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Tocilizumab for steroid refractory acute graft-versus-host disease

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Abstract

Acute graft-versus-host-disease (aGVHD) is a frequent and often lethal complication of allogeneic hematopoietic stem cell transplant despite prophylaxis. Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody that has evidence of activity in patients with steroid refractory (SR) GVHD. We retrospectively report on nine patients with grade 3 or 4 SR aGVHD who received tocilizumab. Eight mg/kg of tocilizumab was administered intravenously every 3–4 weeks. aGVHD grading and responses were based on consensus criteria. Median age at transplant was 48 years. Five patients had alternate donor sources. Median time from aGVHD onset to tocilizumab administration was 44 days. Two patients had complete responses and two had partial responses. Median survival from start of tocilizumab was 26 days (range 13–1054). Our limited experience demonstrated an overall response rate of 44% (CR + PR); however, this response was not durable. Further studies are needed to determine the optimal time for tocilizumab initiation.

Keywords

Antibody-based immunotherapy; cytokine and chemokine biology; clinical results; graft-versus-host disease

Introduction

Graft-versus-host disease (GVHD) is a major and frequent complication after allogeneic hematopoietic cell transplant (allo HSCT) associated with significant transplant-related morbidity and mortality. Despite improvements in post-transplant immunosuppression and

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increased use of reduced-intensity conditioning regimens, up to 30–75% of patients receiving allo HSCT develop acute and chronic GVHD (aGVHD, cGVHD) [1–4].

The initial management of aGVHD is glucocorticoids (methylprednisolone or prednisone). However, clinically significant improvement is seen in approximately 50% of patients [2,4]. For patients who fail to respond to steroids, there is currently no standard second line therapy. Various agents have been employed including antithymocyte globulin, cytostatic agents (mycophenolate mofetil (MMF), pentostatin), immunomodulation agents (mTor inhibitors, thalidomide, photopheresis), and biologic therapies (rituximab, alemtuzumab, and denileukin difitox) [2,4–9]. With second-line treatment, response rates have been low (20–30%) with survival rates averaging 2–4 months after the onset of steroid refractory GVHD, indicating the need for more effective therapies in steroid-refractory GVHD (SRGVHD).

Interleukin 6 (IL-6) is a pleiotrophic cytokine that is produced by a variety of cell types and is reportedly elevated in the serum of patients with ongoing GVHD [10–14]. Polymorphisms in recipient and donor genotypes that result in increased IL-6 production have been associated with an increase in GVHD severity [10]. Studies in murine models of GVHD have shown that treatment with an IL-6R antibody significantly reduces GVHD-associated mortality and pathological damage, particularly in the colon [14]. Preclinical studies have demonstrated with IL signaling blockage, recalibration of the effector and regulatory arms of the immune system occurs [12,13]. This leads to a reduction in proinflammatory T_H1 and T_H17 cells with a proportionate increase in the number of regulatory T cells, allowing for GVHD protection [12,13]. T_H17 cells secrete IL-17, which has shown to be overproduced and associated with the development of scleroderma of the skin. IL-6 plays a pivotal role in the differentiation of T_H17 cells from naïve T cells; therefore blockage of IL-6 may result in a decrease in the production of T_H17 cells and therefore skin sclerosis [12,13].

Tocilizumab (Actemra, Genentech,) is a humanized anti-interleukein-6 receptor antibody that blocks interleukin-6 (IL-6) signaling. It is approved for the treatment of severe active rheumatoid arthritis and has been shown to have some efficacy in systemic juvenile idiopathic arthritis and multicentric Castlemans' disease [15–17]. Recent reports have demonstrated that tocilizumab may reduce the severity of GVHD in SRGVHD, especially in the gastrointestinal tract [18,19]. Drobyski and colleagues described responses, toxicities, and infections in eight patients (six with aGVHD) treated with tocilizumab 8 mg/kg given every 3–4 weeks for steroid-refractory GVHD [14]. They noted an overall response rate (PR + CR) of 67%. Infections were the primary adverse effect, 69% bacterial in origin. Two patients had viral infections; CMV colitis and BK viruria. Based on these findings, the authors concluded that tocilizumab has activity in the treatment of steroid-refractory GVHD and warranted further investigation.

Here, we retrospectively summarize our experience with tocilizumab in nine patients with advanced SR aGVHD.

