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Combination Therapy for Graft-versus-Host Disease Prophylaxis with Etanercept and Extracorporeal Photopheresis: Results of a Phase II Clinical Trial

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A B S T R A C T

Reduced-intensity conditioning (RIC) regimens minimize early toxicity after allogeneic hematopoietic cell transplantation (HCT) by placing greater reliance on establishing a graft-versus-leukemia effect (GVL). Because graft-versus-host disease (GVHD) and GVL are tightly linked, inhibition of T cell populations that cause GVHD may lead to an unintended increased risk of relapse in the RIC setting. Although not completely understood, etanercept and extracorporeal photopheresis (ECP) are thought to ameliorate GVHD without direct T cell inhibition. We hypothesized that adding these 2 agents to a standard GVHD prophylaxis regimen of tacrolimus and mycophenolate mofetil (MMF) would improve survival by reducing GVHD-related mortality without increasing relapse rates. Therefore, we conducted a prospective phase II clinical trial that incorporated tacrolimus, MMF, etanercept, and ECP as GVHD prophylaxis in 48 patients undergoing RIC unrelated donor transplantation. The preferred RIC was fludarabine 160 mg/m^2 + busulfan 6.4 mg/kg to 12.8 mg/kg ± total body irradiation 200 cGy. Etanercept .4 mg/kg (maximum dose, 25 mg) was given subcutaneously twice weekly for 8 weeks after HCT and ECP was given for 12 treatments, starting weekly on day 28 weekly and tapering off by day 180. The median age of the study patients was 60 (range, 18 to 71) years. Donors were 7/8 (n = 14, 29%) or 8/8 (n = 34, 71%) HLA matched. All patients engrafted neutrophils at a median of 12 days. The cumulative incidence of grades II to IV acute GVHD at day 100 was 46%, but it was typically sensitive to initial steroid treatment (84% day 56 complete response/partial response rate). Overall survival at 1 year in this older, frequently mismatched unrelated donor setting was excellent (73%) because of low rates of nonrelapse mortality (21%) and relapse (19%). However, this strategy was not effective at preventing a high incidence of chronic GVHD and late deaths led to a drop in 2-year survival, declining to 56%, reflecting a high incidence of chronic GVHD.

INTRODUCTION

Allogeneic hematopoietic cell transplant (HCT) is increasingly used as a curative option for patients with hematologic malignancies as the expansion of reduced-intensity conditioning regimens (RIC) has allowed for the transplantation of patients who are older and those who have more comorbidities. According to the National Marrow Donor Program, there was greater than a 4-fold increase in the number of patients over the age of 60 who received an unrelated donor (URD) HCT from 2005 to 2009 compared with from 2000 to 2004 [1]. Although utilization of transplantation has increased, there has not been a reduction in the rates of GVHD, and the 3-year survival remains unsatisfactory at around 35% [1]. The major reasons for treatment failure are relapse and graft-versus-host disease (GVHD), the latter of which leads to significant morbidity and mortality. As acute GVHD severity worsens, so does survival, as

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demonstrated by previous studies that show limited mortality after grades I and II acute GVHD and mortality rates that approach 75% with grade III to IV acute GVHD [2]. The large difference in outcomes can be explained by the higher rates of steroid-resistant GVHD, seen with more severe GVHD [3-5]. However, GVHD severity cannot be predicted before transplantation, and as a result, prevention strategies are designed to limit its occurrence rather than its severity.

