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Etanercept plus Topical Corticosteroids as Initial Therapy for Grade One Acute Graft-Versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Clinical diagnosis of grade 1 acute graft-versus-host disease (GVHD) marks the beginning of a potentially progressive and fatal course of GVHD after hematopoietic stem cell transplantation (HSCT). However, interventional studies to treat early GVHD are lacking. We conducted a single-arm prospective phase II trial to test the hypothesis that treatment of newly diagnosed grade 1 acute GVHD with etanercept and topical corticosteroids would reduce progression to grade 2 to 4 within 28 days. Study patients (n = 34) had a median age of 51 years (range, 10 to 67 years) and had undergone unrelated (n = 22) or related (n = 12) donor HSCT. Study patients were treated with etanercept (.4 mg/kg, maximum 25 mg/dose) twice weekly for 4 to 8 weeks. Ten of 34 patients (29%) progressed to grade 2 to 4 acute GVHD within 28 days. The cumulative incidence of grade 2 to 4 and grade 3 to 4 acute GVHD at 1 year was 41% and 3%, respectively. Nonrelapse mortality was 19% and overall survival was 63% at 2 years. Among a contemporaneous control cohort of patients who were diagnosed with grade 1 acute GVHD and treated with topical corticosteroids but not etanercept during the study period, 12 of 28 patients (43%) progressed to grade 2 to 4 GVHD within 28 days, with a 1-year incidence of grade 2 to 4 GVHD and grade 3 to 4 GVHD of 61% (41% versus 61%, $P = .08$) and 18% (3% versus 18%, $P = .05$), respectively. Patients treated with etanercept also experienced less increase in GVHD plasma biomarkers suppression of tumorigenicity 2 ($P = .06$) and regenerating islet-derived 3-alpha ($P = .01$) 28 days after grade 1 acute GVHD diagnosis compared with contemporaneous control patients. This study was terminated early because of poor accrual. Future prospective studies are needed to identify patients with grade 1 acute GVHD at risk of swift progression to more severe GVHD and to establish consensus for the treatment of grade 1 acute GVHD. This trial is registered with ClinicalTrials.gov, number NCT00726375.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is an important therapy for many malignant and nonmalignant conditions [1]. A significant barrier to the more widespread application of HSCT is the potentially severe and fatal complication of acute graft-versus-host disease (GVHD) [2]. Although prophylaxis strategies have lowered the risk of life-threatening GVHD, 40% to 70% of patients are still at risk of developing the complication [3-7]. Moreover, in these patients, treatment approaches have provided inconsistent outcomes [8]. High-dose systemic corticosteroids remain the standard initial therapy for grade 2 to 4 acute GVHD, yet they carry significant risks [9], and complete response rates range from 25% to 40% [10-13]. Patients who do not have at least a partial response to therapy within the first 28 days are at high risk for nonrelapse mortality (NRM) 6 months from the onset of therapy [14-17].

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The standard treatment of grade 1 (skin stage 1 or 2 only) acute GVHD is topical corticosteroid therapy [9]. However, in clinical practice, it is likely that far more patients with grade 1 acute GVHD are treated with systemic corticosteroids than are reported. In a recent multicenter Blood and Marrow Transplant Clinical Trials Network phase II trial, up to 13% of study patients had a clinical diagnosis of grade 1 acute GVHD and were treated with systemic steroids in conjunction with a secondary agent [18]. Nonetheless, to our knowledge, interventional studies targeted at treatment of grade 1 acute GVHD have not been previously reported. We reasoned that a strategy allowing early, standardized treatment of grade 1 acute GVHD would reduce progression in the first 28 days of diagnosis.

TNF-alpha (TNFα) is an important component of the inflammatory cascade that evolves into acute GVHD [19-22]. Our group has previously shown that the magnitude of increase in TNF-receptor-1 (TNFR1), a surrogate for TNFα, 7 days after HSCT relative to pre-HSCT baseline levels, strongly correlates with increased GVHD incidence, NRM, and decreased overall survival (OS) in adults and children [19,20]. Etanercept, a recombinant human soluble TNFα receptor fusion protein, competes for TNFα binding and renders it inactive [23]. Etanercept attenuated rising TNFR1 levels early after HSCT in patients who received non–total body irradiation conditioning and correlated with good clinical outcomes when used in combination with standard immunosuppression for GVHD prophylaxis [24]. Based on preclinical and clinical studies implicating a role for TNF-α in the etiology of acute GVHD [19-22,24], we hypothesized that TNF-α blockade with etanercept for treatment of grade 1 acute GVHD would reduce the progression to grade 2 to 4 within 28 days.

SUBJECTS AND METHODS

Study Cohort

A prospective, open-label, single-arm phase II trial of etanercept combined with topical corticosteroid therapy for grade 1 acute GVHD after allogeneic HSCT was conducted between May 2008 and April 2013. Patients with a clinical diagnosis of grade 1 acute GVHD (stage 1 or 2 skin rash covering <50% body surface area) were eligible for inclusion in the study if sufficient rash were present to biopsy and the results were consistent with the clinical diagnosis of GVHD. Patients of any age who underwent HSCT with donor cells from any source after either a myeloablative or nonmyeloablative preparative regimen and with clinical grade 1 acute GVHD were eligible. Patients with grade 2 to 4 acute GVHD or with an active infection unresponsive to antibiotics were ineligible for this study. Patients who used systemic steroids at any previous time for treatment of GVHD and patients who received etanercept for any other purpose were also ineligible. The protocol and informed consents were approved by the institutional review board at the University of Michigan. All patients and their legal guardians signed informed consents in accordance with the Declaration of Helsinki.

