lines of treatment of aGVHD, after corticosteroid failure with CR rates ranging from 52% to 72%<sup>4,6,7,28</sup> and up to 87% in patients with isolated skin involvement<sup>19</sup>. Importantly, our approach was associated with a high 2-year OS of 74% and a low cumulative incidence of NRM, being 11% at 2 years. These results compare favorably with previously published data. Bolanos-Meade reported a 1-year OS and NRM of 64.7% and 21.5% respectively, with 2 mg/kg corticosteroids<sup>13</sup>. Furthermore, Mielcarek et al. did not find a lower cumulative incidence of NRM when patients received lower doses of corticosteroids, being 15% at 1-year versus 16% with standard dose corticosteroids<sup>25</sup>. More interestingly, in patients with grade I aGVHD, Bacigalupo et al. reported a higher cumulative incidence of NRM compared to that found in our study either in patients treated with corticosteroids at 1 mg/kg or randomized to the observation arm, being 26% and 20% respectively at 5-years<sup>26</sup>. Overall, addition of ECP for first-line treatment of aGVHD is associated with a low cumulative incidence of NRM. Importantly, while infectious complication is one of the leading causes of death in patients with GVHD<sup>29</sup>, only one patient died from infection in our cohort. In our study 30% of patients received no systemic corticosteroids and 62% of patients treated with systemic steroids completely discontinued them at a median of 100 days after their initiation. This rapid corticosteroid withdrawal in patients receiving ECP probably contributed to the low incidence of infectious complication and infection related mortality reported in our study. Nevertheless, we must acknowledge that our study was retrospective and includes a small heterogenous group of patients, possibly contributing to the low NRM compared to larger prospective results.

In conclusion, our analysis confirms a positive impact of ECP as first-line treatment of aGVHD after allo-SCT, with an ORR of 81%. Addition of ECP to aGVHD first-line treatment translates into a rapid corticosteroid withdrawal, probably contributing to the low incidence of complications, particularly infections. These results need to be confirmed by randomized prospective trials to better explore the role of ECP as upfront treatment of aGVHD.

**Competing interests statement:**

M Mohty and F Malard received honoraria for lectures from Therakos/Mallinckrodt

whose device was included in this study. The other authors declare no competing financial interests.

### **Acknowledgements**

The authors acknowledge the Association for Training, Education and Research in Hematology, Immunology and Transplantation for the generous and continuous support of the research work. We thank our nursing staff for their excellent patient care.

### **Authors' contributions:**

S.S. collected and analyzed data and wrote the manuscript. F.M. supervised research, analyzed data, performed statistical analyses and contributed to the writing of the manuscript. M.M. designed the study, supervised research, analyzed data and helped with writing the manuscript. All other co-authors collected, assembled and analyzed data, recruited patients and helped write the manuscript.

## References

1. Zeiser R, Blazar BR. Acute Graft-versus-Host Disease - Biologic Process, Prevention, and Therapy. *The New England journal of medicine* 2017; **377**: 2167-79.
2. Al-Kadhimi Z, Gul Z, Chen W, et al. High incidence of severe acute graft-versus-host disease with tacrolimus and mycophenolate mofetil in a large cohort of related and unrelated allogeneic transplantation patients. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2014; **20**: 979-85.
3. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *The New England journal of medicine* 2010; **363**: 2091-101.
4. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high- or low-dose 6-methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. *Blood* 1998; **92**: 2288-93.
5. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood* 1990; **76**: 1464-72.
6. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: secondary treatment. *Blood* 1991; **77**: 1821-8.
7. Bacigalupo A, Palandri F. Management of acute graft versus host disease (GvHD). *Hematol J* 2004; **5**: 189-96.
8. Cahn JY, Bordigoni P, Tiberghien P, 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.
9. Cragg L, Blazar BR, Defor T, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2000; **6**: 441-7.
10. Lee SJ, Zahrieh D, Agura E, 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.
11. Martin PJ, Nelson BJ, Appelbaum FR, et al. Evaluation of a CD5-specific immunotoxin for treatment of acute graft-versus-host disease after allogeneic marrow transplantation. *Blood* 1996; **88**: 824-30.
12. Bolanos-Meade J, Logan BR, Alousi AM, 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; quiz 335.
13. Rossetti F, Dall'Amico R, Crovetti G, et al. Extracorporeal photochemotherapy for the treatment of graft-versus-host disease. *Bone marrow transplantation* 1996; **18 Suppl 2**: 175-81.
14. Messina C, Locatelli F, Lanino E, et al. Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. *British journal of haematology* 2003; **122**: 118-27.
15. Apisarnthanarax N, Donato M, Körbling M, et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone marrow transplantation* 2003; **31**: 459-65.
16. Florek M, Segal EI, Leveson-Gower DB, et al. Autologous apoptotic cells preceding transplantation enhance survival in lethal murine graft-versus-host models. *Blood* 2014; **124**: 1832-42.
17. Gatza E, Rogers CE, Clouthier SG, et al. Extracorporeal photopheresis reverses experimental graft-versus-host disease through regulatory T cells. *Blood* 2008; **112**: 1515-21.
18. Perfetti P, Carlier P, Strada P, et al. Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. *Bone marrow transplantation* 2008; **42**: 609-17.