Traditional GVHD prevention strategies rely on combinations of immunosuppressants that block T cell expansion and cytotoxicity. A common GVHD prophylaxis regimen after RIC includes the calcineurin inhibitor tacrolimus plus mycophenolate mofetil (MMF) and results in rates of GVHD grades II to IV of 54% to 79% [6-8]. However, further augmenting GVHD prophylaxis with additional agents that directly target T cells, such as antithymocyte globulin, increases the risk of relapse, graft failure, and/or infection, which may be especially relevant in the context of RIC [9-11]. We have previously explored whether we could offset the risks from GVHD and its treatment by adding agents to the prophylaxis regimen that have indirect effects on T cell function. In our prior study, tumor necrosis factor alpha (TNF-α) blockade with etanercept was given from admission through day 56 after HCT to a standard tacrolimus and methotrexate backbone in the myeloablative setting. This approach did not reduce the cumulative incidence of GVHD grades II to IV from 45%, but an exceptionally high proportion (93%) of those patients who required treatment for GVHD achieved a complete response (CR) [12], which compared favorably to the expected CR rates of 40% to 50% [13,14]. These results led us to speculate that TNF inhibition during the early post-HCT period increased the steroid-responsiveness of GVHD when it developed.

Extracorporeal photopheresis (ECP) is an immunomodulatory approach that appears to ameliorate GVHD without increasing relapse and infection rates [15-21]. ECP has not been well studied for GVHD prophylaxis, but in 1 study, ECP treatment before HCT, followed by cyclosporine, methotrexate, and MMF, resulted in high rates of donor engraftment (98%), low rates of nonrelapse mortality (NRM) at day 100 (11%), and unexpectedly low rates of acute GVHD (9%) [22]. The effectiveness of ECP delivered after HCT for the prevention of acute GVHD has not been studied.

Given the extensive data to support the importance of TNF-α in the initiation of the GVHD reaction [23-25] and the potential for additional immune modulation via ECP therapy, we decided to study standard GVHD prophylaxis (tacrolimus and MMF) in combination with etanercept and ECP in older patients receiving a RIC unrelated donor HCT. Our hypothesis was that augmenting GVHD prophylaxis in this way would reduce the incidence of steroid-refractory GVHD and NRM yet preserve the graft-versus-leukemia (GVL) effect, thereby leading to improved overall survival. To further study this question, we explored whether a novel endpoint of steroid-free, relapse-free survival at 6 months after HCT could serve as a surrogate endpoint for long-term survival in a GVHD prophylaxis study.

METHODS

Study Population

The study was designed to target patients at high risk for NRM after unrelated donor HCT. Patients who lacked related donors were eligible if they were older than 50 years or if they had comorbid conditions that precluded intensive conditioning regimens regardless of age. Single allele–level HLA mismatches (ie, 7/8 matches) of the HLA-A, -B, -C, and -DRB1 loci by high-resolution typing were allowed when peripheral blood or bone marrow were used. Cord blood units were required to match for at least 4/6 loci (intermediate-resolution typing for the HLA-A and -B loci; high-resolution typing for HLA-DR). Patients with infections not responsive to treatment or who were unlikely to tolerate the fluid shifts associated with ECP were ineligible. The protocol and informed consents were approved by the institutional review board at the University of Michigan. All patients gave informed consent per the Declaration of Helsinki.

Study Design

The study was conducted as an open-label, nonrandomized phase II clinical trial (registered at ClinicalTrials.gov; NCT00639717). Pre-HCT conditioning was selected according to institutional practice given the underlying disease, previous therapy, and comorbidities, provided the regimen was recognized as reduced intensity or reduced toxicity, according to the established literature [26]. The preferred regimen was fludarabine + intravenous busulfan [27-30].

The GVHD prophylaxis schema is shown in Figure 1 and consisted of a standard backbone supplemented by the investigational agents. The backbone consisted of the widely used regimen of tacrolimus and MMF [31,32]. Tacrolimus was begun on day -3 before HCT, titrated to a therapeutic trough level of 8 ng/mL to 12 ng/mL, and tapered by 25% per month starting 56 days after HCT in the absence of GVHD. Cyclosporine was substituted for patients who could not tolerate tacrolimus. MMF 10 mg/kg/dose (max dose, 1 gm) was administered either orally or intravenously every 8 hours from day 0 through day 28.