The GVHD prophylaxis regimens consisted of tacrolimus initiated on day -3 before HSCT (titrated and maintained at a level of 8 to 12 ng/mL) either with mini-methotrexate administered at a dose of 5 mg/m^2 i.v. on days 1, 3, 6, and 11 after HSCT or with mycophenolate mofetil at 10 mg/kg/dose every 8 hours on days 0 through 28. In the absence of GVHD, tacrolimus was tapered starting from day 56 after HSCT and was discontinued by day 180.

Supportive care therapies were administered according to institutional clinical practice guidelines. Antimicrobial prophylaxis included levofloxacin 500 mg once daily for prevention of bacterial infections, voriconazole 200 mg twice daily, acyclovir 400 mg twice daily for viral prophylaxis, and sulfamethoxazole/trimethoprim or pentamidine for prevention of *Pneumocystis carinii* pneumonia. Pediatric patients received age and/or weight equivalent dosing of antibiotics. Cytomegalovirus (CMV) DNA was monitored weekly by quantitative PCR [25] and preemptive therapy with antiviral agents was begun in the event of a positive assay. Intravenous immunoglobulin (Ig) replacement therapy (400 mg/kg) was given for IgG levels <400 mg/dL.

Infection

Infections were enumerated for each patient for 180 days, beginning on the first day of etanercept treatment. An infection was defined using the following criteria: 1 or more positive blood and/or fluid cultures or the detection of DNA in the plasma by quantitative PCR. Proven, probable, and possible invasive fungal infections were classified according to international consensus criteria [26].

GVHD Treatment

All study patients were treated with topical corticosteroids (.1% triamcinolone cream applied to affected areas 3 times daily) at the time of grade 1 acute GVHD diagnosis, according to institutional clinical practice guidelines. Etanercept (.4 mg/kg, maximum 25 mg/dose) was administered subcutaneously twice weekly on nonconsecutive days for 4 weeks, as previously reported at our center [20], for a total of 8 doses. In some patients, etanercept was continued for an additional 4 weeks, as described below. Doses were held and not replaced in patients with bacteremia, hemodynamic instability, fever, or persistent viral infection. If signs and symptoms of infection resolved (blood pressure stable, negative blood cultures for a minimum of 48 hours, 50% reduction in viral copy number) before needing to hold a third consecutive dose of trial drug, etanercept dosing was resumed and the patient was allowed to continue on the trial. In patients who progressed to grade 2 to 4 acute GVHD, standard high-dose systemic corticosteroid therapy was initiated and etanercept was permanently discontinued.

GVHD Scoring and Evaluation of Response

GVHD was monitored weekly in all patients using the modified Glucksberg criteria [27]. Formal GVHD grading to evaluate response in all patients was performed at the start of etanercept treatment (day 0 of trial), week 4, and week 8. Overall GVHD grade was used to determine the response. A *complete response* (CR) was defined as the complete resolution of all manifestations of GVHD (all organs grade 0). Patients achieving a CR at 4 weeks stopped etanercept treatment (8 total doses). Patients with no change in overall grade of GVHD (stable disease, SD) at 4 weeks received 4 additional weeks of etanercept treatment (16 total doses). *Treatment success* was defined as having CR or SD at the 4-week assessment (ie, no systemic corticosteroid therapy). *Treatment failure* was defined as progression to grade 2 to 4 acute GVHD within the first 4 weeks of etanercept treatment. All patients, including treatment failures, were re-evaluated for GVHD grade and response at 8 weeks. Chronic GVHD was diagnosed and staged according to published criteria [28] and treated according to institutional clinical practice guidelines.

Comparison with a Contemporaneous Control Cohort

A contemporaneous control cohort was constructed from the Blood and Marrow Transplantation Program Clinical Database to provide a comparator for the study patients, given a lack of published data on clinical outcomes associated with grade 1 acute GVHD and its treatment. The contemporaneous control cohort comprises all patients who underwent HSCT according to study criteria and were diagnosed with grade 1 acute GVHD during the same time interval as the study patients (2008 to 2013) but who chose not to enroll in the study (n = 28). All contemporaneous control patients were treated with topical corticosteroids (.1% triamcinolone cream applied to affected areas 3 times daily) at the time of grade 1 acute GVHD diagnosis, according to institutional clinical practice guidelines. GVHD was monitored weekly using the modified Glucksberg criteria [27] and standard high-dose systemic corticosteroid therapy was initiated in patients who progressed to grade 2 to 4 acute GVHD.

Correlative Studies: Plasma Biomarkers

Peripheral blood samples were collected on the day of clinical grade 1 GVHD diagnosis and 14 and 28 days thereafter. Plasma was obtained after Ficoll (Amersham, Piscataway, NJ) gradient centrifugation on the day of collection. Samples were dispensed without additives into cryovials and frozen at −80°C for later analysis. Suppression of tumorigenicity 2 (ST2), regenerating islet-derived 3-alpha (Reg3α), TNFR1, and elafin concentrations in each plasma sample were determined using an enzyme-linked immunosorbant assay (ELISA) as previously described [20,24,29-31]. Day-28 biomarker levels were compared between study and contemporaneous control patients after normalizing to day 0 levels (ie, ratio of day 28 over day 0 concentration) for each patient. The normalized value thus indicates the fold change in biomarker concentration from day 0 to day 28. Samples and standards were run in duplicate. Absorbance was measured using a Synergy HT plate reader (BioTek Instruments, Winooski, VT) and results were calculated using Gen 5.1 software (BioTek Instruments). Assays were performed at the Immunologic Monitoring Core of the University of Michigan Cancer Center.