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Safety and Efficacy of Infliximab Therapy in the Setting of Steroid-Refractory Acute Graft-versus-Host Disease

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A B S T R A C T

Acute graft-versus-host disease (aGVHD) is the leading cause of morbidity and mortality after allogenic hematopoietic cell transplantation (HCT). Corticosteroids are the first-line treatment; however, less than one-half of patients achieve durable remission. Studies suggest that TNF-α, a cytokine released from the bone marrow during conditioning, is involved in the pathogenesis of aGVHD. We retrospectively evaluated the outcome of anti-TNF-α therapy with infliximab in 35 patients with steroid refractory (SR) aGVHD. Infliximab was administered intravenously at 10 mg/kg for a median of 4 doses (range, 1 to 6) on a weekly basis. The overall response rates were 40% (17% complete response [CR], 23% partial response [PR]) at 4 weeks, 23% (9% CR, 14% PR) at 8 weeks, and 17% (all CR) at 12 weeks. Twenty-nine (83%) patients had infectious complications within 12 weeks of initiation of infliximab. These infections included 40 bacterial infections, 6 invasive fungal infections, and 5 viral reactivations. Twelve patients (34%) died secondary to infections. Overall survival at 12 weeks and 6 months from the start of infliximab therapy was 37% (13 of 35) and 17% (6 of 35), respectively; with most deaths secondary to complications from GVHD and infections. In conclusion; the use of infliximab therapy in patients with SR-aGVHD is associated with a modest poorly sustained response along with a heightened risk of severe infections. Future studies with more effective and less toxic therapies are needed for these patients.

INTRODUCTION

Acute graft-versus-host disease (aGVHD) is an important cause of morbidity and mortality in patients undergoing allogeneic hematopoietic cell transplantation (HCT). Reported incidence rates range from 10% to 80%, depending upon prevalent risk factors [1]. Corticosteroids are the mainstay of treatment and response to steroids is a key predictor of outcome [2]. However, more than one-half of treated patients will be steroid refractory (SR), with mortality rates ranging between 50% and 60% [3-5]. There is no consensus on the optimal strategy for managing SR patients and it remains an area of unmet medical need. Second-line therapies, such as antithymocyte globulin (ATG) and monoclonal antibodies, have been studied in this setting, but outcomes, especially for advanced aGVHD, remain dismal [6-9].

Inflammatory cytokines are important mediators of aGVHD [10-12]. TNF-α released during the conditioning regimen is involved in the pathogenesis of aGVHD by activating antigen-presenting cells, recruiting effector cells, and causing direct tissue damage [13,14]. Infliximab is a chimeric monoclonal antibody that binds both the soluble subunit and the membrane-bound precursor of TNF-α. Small retrospective case series have provided conflicting results with regard to efficacy in the setting of SR-aGVHD. In a pilot study assessing the efficacy of infliximab in patients with SR-aGVHD, Couriel et al. investigated a cohort of 21 patients and reported an overall response rate (ORR) of 67% [15]. This finding was supported by additional small retrospective studies [16-22]. A more recent study assessing infliximab salvage therapy in 52 patients reported a complete response (CR) of 15% [23], while a randomized, upfront, phase 3 study comparing infliximab with corticosteroids to corticosteroids alone in aGVHD did not show any benefit [24].

At our institution, infliximab is used for treatment of SR grades III and IV aGVHD. In this article, we report our experience using infliximab in a series of 35 consecutive patients with SR-aGVHD.

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METHODS

Patients

After institutional review board approval, adult patients ≥ 18 years of age who received infliximab therapy for SR-aGVHD from January 1, 2003 until

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May 30, 2016 were identified thorough a retrospective review of our clinical database. The selection criteria included patients who presented both with classic aGVHD occurring within 100 days after HCT and persistent or late-onset aGVHD occurring after 100 days in the absence of features consistent with chronic GVHD (cGVHD). All relevant demographic, clinical, laboratory, and pathologic data were retrospectively abstracted.

Definitions

Acute GVHD was staged and graded according to the Glucksberg scale [25]. *Steroid refractoriness* was defined as any grade progression within 3 days of therapy onset or failure to achieve at least 1 grade improvement within 7 days of initiation of systemic steroids.

CR was defined as sustained resolution of all clinical signs of aGVHD; *partial response* (PR) was defined as an improvement in aGVHD stage in at least 1 of the initially involved organs without complete resolution and without worsening of severity in other affected organs; *no response* (NR) was defined as the same stage of GVHD in all organs or progression of aGVHD in any organ. *Overall response* was defined as either CR or PR. Those who achieved a response after additional agents beyond infliximab were also defined as NR to infliximab. *Overall survival* (OS) was calculated from the first day of infliximab therapy until the date of death from any cause. *Nonrelapse mortality* was defined as time to death without evidence of disease relapse.

Invasive fungal infections (IFI) were classified and defined according to the revised version of the European Organization for Research and Treatment of Cancer/Mycosis Study Group criteria [26].