The investigational agents were administered on an overlapping schedule such that patients received at least 1 study agent continuously through the first 180 days after HCT. Etanercept was given subcutaneously twice weekly (.4 mg/kg; max dose, 25 mg) at least 72 hours apart, from day 0 to day 56 for a total of 16 doses. To mitigate risk of infectious-related complications, etanercept was held for persistent bacteremia (>1 positive blood cultures on separate days) until appropriate antimicrobial treatment was started, hemodynamic instability until resolved for 24 hours, newly diagnosed fungal or mycobacterial infection until 7 days of effective treatment were administered, rising cytomegalovirus viral copy number despite appropriate treatment, or fever ≥102°F daily for > 5 days until afebrile (<100.5°F) for 24 hours. Etanercept was not held for uncomplicated fever < 102°F. Missed doses of etanercept were not made up unless due to patient error. Failure to receive all 16 doses did not require removal from the study.

For practical reasons, ECP could not be administered before white blood cell engraftment. Institutional minimum criteria for hematocrit (>28%) to ensure an adequate separation of red blood cells, white blood cells, and plasma and for platelet count (>35,000/μL) to mitigate risk of bleeding when heparin was used for anticoagulation during ECP treatments were followed. To minimize the need for transfusions to meet these criteria, once weekly ECP was scheduled to begin no earlier than day +28 (±5 days) for 7 treatments until day +70, then tapered to every other week × 2 treatments, then monthly until discontinuation at day +180 (2 to 3 treatments). Depending on the start and end dates, patients received 11 or 12 total ECP treatments. All patients received ECP treatment with the Therakos UVAR XTS photopheresis system (Mallinckrodt Pharmaceuticals [formerly Therakos, Inc.], West Chester, PA); according to the manufacturer's instructions. A treatment consisted of collection of leukocytes, methoxypsoralen incubation, photoactivation, and reinfusion of activated cells via intravenous access. ECP could be given more often at the discretion of the treating physician in the event of GVHD and the patient remained on study to be assessed for primary and secondary endpoints. Transfusion and/or cytokine

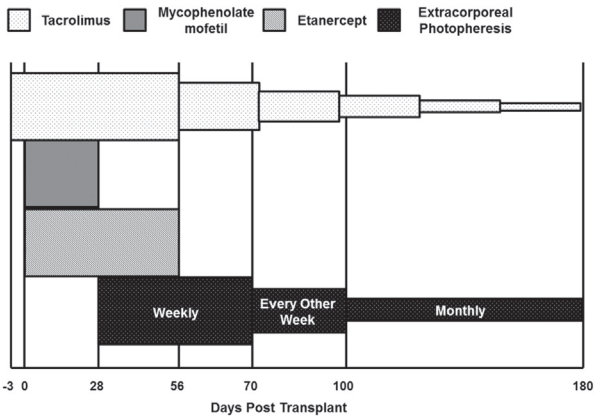

Figure 1 Graft-versus-host disease prophylaxis schema

support were administered when necessary to allow ECP treatment. To mitigate risks associated with ECP delivery, treatments were not given within 72 hours of a positive blood culture, within 24 hours of fever > 100.5°F or hemodynamic instability, within 12 hours of clinically significant bleeding, or on the same day as surgical procedures except bone marrow biopsy and other low bleeding risk procedures. Missed treatments were made up within 1 week. Patients who received < 2 ECP treatments were deemed inevaluable, removed from the study, and replaced. Physicians were allowed but not required to treat GVHD with increased frequency of ECP treatments.