Methods

Patient population

Nine patients who underwent allo HSCT at The Ohio State University (OSU) were treated with off-label tocilizumab for SR aGVHD between July 2011 and July 2012. All patients were deemed steroid-refractory if they had no response after at least 1 week of high dose steroids (2 mg/kg) or had progression after at least 72 hours of treatment with high dose steroids. All patients undergoing allogeneic HSCT at OSU sign written informed consent allowing prospective data collection on toxicities, outcomes, and GVHD. The OSU Institutional review board approved this retrospective analysis. The authors have nothing to disclose.

Treatment

All patients received tocilizumab at 8 mg/kg per dose (rounded to the nearest vial size) IV every 3–4 weeks [18,19]. A maximum of eight doses was planned. Other immune suppressive medications and systemic steroids were maintained and gradually weaned off per institutional guidelines at the discretion of the treating physician. Tocilizumab therapy was discontinued in those patients who did not respond or had progression of aGVHD. Patients who had significant adverse events (i.e. severe infections) did not continue treatment.

GVHD and toxicity assessment

Acute GVHD grading and staging was done according to the consensus criteria [20]. Toxicity was assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Response definitions

Acute GVHD response was determined by the International Bone Marrow Transplant Registry (IBMTR) scoring system. Responses were assessed weekly until the end of tocilizumab treatment. Complete response (CR) indicated that all manifestations of acute GVHD resolved in all organs. A partial response (PR) indicated improvement in at least one organ without any progression in others. Mixed response (MR) was an improvement in one or more organs with progression in another organ or development of symptoms of GVHD in a new organ. No response (NR) was progression with new organ involvement or increased organ-specific symptoms sufficient to increase the organ stage by one or more after at least 7 days of tocilizumab administration. No reduction or stable disease 7 days after tocilizumab administration was also considered NR.

Infection monitoring

Blood, fluids, and tissue-directed cultures for bacterial and fungal pathogens were obtained at the discretion of the treating physician when clinically indicated. All patients had weekly cytomegalovirus (CMV) checked in real time by quantitative polymerase chain reaction (qRT-PCR) in peripheral blood. Epstein-Barr virus (EBV) was measured by qRT-PCR as clinically indicated and weekly in patients with anti-thymocyte globulin (ATG) containing

preparative regimens. Human herpes virus 6 (HHV-6) DNA, adenovirus DNA, and BK virus DNA were obtained as clinically indicated. Pre-emptive therapy for CMV is initiated if weekly CMV qRT-PCR result is greater than 4000 copies/ml. Initial pre-emptive therapy is typically valganciclovir; alternative therapies are ganciclovir, foscarnet, and cidofovir.

Statistical analysis

Descriptive statistics were used to describe responses and outcomes. GVHD grading and staging were described on an individual patient basis.

Results

Patient characteristics

Table I lists the patients' characteristics. The median age at transplant was 48 years (range 25–61). Six patients received myeloablative conditioning (MAC). All but one patient received tacrolimus (0.02 mg/kg every 24 hours as a continuous infusion beginning on day −2, then changed to oral at 2–3 times the total 24-hour intravenous dose, split into 2 doses given every 12 hours as soon as clinically feasible to a target drug level of 5–12 ng/ml), with either methotrexate (15 mg/m^2 on day + 1 after stem cell infusion, and at a dose of 10 mg/m^2 on days +3, +6, and +11 for patients getting MAC, and 5 mg/m^2 on days +1, +3, and +6 for patients getting RIC) or MMF (1000 mg every 8 to 12 hours: dependent upon regimen) for aGVHD prophylaxis. According to institution guidelines, tapering of tacrolimus started on day+100 post all HSCT in the absence of GVHD and disease relapse with a goal of complete discontinuation by 6 months. All were in complete remission of their underlying disease at onset of aGVHD.

Acute GVHD characteristics

All patients had lower gastrointestinal tract (GI) involvement proven by biopsy with negative CMV stains. Seven patients (78%) had involvement of two organs. The median aGVHD overall grade was 3 (range 3–4). The median time from allo HSCT to aGVHD onset was 29 days (range 18–90) (Table II). Tocilizumab was administered as a second line treatment in one patient (11%) and as a third line agent in eight patients (89%).

Infusion-related toxicity and other adverse events

The median number of tocilizumab infusions was two (range: 1–6). The two patients who received six doses did not proceed to complete eight doses at the discretion of their treating physicians. One patient had an infusion reaction with the first dose characterized by acute shortness of breath with pulmonary edema requiring intubation. The patient quickly improved with high dose methylprednisolone and was extubated within 24 hours and went on to receive a total of six doses with acetaminophen and diphenhydramine premedications; further infusion-related events did not occur. No patient discontinued treatment because of toxicity. The main reason for treatment discontinuation was lack of response and/or progression of aGVHD.