19. Greinix HT, Knobler RM, Worel N, 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.
20. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone marrow transplantation* 1995; **15**: 825-8.
21. Greinix HT, Volc-Platzer B, Kalhs P, et al. Extracorporeal photochemotherapy in the treatment of severe steroid-refractory acute graft-versus-host disease: a pilot study. *Blood* 2000; **96**: 2426-31.
22. Martin PJ, Bachier CR, Klingemann H-G, et al. Endpoints for clinical trials testing treatment of acute graft-versus-host disease: a joint statement. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2009; **15**: 777-84.
23. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2015; **21**: 389-401.e1.
24. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood* 2014; **123**: 3664-71.
25. Mielcarek M, Furlong T, Storer BE, et al. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. *Haematologica* 2015; **100**: 842-8.
26. Bacigalupo A, Milone G, Cupri A, et al. Steroid treatment of acute graft-versus-host disease grade I: a randomized trial. *Haematologica* 2017; **102**: 2125-33.
27. Castagna L, Morabito L, Mauro E, et al. First-line extracorporeal photochemotherapy for acute GVHD after unmanipulated haploidentical BMT following nonmyeloablative conditioning and post transplantation CY. *Bone marrow transplantation* 2014; **49**: 317-8.
28. Worel N, Lehner E, Fuhrer H, et al. Extracorporeal photopheresis as second-line therapy for patients with acute graft-versus-host disease: does the number of cells treated matter? *Transfusion* 2018; **58**: 1045-53.
29. Miller HK, Braun TM, Stillwell T, et al. Infectious Risk after Allogeneic Hematopoietic Cell Transplantation Complicated by Acute Graft-versus-Host Disease. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2017; **23**: 522-8.

## **Figure legends**

**Figure 1.** Overall response and complete remission rates after ECP procedures according to acute GVHD grade (A). Steroid discontinuation after ECP treatment (B).

**Figure 2.** Overall survival in patients that achieved response at day 56 compared to other patients.

**Table 1.** Study population and transplant characteristics

<b>Characteristic</b>	<b>Value</b>
Sample size, no.	37
Patient age, median (range)	57 (22-66)
Patient gender (male)	26 (70%)
Donor gender (male)	19 (51%)
Female donor → male patient	14 (38%)
<b>Diagnosis</b>	
Myeloid malignancies	30 (81%)
AML	19 (51%)
MDS	3 (8%)
MPN	3 (8%)
MDS/MPN	5 (14%)
Lymphoid malignancies	7 (19%)
ALL	6 (16%)
Lymphoma	1 (3%)
<b>Disease status at transplant</b>	
CR	21 (57%)*
PR	6 (16%)
Progressive	8 (22%)
Never treated	2 (5%)
<b>DRI at transplant</b>	
Very high	2 (5%)
High	14 (38%)
Intermediate	18 (49%)
Low	3 (8%)
<b>Stem cell source</b>	
PBSC	33 (89%)
BM	3 (8%)
double UCB	1 (3%)
<b>Donor type</b>	
HLA-matched relative	9 (24%)
HLA-haploidentical	7 (19%)
HLA-matched unrelated donor	15 (41%)
HLA-mismatched unrelated donor	6 (16%)**
<b>Conditioning regimen</b>	
reduced toxicity MAC	34 (92%)
RIC	3 (8%)
<b>TBI based regimen</b>	