Infections

Infections were identified based on positive blood or body fluid cultures or by detection of viral DNA or RNA in plasma or body fluid by quantitative PCR. Severity was graded according to Blood and Marrow Transplant Clinical Trials Network Technical Manual of Procedures, Version 3.0 [33]. *Grade 3 infections* were defined as bacteremia with deep organ involvement; severe sepsis with bacteremia; fasciitis requiring debridement; pneumonia requiring intubation; brain abscess or meningitis without bacteremia; *Clostridium difficile* toxin positive stool with toxic dilation; fungemia including Candidemia; *Pneumocystis jiroveci* pneumonia; proven or probable invasive fungal infections; disseminated infections with Histoplasmosis, Blastomycosis, Coccidiomycosis or Cryptococcus; severe varicella zoster virus infection; cytomegalovirus infection with end-organ involvement; Epstein-Barr virus–associated post-transplantation lymphoproliferative disorder; adenovirus with end-organ involvement; lower tract respiratory viruses; any viral encephalitis/meningitis; and end-organ toxoplasmosis.

GVHD Scoring and Treatment

A limited number of observers scored acute GVHD according to the modified Glucksberg criteria [34]. The diagnosis of GVHD was made clinically but confirmatory biopsies of affected organs were usually obtained. GVHD was graded weekly until day +100 or resolution of acute GVHD, whichever occurred later. Scores were reviewed by an independent investigator and discrepancies were adjudicated by a study investigator (C.K.) when necessary. Grades II to IV acute GVHD were initially treated with 2 mg/kg/day of methylprednisolone or prednisone equivalent, then tapered at the discretion of the treating physician. Patients continued study treatment after development of acute GVHD except where toxicities precluded doing so. Treating physicians were permitted to increase ECP frequency or add additional treatments at their discretion. Chronic GVHD was assessed according to the National Institutes of Health Consensus criteria [35].

Primary and Secondary Endpoints

We reasoned that a novel endpoint (alive, in remission, and on no more than low-dose steroids [4 mg methylprednisolone or equivalent] for treatment of acute GVHD) at 6 months after transplantation could serve as an acceptable surrogate for long-term survival for patients undergoing RIC URD. We calculated that a sample size of 48 evaluable subjects would provide 80% power to detect an improvement in the proportion of patients who met all these criteria for success from 40% (the historical rate in patient who met study eligibility criteria at our center) to 60% with an alpha level of .05. Secondary endpoints included the incidence of acute GVHD grades II to IV, the incidence of steroid-refractory GVHD, the incidence of chronic GVHD, NRM, and overall survival.

Statistical Analysis

Continuous patient characteristics were summarized with medians and ranges, and categorical patient characteristics were summarized with proportions. Overall survival was estimated using Kaplan-Meier methods and the cumulative incidences of GVHD, relapse, and NRM were estimated using Gray's method. All analyses were done in the statistical package R, Version 3.0.1.

RESULTS

Study Feasibility and Population

The study enrolled 52 patients from April 2, 2009 to July 11, 2012 to obtain 48 patients who received at least 2 ECP treatments and were, therefore, evaluable. Thus, the study treatment plan was feasible in 92% of all patients who provided consent. Per study design, 4 patients were removed from study treatment secondary to failure to receive ECP; primary graft failure (n = 1), noncompliance (n = 1), severe veno-occlusive disease with thrombocytopenia that precluded initiating ECP (n = 1), and early relapse (n = 1). These patients did not receive any ECP treatments and were excluded from this analysis. Table 1 shows the baseline demographic and clinical characteristics of the 48 evaluable patients. By design, the study population was composed of patients at high risk for NRM. The primary risk factors were advanced age (median age, 60 years; range, 18 to 71 years), high (n = 28, 58%) or intermediate (n = 16, 34%) HCT comorbidity index [36,37], and frequent use of HLA-mismatched donors (n = 14, 29%). All but 2 patients received peripheral blood stem cells; there was 1 bone marrow transplantation and 1 cord blood transplantation.