Infection assessment

Two patients had CMV reactivation; the first patient had viremia during tocilizumab treatment, which cleared with valganciclovir. The second patient initially developed CMV viremia 1 month after the last dose of tocilizumab and obtained a complete response to aGVHD, but unfortunately the patient failed to respond to CMV therapy and died from CMV infection with colitis and pneumonitis. One patient who had mixed response (CR in GI and NR in liver) after two doses unfortunately developed klebsiella pneumoniae that led to septic shock and death. One patient developed a methicillin sensitive staphylococcus aureus sinus infection while another patient developed a methicillin resistant staphylococcus aureus bacteremia that were successfully treated. No patients were identified with EBV, adenovirus, or HHV6 reactivation during tocilizumab treatment.

Tocilizumab treatment response

The median time from aGVHD onset to tocilizumab administration was 44 days (range: 14–176). The responses to tocilizumab are listed in Table II. The overall response was 44% (two CR and two PR). Six patients (67%) died from aGVHD and its complications. The median survival from start of tocilizumab was 26 days (range: 13–1054). Only one patient was alive at the time of this analysis. This patient remains GVHD-free without the use of immunosuppressive therapies.

Discussion

Steroid-refractory aGVHD remains a significant contributor to transplant-related morbidity and mortality. Based on an understanding of the etiologic role of IL-6 in the pathogenesis and maintenance of aGVHD, tocilizumab has been utilized as a salvage therapy for SR aGVHD.

The case series by Drobyski *et al*. showed very promising results with four out of six patients (67%) with aGVHD showing partial response or better [19]. Our study was not as impressive with only four patients (44%) showing a response. Despite the difference, the patient populations were not remarkably different. The aGVHD prophylaxis with tacrolimus and MMF was similar between the two groups with 77% (our group) and 67% (Drobyski group). The median time from aGVHD onset to tocilizumab administration was similar between the two groups (44 days; range: 14–176) in our group vs. 36 days (range: 8–260) in the Drobyski group). In both studies, the majority of patients received tocilizumab as a third or later line of therapy. Lastly, aGVHD organs involved and overall grading with 7/9 (78%) and 4/6 (67%) having two organs involved respectively were not different. However, one major difference, which seems unlikely to account for the difference in responses, was the graft source. Our study included four cord blood and one haploidentical transplant indicating a patient population with a higher risk for development of aGVHD.

While we showed a 44% ORR to tocilizumab, it was not durable, as six patients died from aGVHD or its complications. Four patients had infections; whether these were related to tocilizumab is difficult to associate given the immunosuppressed states of these patients.

Limitations of this study are its retrospective nature, small sample size and heterogeneity of the graft source. It may be worth considering anti-IL6 therapy as a much earlier intervention or as a prophylactic approach [21]. Additionally, the optimal dosing and frequency of tocilizumab administration is worth exploring. Our findings further underscore the need for prospective clinical trials investigating newer agents in the early stages of SR aGVHD.

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Table I

Patient characteristics.

Patient	Age	Sex	Disease	Response at time of transplant	Type of transplant	CMV status recipient/donor	Stem cell source	Donor sex/age	Patient/donor ABO type	Conditioning* regimen	aGVHD prophylaxis	Disease response post transplant
1	38	M	MDS with t (3;12)	Persistent disease	Double cord	IgG+IgM-/Neg	Cord	Both F	O/B O/O	MA Flu/Cy/TBI	Tacro/MMF	CR
2	62	M	Pre B ALL Ph+ (transformed from CML)	CR1	Matched Sibling	IgG +IgM-for both	PB	M/70yrs	A/O	RIC Flu/Bu	Tacro/MTX	Morphological CR
3	48	F	AML primary induction refractory	Minimal residual disease	Double Cord	Recipient neg	Cord	M F	A/A A/O	MA Flu/Cy/TBI	Tacro/MMF	CR
4	50	F	follicular lymphoma	PR2	Double Cord	Recipient neg	Cord	M F	A/O A/O	RIC Flu/Cy/TBI	Tacro/MMF	CR
5	41	M	AML Inv 16	CR2	9/10 DQ mismatch, unrelated	Neg/IgG+IgM-	Bone marrow	M/32yrs	A/O	MA Cy/TBI	Tacro/MMF/RGI 2001	CR
6	42	M	CLL del 17P and del 11q	PR	Matched Sibling	Neg/IgG+IgM-	PB	F age unknown	Unknown. Allo HSCT done outside hospital	MA TBI	CSA/MMF	CR
7	49	F	MDS with monosomy 7	Persistent disease	Cord failed Haploidentical	Recipient neg Neg/	Cord PB	F M/47	O/O O/O	MA Flu/Mel/Cy MA Flu/Cy/TBI	Tacro/MMF Tacro/MMF	CR
8	61	M	CLL del 17P	PR	Matched unrelated	Neg/IgG+IgM-	PB	M/28yrs	O/O	RIC Bu/Flu/ATG	Tacro/MTX	CR
9	25	F	B cell ALL	CR1	Double Cord	Recipient neg	Cord	M M	O/O O/B	MA Flu/Cy/TBI	Tacro/MMF	CR