Treatment and response evaluation

All patients signed a written consent for data collection and analysis. Patients were on antiviral prophylaxis with acyclovir or valacyclovir, antibiotic prophylaxis with penicillin (doxycycline for penicillin intolerance/allergy) ± levofloxacin/ciprofloxacin (only if absolute neutrophil count was < .5 x 10(9)/L), trimethoprim-sulfamethoxazole, and fungal prophylaxis either with an azole (voriconazole n = 27, 77%; posaconazole n = 4, 11%; fluconazole n = 2, 6%) or an echinocandin (caspofungin n = 1, 6%) at the start of infliximab therapy, according to the Mayo Clinic protocol for antimicrobial prophylaxis for active GVHD. Infliximab was dosed at 10 mg/kg intravenously on a weekly basis, with an initial plan for 4 doses. Additional doses were allowed at the discretion of the treating physician and corticosteroids were tapered, also at the discretion of the treating physician, based on response assessment.

Acute GVHD responses were evaluated retrospectively at 4 weeks, 8 weeks, and 12 weeks from the first day of infliximab administration or at the time of last follow-up, if occurring earlier than the stated time points. All infections detected from the first day of infliximab therapy until 12 weeks after completion of therapy were noted. Recurrent aGVHD and relapse of the underlying hematological malignancy were recorded until the date of death or last follow-up.

Statistics

Baseline patient, disease, and treatment-related variables were reported using descriptive statistics (counts, medians, and percentages). Survival analysis was performed using the Kaplan-Meier method. Univariate logistic regression models were utilized to assess the association between patient characteristics and treatment outcomes. The baseline and follow-up liver enzyme levels were compared using a paired *t*-test. Statistical analyses were performed using JMP Pro Version 11 (SAS Institute, Cary, NC) software.

RESULTS

Patient and Disease Characteristics

Thirty-five patients were treated with off-label use of infliximab for SR-aGVHD. The median age was 55 years (range, 35 to 68) and there were 23 males (66%). The most common indication for transplantation was acute leukemia (n = 14, 40%) followed by chronic lymphocytic leukemia (n = 9, 26%), multiple myeloma (n = 4, 11%), myelodysplastic syndrome (n = 3, 9%), myeloproliferative neoplasm (n = 2, 6%), chronic myelomonocytic leukemia (n = 2, 6%), and non-Hodgkin lymphoma (n = 1, 2%). One patient received a bone marrow graft (3%), while the remainder received peripheral blood (n = 34, 97%) grafts, with stem cell sources from matched related (n = 19, 54%), matched unrelated (n = 11, 31%), mismatched related (n = 1, 3%), or mismatched unrelated (n = 4, 11%) donors. There were no umbilical cord blood or haploidentical blood/bone marrow recipients. Patients received pretransplantation conditioning with reduced-intensity regimens (n = 20, 57%) and myeloablative regimens (n = 15, 43%). Primary GVHD prophylaxis was with the following: (1) cyclosporine combined with either mycophenolate mofetil (MMF) (n = 8, 23%) or methotrexate (n = 7, 20%), (2) tacrolimus combined either with methotrexate (n = 16, 46%) or sirolimus (n = 1, 3%), or (3) prednisone combined with either cyclosporine (n = 2, 6%) or MMF (n = 1, 3%). Patient and transplantation characteristics are summarized in Table 1.

Table 1
Patient Demographics and Transplantation Characteristics (n = 35)

Characteristic	Value
Age at HCT, median (range), yr	55 (35-68)
Gender, male	23 (66)
Diagnosis	
Acute myeloid leukemia	12 (34)
Chronic lymphocytic leukemia	9 (26)
Myelodysplastic syndrome	3 (9)
Myeloma	4 (11)
Myeloproliferative neoplasms	2 (6)
Other*	5 (14)
Disease status at HCT	
CR	11 (31)
Not in CR	24 (69)
ABO mismatch	
Matched	19 (54)
Minor mismatch	6 (17)
Major/bidirectional mismatch	10 (29)
Donor type	
Related	20 (57)
Unrelated	15 (43)
HLA match	
Matched	30 (86)
Mismatched†	5 (14)
Conditioning regimen	
RIC	20 (57)
MA	15 (43)
Donor/recipient sex	
Female/male	7 (20)
Other	28 (80)
Stem cell source	
Bone marrow	1 (3)
Peripheral blood	34 (97)
CMV status	
D+/R–, D+/R+, or D–/R+	27 (77)
D-/R-	8 (23)
GVHD prophylaxis	
Cyclosporine ± MTX	17 (49)
Tacrolimus ± MTX	16 (45)
Other	2 (6)
Overall GVHD grade at the beginning of infliximab	
Grade 3	15 (43)
Grade 4	20 (57)

Data presented are n (%) unless otherwise indicated.
RIC indicates reduced-intensity conditioning; MA, myeloablative; CMV, cytomegalovirus; D/R, donor/recipient; MTX, methotrexate.
* Other diagnosis were acute bilineal leukemia, acute lymphoblastic leukemia, primary myelofibrosis, non-Hodgkin lymphoma.
† Four patients were 9/10 and 1 patient was8/10 matched.

GVHD and Treatment Response

The median time to onset of aGVHD was 43 (range, 17 to 154) days after transplantation (Table 2). Initial treatment was started at a median of 3 (range, 0 to 12) days after aGVHD onset, with an initial prednisone-equivalent corticosteroid dose of 1 mg/kg per day (n = 13, 37%) or 2 mg/kg per day (n = 22, 63%), at the discretion of the treating physician, and any prior treatment with calcineurin inhibitors (n = 18, 50%), MMF (n = 9, 27%), or sirolimus (n = 1, 3%) was continued.

Infliximab was administered as second-line therapy (n = 28, 80%) at a median of 17 (range, 6 to 50) days after the initiation of corticosteroids and as third-line therapy (n = 7, 20%)