Engraftment, Chimerism, and Toxicities

We did not find evidence that etanercept or ECP affected neutrophil or T cell engraftment. The median time to neutrophil engraftment of 12 days (range, 8 to 26 days) was consistent with expectations [38-40]. The median donor chimerism for $CD3^+$ T cells at day 30 was 93% (range, 48% to 100%) and increased to 100% at 1 year (range, 91% to 100%). Exact date of platelet engraftment was difficult to determine based on need for platelets transfusions to perform ECP in some patients.

Both etanercept and ECP were generally well tolerated. No deaths were attributed to study treatment. An early lymphoma relapse at day 99 after HCT was considered possibly related to study treatment because the etanercept package insert describes the development of lymphoma in nontransplantation patients treated with the drug. Two patients who experienced chest pain without electrocardiogram changes during their sixth and eighth ECP procedure were removed from study treatment as a precaution. No etiology for the chest pain was identified. No other toxicities were considered to be related to ECP. Two early deaths (sudden death at home on day 151, 5 days after an ECP

Table 1
Patients' Clinical Characteristics

Characteristic	Value
Age of recipient, median (range), yr	60 (18-71)
Female	22 (46%)
Diagnosis	
Acute myeloid leukemia	19 (40%)
Myelodysplastic syndrome	12 (25%)
Non-Hodgkin lymphoma	8 (17%)
Acute lymphoblastic leukemia	4 (8%)
Myeloproliferative disorder	3 (6%)
Chronic lymphocytic leukemia	1 (2%)
Multiple myeloma	1 (2%)
Disease status	
Low	19 (40%)
Intermediate	18 (37%)
High	11 (23%)
Comorbidity index	
Low (0)	4 (8%)
Intermediate (1 or 2)	16 (34%)
High (≥ 3)	28 (58%)
HLA matching*	
8/8 HLA–matched unrelated donor	34 (72%)
7/8 HLA–mismatched unrelated donor	13 (28%)
Cytomegalovirus status	
R– D–	18 (38%)
R– D+	2 (4%)
R+ D–	17 (35%)
R+ D+	11 (23%)
$CD34^+$ count, median (range), 10^6 cells per kg*	5.45 (.7-9.8)

R indicates recipient; D, donor.
* Excludes 1 cord blood recipient who received 2 5/6 HLA–mismatched cord blood units.

treatment and a fatal intracranial hemorrhage on day 55 from profound thrombocytopenia 8 days after ECP treatment) were deemed unrelated to study treatment based on their timing. Other Common Terminology Criteria grade 3 and 4 toxicities are summarized in Table 2 but none of these toxicities were considered related to the study interventions by the investigators or after review by the University of Michigan Cancer Center Data and Safety Monitoring Board.

We considered the possibility that the addition of etanercept and ECP would increase infection risk and, therefore, patients were carefully monitored for signs and symptoms of infection at least weekly. The majority of patients (34 of 48, 71%) developed at least 1 infection that required treatment during the 180-day study period (Table 3). Although the exact contributions of etanercept and ECP to the risk of infection is difficult to quantify, the incidence of grade 3 infections observed on study was similar to that reported in the literature [12,41] and similar to the rates of infection that occurred in nonstudy patients during approximately the same time as the study period (unpublished data). Two patients died from infections—1 from Human herpesvirus 6 encephalitis on day 83 and 1 from fungal pneumonia (*Aspergillus fumigatus* and *Rhizopus*) on day 88. We observed 12 grade 3 nonfatal infections in 7 (15%) patients, 4 of who were also on systemic steroid treatment for GVHD at the time, which is a well-known major risk factor for post-HCT infection [42,43]. Grade 3 viral infections developed in 3 patients (all cytomegalovirus end-organ disease, complicated in 1 case by simultaneous Human herpesvirus 6, adenovirus, and Epstein-Barr virus infection). There were 4 grade 3 bacterial infections (1 each of *Streptococcus mitis* sepsis, *Corynebacterium striatum* septic joint hardware, *Achromobacter* pneumonia, *Staphylococcus aureus* pneumonia). In addition to the fatal fungal pneumonia, there were 2 cases of nonlethal grade 3 fungal pneumonia (1 case of *Aspergillus fumigatus* and 1 probable case based on radiographic findings and positive galactomannen result from bronchoalveolar lavage). Study treatment was held per study design for severe infections and then resumed in patients who had an appropriate response to therapy. All other infections were either grade 1 or 2 and resolved with appropriate antimicrobial therapy.