GVHD, graft-versus-host disease; CMV, cytomegalovirus; MDS, myelodysplastic syndrome; CLL, chronic lymphocytic leukemia; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; TBI, total body irradiation; MMF, mycophenolate mofetil; PB, peripheral blood; ATG, antithymocyte globulin; Tacro, tacrolimus; MTX, methotrexate; CSA, cyclosporine; MA, myeloablative; RIC, reduce intensity conditioning, Flu, fludarabine; Bu, Busulfan; Cy, cyclophosphamide; CR, complete response; PR, partial response

*Dosing: all by intravenous infusion where indicated. MA Flu/Cy/TBI: Flu 25 mg/m^2/day × 3 doses day −8 to−6, Cy 60 mg/kg/day × 2 doses day −7 to −6, TBI 12 Gy (in divided doses given twice a day over 4 days, day −4 to−1). Day 0 is day of stem cells infusion. MA Cy/TBI: Cy 60 mg/kg/day × 2 doses day −5 to−4, TBI 12 Gy (in divided doses given twice a day over 3 days, day −3 to −1). MA Flu/Mel/Cy: Flu 30 mg/m^2/day × 5 doses days −6 to −2, Mel 140 mg/m^2 divided on days −3 and −2, Cy 50 mg/kg/day × 2 doses, day +3 and +4. MA TBI: sequence administration unknown as allo HSCT done at outside hospital. RIC Flu/cy/TBI: Flu 40 mg/m^2/day × 5 doses days −6 to −2, Cy 50 mg/kg once day −6, TBI 2 Gy once day −1. RIC Bu/Flu/ATG: Flu 30 mg/m^2/day × 5 doses day −7 to −3, Bu 0.8 mg/kg every 6 hours × 8 doses day −4 to −3, ATG 2 mg/kg/day, day −4 to −2.

Table II

aGVHD characteristics and tocilizumab response.

Patient	Day of aGVHD onset	Overall grade of GVHD prior	Organ involvement (stage)	GVHD treatments prior to tocilizumab	Days to tocilizumab administration from aGVHD onset	Line of therapy of tocilizumab	No. of doses	Overall response to tocilizumab	Current status	Days of survival from tocilizumab initiation	Primary cause of death
1	+26	3	GI (2) Liver (2)	Steroids basiliximab	44	3	6	CR	Dead	308	Infection-CMV
2	+30	4	GI (3) Liver (4)	Steroids	146	2	2	NR	Dead	25	aGVHD
3	+18	3	GI (4) Liver (1)	MMF* steroids	21	3	1	GI : NR Liver: resolved-CR	Dead	20	aGVHD
4	+60	3	GI (2)	Steroids MMF*	14	3	6	CR	Alive and disease free	1054	NA
5	+25	3	Skin (2) GI (4)	Steroids sirolimus	61	3	1	NR	Dead	13	Alveolar hemorrhage aGVHD
6	+90	3	GI (1) Liver(2)	Steroids tacrolimus#	176	3	2	GI resolved – CR Liver –NR	Dead	26	Klebsiella pneumonia septic shock
7	+28	3	GI (4)	Sirolimus steroids	69	3	2	NR	Dead	33	aGVHD
8	+43	3	Liver (3) GI(3)	MMF steroids	42	3	2	NR	Dead	16	aGVHD
9	+29	4	GI (4) Liver (4)	Steroids MMF*	14	3	2	NR	Dead	107	aGVHD

GVHD, graft-versus-host disease; aGVHD, acute graft-verus-host disease; CMV, cytomegalovirus; CR, complete response; NR, no response.

*The agent was reinitiated or dose escalated for the treatment of aGVHD.

#Patient did not receive tacrolimus for prophylaxis.