Yes	2 (5%)
No	35 (95%)
Use of ATG	
Yes	35 (95%)
No	2 (5%)
GVHD prophylaxis	
CsA alone	9 (24%)
CsA + MMF	22 (57%)
CsA + MMF+ PTCy	7 (19%)

Abbreviations : AML, acute myeloid leukemia; MDS, myelodysplastic syndrome ; MPN, myeloproliferative neoplasm; ALL, acute lymphoid leukemia; DRI, disease risk index ; PBSC, peripheral blood stem cells ; BM, bone marrow; UCB, umbilical cord blood; HLA, human leukocyte antigen ; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; TBI, total body irradiation; ATG, Anti-thymocyte globulin ; GVHD, graft-versus- host disease; CsA, Cyclosporine A; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide.

\*Three patients were in CR with a positive minimal residual disease

\*\*Four patients received a single HLA mismatch unrelated donor (9/10) and one patient received 2 UCB mismatched at 2 HLA loci each (4/6).

\*\*\* fludarabine and busulfan based reduced toxicity myeloablative conditioning (MAC).

**Table 2.** Acute GVHD characteristics at baseline

<b>Revised Glucksberg criteria</b>	<b>Stage I</b>	<b>Stage II</b>	<b>Stage III</b>	<b>Stage IV</b>
Skin, n (%)	3 (8%)	22 (59%)	12 (32%)	0
Gastrointestinal tract, n (%)	6 (16%)	0	0	0
Liver, n (%)	2 (5%)	2 (5%)	0	0
Overall grade	17 (46%)	18 (49%)	2 (5%)	0

<b>Characteristic</b>	<b>N (%)</b>
Number of involved sites	
1	29 (79%)
2	6 (16%)
3	2 (5%)
Acute GVHD onset type	
Classic	34 (92%)
Late onset	3 (8%)
Acute GVHD onset after allo-HCT (median)*	28 days (range, 11-333)
Acute GVHD therapy	
Systemic corticosteroids	26 (70%)
Dermo-corticosteroids alone	11 (30%)
ECP weekly	23 (62%)
ECP twice weekly	14 (38%)

Abbreviations: GVHD, graft-versus-host disease; ECP, extra-corporeal chemotherapy.

\* One patient had late-onset acute GVHD 76 days after donor lymphocyte infusion ( $0.8 \times 10^7$  CD3<sup>+</sup>/Kg).

**Figure 1.**

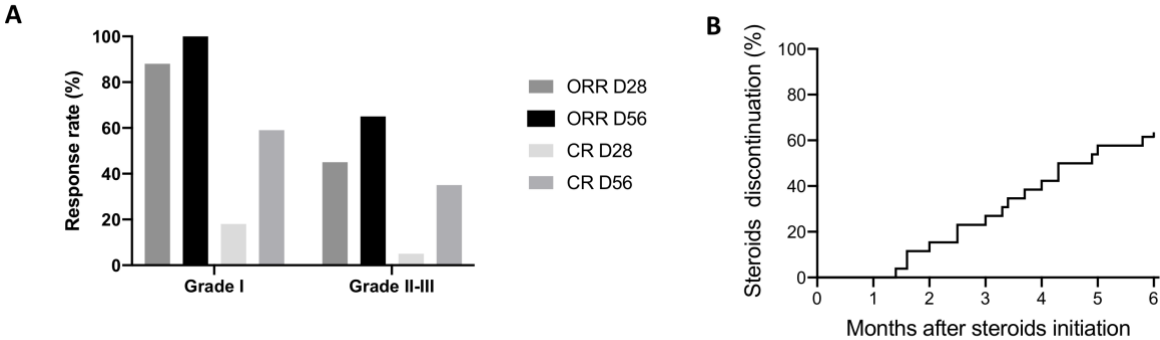


Figure 2.