ECP appeared to have little impact on transfusion requirements. Study subjects received a median of 3 packed red blood cell transfusions and 1 pooled platelet transfusion during the 5 months of ECP administration.

Table 2
Grade 3 and 4 non-hematological toxicity according to Common Terminology Criteria

Event	n
Cardiac events	5 (2 episodes atrial fibrillation, 1 each syncope, orthostatic hypotension, NSTEMI)
Deep vein thrombosis	4
Altered mental status secondary to calcineurin inhibitor	3
Musculoskeletal abnormality	3 (1 each daptomycin-associated rhabdomyolysis, trauma-associated ankle pain, steroid myopathy)
Electrolyte abnormality	2
Acute cholecystitis	1
Depression	1
Diverticulitis	1
Evan's syndrome	1
Headache	1
Hematemesis	1
Renal calculi	1

CTC indicates Common Terminology Criteria for Adverse Events; NSTEMI, Non-ST segment elevation myocardial infarction.

Table 3
Infectious Complications

Type of Infection	Grade I	Grade II	Grade III
Bacterial*	21	17	4
Viral†	10	22	6
Fungal	–	–	2
Acid fast bacilli‡	–	3	–

* Grade 1: bacteremia with coagulase negative Staph or Corynebacterium, uncomplicated urinary tract infections; grade 2: bacteremia other than grade 1 and without severe sepsis.

† Grade 1: Herpes simplex virus mucositis, asymptomatic cytomegalovirus (CMV) viremia with appropriate viral load decline with therapy; grade 2: Epstein-Barr virus reactivation treated with rituximab, documented viral upper respiratory infection, symptomatic CMV or CMV not responding to appropriate therapy within 14 days, BK viremia or viruria requiring therapy or surgical intervention.

‡ Grade 2: Acid fast bacilli recovered from bronchoalveolar lavage or bacteremia.

GVHD

The median day of onset of GVHD grades II to IV was 47 days (range, 9 to 201) and GVHD occurred before the initiation of ECP in 10 patients. The cumulative incidence of grades II to IV GVHD by 6 months after URD HCT ranges from 50% to 59% [44,45], and, as expected, the cumulative incidence in this study fell into that range (57%, 95% confidence interval [CI], 42% to 71%) (Figure 2A), with 19% experiencing severe GVHD (overall grades III to IV) by 6 months (95% CI, 8% to 30%). However, as hoped for, we observed a predominance of moderate GVHD (overall grade II, 20 of 29) and these cases of GVHD were highly steroid sensitive (day 56 CR/partial response = 84). Given the steroid-sensitive nature of the GVHD, it is not surprising that the median steroid dose reduction by day 56 was 88% (range, 65% to 94%). Steroid-refractory gastrointestinal GVHD is the primary cause of NRM after HCT [46]. The cumulative incidence of steroid-refractory gastrointestinal GVHD was 23% by 6 months after HCT (95% CI, 13% to 38%) (Figure 2B), which may explain the low incidence of NRM at 1 year (21%; 95% CI, 9% to 32%) (Figure 2C). Notably, attenuation of GVHD severity did not appear to influence the GVL effect, given the cumulative incidence of relapse at 1 year was low at 19% (95% CI, 8% to 30%) (Figure 2D). Thus, low rates of lethal acute GVHD and relapse contributed to excellent 1-year survival in this high-risk population (73%; 95% CI, 61% to 87%) (Figure 2E). Unfortunately, the apparent survival benefit was not durable, as by 2 years, survival declined to 56% (95% CI, 44% to 72%).

