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TNF-Receptor Inhibitor Therapy for the Treatment of Children with Idiopathic Pneumonia Syndrome. A Joint Pediatric Blood and Marrow Transplant Consortium and Children's Oncology Group Study (ASCT0521)

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A B S T R A C T

Idiopathic pneumonia syndrome (IPS) is an acute, noninfectious lung disorder associated with high morbidity and mortality after hematopoietic cell transplantation. Previous studies have suggested a role for TNFα in the pathogenesis of IPS. We report a multicenter phase II trial investigating a soluble TNF-binding protein, etanercept (Enbrel, Amgen, Thousand Oaks, CA), for the treatment of pediatric patients with IPS. Eligible patients were < 18 years old, within 120 days after transplantation, and with radiographic evidence of a diffuse pneumonitis. All patients underwent a pretherapy broncho-alveolor lavage (BAL) to establish the diagnosis of IPS. Systemic corticosteroids (2.0 mg/kg/day) plus etanercept (.4 mg/kg twice weekly × 8 doses) were administered. Response was defined as survival and discontinuation of supplemental oxygen support by day 28 of study. Thirty-nine patients (median age, 11 years; range, 1 to 17) were enrolled, with 11 of 39 patients nonevaluable because of identification of pathogens from their pretherapy BAL. In the remaining 28 patients, the median fraction of inspired oxygen at study entry was 45%, with 17 of 28 requiring mechanical ventilation. Complete responses were seen in 20 (71%) patients, with a median time to response of 10 days (range, 1 to 24). Response rates were higher for patients not requiring mechanical ventilation at study entry (100% versus 53%, $P = .01$). Overall survival at 28 days and 1 year after therapy were 89% (95% confidence interval [CI], 70% to 96%) and 63% (95% CI, 42% to 79%), respectively. Plasma levels of proinflammatory cytokines were significantly increased at onset of therapy, subsequently decreasing in responding patients. The addition of etanercept to high-dose corticosteroids was associated with high response rates and survival in children with IPS.

INTRODUCTION

Idiopathic pneumonia syndrome (IPS) describes an acute, noninfectious lung injury after hematopoietic cell transplantation (HCT). IPS responds poorly to conventional therapy, with mortality rates of 50% to 80% within 28 days of diagnosis

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[1-3]. Criteria for IPS include symptoms of respiratory distress plus radiographic evidence for diffuse alveolar injury in the absence of infection [4]. A recent update further categorized IPS by the primary anatomic site of cellular damage [5]. The incidence of IPS ranges from 2% to 12%, with a median onset 17 to 42 days after HCT and median time to death of 13 days from diagnosis [1,3,5-8]. Risk factors include acute graft-versus-host disease (GVHD) in both adult and pediatric HCT recipients, with a prior history of HCT or viral pneumonitis noted as additional risk factors in children [9-11].

Preclinical studies have revealed that inflammatory cytokines play a role in the development of IPS [5,12-15]. Specifically, TNFα contributes to endothelial cell injury and apoptosis and directs leukocyte recruitment by regulating pulmonary chemokine expression [12,13,15-18]. Increased levels of TNFα and its soluble receptors have also been noted in the bronchoalveolar lavage (BAL) fluid of humans with IPS [12-15,19].

The management of IPS traditionally involves supplemental oxygen, systemic corticosteroids, and advanced supportive care. Recent limited institution clinical trials using a soluble, dimeric, TNFα-binding protein (etanercept, Enbrel; Amgen, Thousand Oaks, CA), when given in combination with systemic corticosteroids, have noted significant improvements in response rate and early survival for patients with IPS [3,6,20]. In collaboration with the Pediatric Blood and Marrow Transplant Consortium and Children's Oncology Group, we conducted a multicenter phase II trial to determine whether the addition of etanercept to standard treatment would improve outcomes for children with IPS.

PATIENTS AND METHODS

Eligibility

Eligible patients were < 18 years old, received an allogeneic HCT within the previous 120 days, and met initial clinical and radiographic criteria for IPS. There were no exclusions to enrollment based on the underlying diagnosis, graft source, conditioning regimen, HLA match, or end-organ function. Patients with bacteremia within the prior 48 hours, cytomegalovirus (CMV) reactivation or CMV disease, mechanical ventilation >7 days, or a history of tuberculosis, prior tuberculosis exposure, or chronic active hepatitis B or C infections were ineligible. Patients receiving > 2.0 mg/kg/day methylprednisolone equivalent were ineligible. Written informed consent was required from all patients (or legal guardians). The trial was registered at ClinicalTrials.gov as NCT00309907.

Study Design

All patients underwent BAL at study entry to establish the diagnosis of IPS, including exclusion of infectious etiologies for the diffuse pneumonitis (Table 1). BAL samples were collected and subsequently subdivided for assays, outlined in Table 1. A clinical assessment of pulmonary dysfunction was obtained at study entry, recording the method of delivery and amount of supplemental oxygen. Other required observations at study entry included an echocardiogram (to exclude cardiogenic shock and pulmonary hypertension), chest x-ray (or computed tomography scan), CMV PCR assay (whole blood or plasma), and blood cultures. C-reactive protein (CRP), serology, and cytokine assays were performed at study enrollment and then weekly through day 28.