Chronic GVHD was a major contributor to deaths that occurred after 1 year (Table 4). The median day of onset of chronic GVHD was 209 days (range, 99 to 1248), which was shortly after the study intervention completed. The cumulative incidences of moderate-to-severe chronic GVHD according the National Institutes of Health consensus criteria [35] at 1 and 2 years were 42% (95% CI, 27% to 56%) and 58% (95% CI, 44% to 73%), respectively (Figure 2F).

The proportion of patients who were alive, in remission, and not requiring steroid therapy for treatment of acute GVHD (defined as more than 4 mg methylprednisolone or equivalent) at 6 months after URD HCT was 58% (n = 28), which was below the 60% required to demonstrate a statistically significant improvement over historical control rate of 40% to support our novel primary endpoint. When use of steroids for any cause was used to redefine endpoint failure, the rate of success fell to 42% (n = 20), reflecting a high

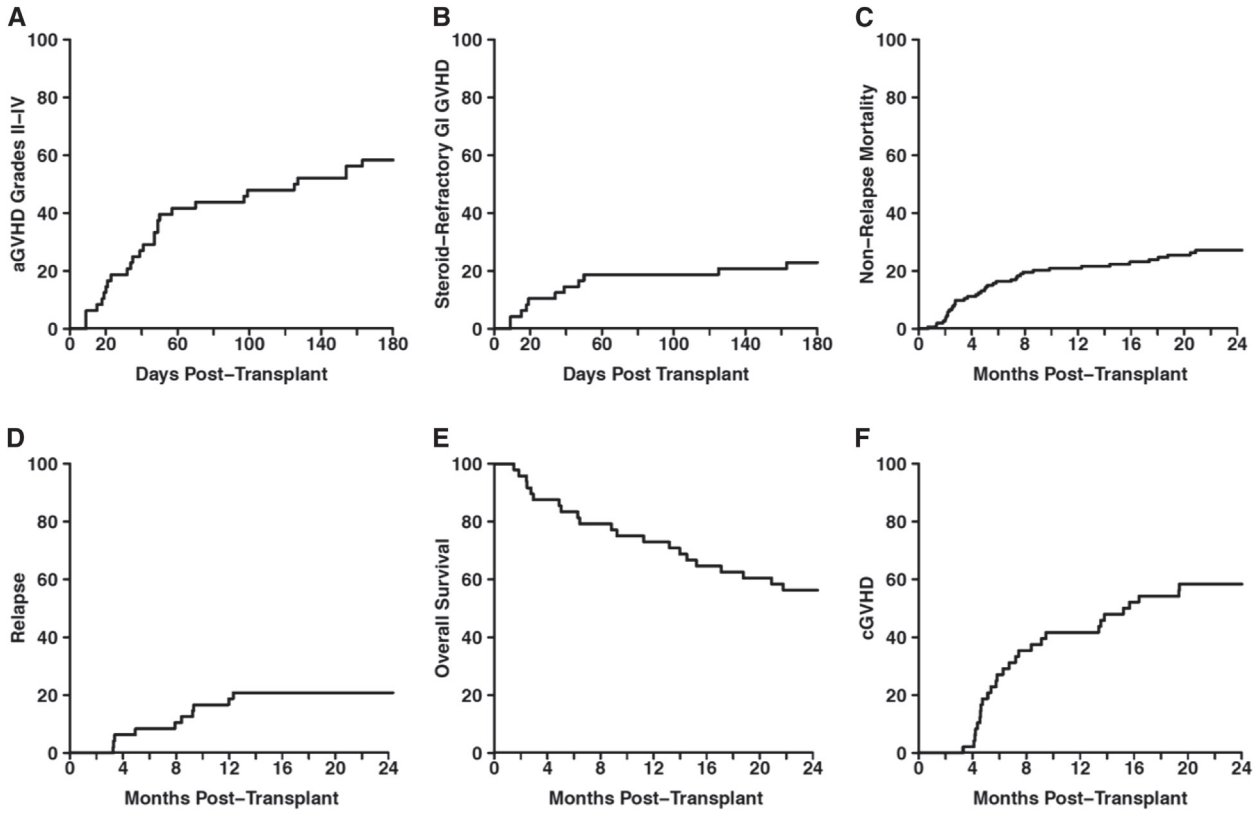

Figure 2. (A) Cumulative incidence of acute GVHD at day 100 was 46% (95% CI, 32% to 60%) and at day 180 was 57% (95% CI, 42% to 71%). (B) Cumulative incidence of steroid-refractory gastrointestinal GVHD at day 180 was 23% (95% CI, 13% to 38%). (C) Cumulative incidence of NRM at 1 year was 21% (95% CI, 14% to 27%) and at 2 years was 27% (95% CI, 14% to 40%). (D) Cumulative incidence of relapse at 1 year was 19% (95% CI, 8% to 30%) and at 2 years was 21% (95% CI, 9% to 32%). (E) Overall survival at 1 year was 73% (95% CI, 61% to 87%) and at 2 years was 56% (95% CI, 44% to 72%). (F) Cumulative incidence of chronic GVHD at 1 year was 42% (95% CI, 27% to 56%) and at 2 years was 58% (95% CI, 44% to 73%).

proportion of patients receiving treatment for chronic GVHD at 6 months after HCT. The proportion of patients who had discontinued steroid treatment was 57% at 1 year after HCT and 60% at 2 years after HCT.

DISCUSSION

The majority of GVHD-related deaths occur in allogeneic HCT recipients who develop steroid-refractory or steroid-dependent GVHD [5,47]. Older and/or infirm recipients, especially of unrelated donor HCT, are particularly susceptible to the toxic effects of steroid treatment and in need of new GVHD prevention strategies that can decrease steroid exposure without further suppressing T cell activity, which could compromise the GVL effect and increase the incidence of graft failure and severe infections. The 73% 1-year survival in the high-risk study population of older and infirm patients, who underwent unrelated donor HCT, often mismatched, compares favorably to the 53% 1-year survival reported for a large series of patients who recently underwent transplantation patients > 60 years facilitated by the National Marrow Donor Program [1]. Unfortunately, the possible benefit from the investigational approach tested in this study appeared to be relatively short-lived, as a significant number of deaths continued to occur after 1 year after HCT.

Table 4
Causes of Death Greater than 1 Year post-HCT

Day of Death after HCT	Primary Cause	Secondary Cause
419	cGVHD	Fungal pneumonia
457	cGVHD	Fungal pneumonia
563	cGVHD	Failure to thrive
795	cGVHD	Pulmonary failure
915	cGVHD	Pulmonary embolism

cGVHD indicates chronic graft-versus-host disease.

We speculate that the possible early survival advantage we observed may be related to the high incidence of steroid-responsive GVHD, which was almost double that expected [13,14]. Although all GVHD developed during or after etanercept treatment, in the small number of cases of early onset before day 28, the initiation of ECP can rightly be considered early treatment. It is possible that some of the observed steroid sensitivity may be related to the benefit of early treatment with ECP. Acute GVHD is a well-described risk factor for the development of chronic GVHD [48]. In this study, concurrent or shortly after completion of investigational therapy, the majority of patients developed chronic GVHD. Thus, it is possible that whatever reduction in steroid-refractory acute GVHD achieved by our treatment strategy was offset by the development of steroid-dependent chronic GVHD, which was the primary cause of most deaths that occurred more than 1 year after HCT.

Our study design did not allow us to independently assess the potential benefit of augmenting GVHD prophylaxis with etanercept alone, as we previously studied [12], or ECP alone in this study population. However, late treatment failures were the major contributor to the lack of sustained improvement in long-term survival, raising the possibility

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