Study therapy (etanercept plus corticosteroids) was begun within 24 hours of the BAL, provided that required BAL fluid microbial stains (gram stain and fungal stain) were negative. The date therapy was initiated was defined as day 0 of study. Patients received etanercept (.4 mg/kg/dose, maximum 25 mg) twice weekly over 4 weeks (total of 8 doses). The day 0 etanercept dose was administered intravenously to expedite attainment of maximum plasma levels. Subsequent doses were administered subcutaneously 72 to 96 hours apart. If, at any point after initiation of therapy, pretherapy BAL fluid samples became positive for a pathogen, etanercept was discontinued and not reinstituted. The patient was considered nonevaluable for response and replaced on the study, though he or she was still followed for toxicity and survival.

Corticosteroids were begun at 2 mg/kg/day (methylprednisolone equivalent) on day 0. Intravenous corticosteroids were required the first 3 days, with subsequent change to oral dosing permitted thereafter. No dose reduction was allowed through day 7, with subsequent taper as clinically indicated. Patients already receiving corticosteroids before the study had dosing adjusted to 2 mg/kg/day on day 0. Other immunosuppressive agents were continued, without dosing adjustment, unless clinically indicated. Antimicrobial prophylaxis was given per local institutional practice.

Patients who developed sepsis syndrome, invasive fungal infections, disseminated viral infections, CMV reactivation (by PCR or antigenemia assay), or persistent bacteremia (>72 hours on appropriate antimicrobial therapy) while undergoing study therapy were removed from the study and not replaced. In each scenario, patients were followed for response, toxicity, and survival. Patients who had not met the response criteria before the time of study removal were deemed *nonresponders*.

Table 1
IPS Diagnostic Criteria

1. Presence of widespread alveolar injury:
   a. Diffuse radiographic infiltrates on CXR or CT
   b. SpO2 ≤ 93% on room air, or supplemental oxygen required to achieve SpO2 > 93%.
   c. Clinical signs and symptoms (cough, rales, dyspnea)
2. Absence of lower respiratory tract infection, based upon BAL studies:
   a. Gram stain, fungal stain, acid fast bacilli stain.
   b. Bacterial*, fungal, viral (RSV, parainfluenza, adenovirus, influenza A and B, CMV, rhinovirus) and mycobacterial cultures.
   c. *Pneumocystis jiroveci* assay (PCR, direct fluorescent antibody or cytology).
   d. Viral PCR assays for CMV, HSV, VZV, HHV-6 and community acquired respiratory viruses†.
   e. Galactomannan ELISA assay†.
3. Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload.

CXR indicates chest x-ray; CT, computed tomography; SpO2, peripheral capillary oxygen saturation; RSV, respiratory syncytial virus; HSV, herpes simplex virus; VZV, varicella zoster virus; HHV-6, human herpes virus–6.

* Quantitative bacterial culture ≥ 10^4 colony-forming units per milliliter considered positive.

† Per investigator discretion.

Plasma Biomarker Analysis

Whole blood samples for cytokine assays were collected in heparinized tubes on day 0 and then weekly through day 28. Frozen plasma samples were thawed and analyzed in batch using enzyme-linked immunosorbant (ELISA) assays for inflammatory cytokines, including TNFα, tumor necrosis factor receptor 1 (TNFR1), TNFR2, IL-6, IL-8, sCD14, IFNγ, angiopoietin-2 (Ang-2), and lipopolysaccharide-binding protein (LPB). Plasma samples were also obtained from healthy controls (n = 4) and allogeneic HCT recipients without complications (n = 5). For each assay, samples were diluted and analyzed in replicate per manufacturer's guidelines. Plasma samples from the transplantation controls were obtained from a separate institutional review board–approved study.

Statistical Analysis

The primary study endpoint was response to therapy, defined as survival to day 28 of study plus complete discontinuation of supplemental oxygen support for > 72 consecutive hours. The time to response was defined as the first of 3 consecutive days off all supplemental oxygen. Secondary endpoints included day-56 survival, overall survival (OS), and toxicity assessment using Common Terminology Criteria for Adverse Events version 3.0 (through June 30, 2011), then Common Terminology Criteria for Adverse Events version 4.0 thereafter. Patients were evaluable for response if they received at least 1 dose of etanercept and their pretherapy BAL studies remained negative for pathogen identification. OS was computed using the Kaplan-Meier method, with survival defined from the time of study entry to the date of death or last contact. Statistical comparisons of plasma protein levels were performed using the nonparametric Mann-Whitney test. The study was designed to have 90% power and type I error rate of 5% for detecting a 25% difference in response rates from 30% (historical controls) to 55%. The planned sample size was 40 patients evaluable for response. The protocol was approved by the Children's Oncology Group, Pediatric Blood and Marrow Transplant Consortium, and institutional review boards. A data safety monitoring board, appointed by the Children's Oncology Group, reviewed toxicity and response assessments.

RESULTS

Thirty-nine patients enrolled between 2006 and 2011 from 22 centers, with 28 patients evaluable for response assessment (Table 2). Eleven patients enrolled and began