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Inflammatory Cytokine Inhibition with Combination Daclizumab and Infliximab for Steroid Refractory Acute Graft-Versus-Host Disease

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Abstract

Treatment options for steroid-refractory GVHD (SR-GVHD) are unsatisfactory and prognosis is poor. Inflammatory cytokines IL-2 and TNF- α are important mediators of GVHD, and may be critical targets for therapy. We retrospectively reviewed our experience using combination anti-cytokine therapy of daclizumab and infliximab. Seventeen evaluable patients had a median age of 47 years (range 35–63). The conditioning regimen was myeloablative in 13 and nonmyeloablative in 4 cases. GVHD occurred a median of 49 days after transplant in 12 patients (range 21–231) and a median of 46 days (range 25–119) after donor lymphocyte infusion in 5 patients. All patients had persistent or progressive GVHD despite 1–2 mg/kg/day of corticosteroids for a median of 7 days (range 2–26). They received combination daclizumab and infliximab for acute GVHD IBMTR severity index B (3), C (10) or D (4). 47% of patients responded; 24% had complete resolution of symptoms and 24% had partial responses. Survival was limited and all died a median of 6.7 months (range 1.6–26) from transplant and 35 days from initiation of daclizumab/infliximab. This retrospective analysis suggests that combination anti-cytokine therapy with daclizumab/infliximab has significant activity in SR-GVHD, but outcomes remain poor. New methods to prevent and treat GVHD are urgently needed.

INTRODUCTION

Acute graft-versus-host disease (aGVHD) results in significant mortality and remains a major limitation to successful allogeneic HSCT. Corticosteroids are typical first-line therapy for aGVHD, but only 25%–35% of patients achieve a complete response with another 15–20% achieving partial responses (1) (2) (3) (4). Antithymocyte globulin (ATG) has been the

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most common therapy for SR-GVHD and leads to overall clinical improvement in 31–40% of patients. Unfortunately, this results in a median survival of only 2 to 4 months from initiation of treatment (5, 6). Regardless of treatment for SR-GVHD, only 5–30% of patients that fail initial therapy survive long term, compared to 50–60% of those patients with stable response or better (7) (8). Given the dismal prognosis for patients with SR-GVHD, there is an immediate need for more effective treatment approaches.

There is compelling rationale for incorporating anti-cytokine therapy into GVHD management. Acute GVHD pathogenesis is a multi-step process, initiated in part by cytokine release from tissue damaged during cytotoxic preparative regimens, resulting in donor T-cell activation, and subsequent release of interleukin-2 (IL-2), tumor necrosis factor α (TNF- α), and interferon γ (IFN- γ). These molecules cause expansion and activation of cytotoxic T-cells and other inflammatory cells, creating the characteristic tissue damage of the liver, gut and skin seen in aGVHD (9). Daclizumab and infliximab can block T cell activation mediated by IL-2 and TNF- α respectively; daclizumab binds CD25 (IL2 receptor α -chain) and infliximab can bind the soluble subunit and the membrane-bound precursor of TNF- α . These antibodies have shown modest success independently in achieving durable responses against SR- GVHD (10) (11) (12) (13). Concurrent use of these agents was evaluated in a small number of patients receiving non-myeloablative HCT, and resulted in superior survival compared to patients on an ATG-based regimen (14) (15). In an attempt to enhance response and improve prognosis, we have used a combination of anti-cytokine therapy and report our experience treating 17 patients with SR-GVHD with combination daclizumab and infliximab.

METHODS

Patient population

All patients treated with a combination of daclizumab and infliximab for SR-GVHD following allogeneic HSCT at the Hospital of the University of Pennsylvania were identified through query of the hospital pharmacy database and then confirmed through retrospective chart review. We identified 22 patients from a total of 354 recipients of an allogeneic HSCT between June 2001–May 2008. This report is limited to the 17 patients whose records contained sufficient information regarding presentation, treatment and response to GVHD therapy for analysis. This retrospective study was approved by and conducted in accordance with the requirements of the Institutional Review Board of the Hospital of the University of Pennsylvania.

Treatment

Acute GVHD was defined as both classic aGVHD and late GVHD, occurring beyond 100 days post-transplant but without features characteristic of chronic GVHD. Initial steroid doses of 1 to 2mg/kg/day were used to treat aGVHD. GVHD was refractory to steroids in all cases, and initiation of daclizumab and infliximab was at the discretion of the treating physician. Daclizumab was intended to be given at 1.5 mg/kg on day 1 and 1 mg/kg day on 4, 8, 15, and 22. Infliximab was intended to be given at 10 mg/kg on day 1, 8, 15, and 22.

Evaluation of response

Responses were assessed weekly until death or date of last follow-up. Data was collected regarding dose and duration of steroids, time to steroid failure, additional immunosuppressant agents given following therapy with daclizumab and infliximab, as well as the ability to reduce the steroid dose. Acute GVHD was graded using either modified Glucksberg criteria (16) or IBMTR severity index(17). For consistency, for all patients included in this analysis, we determined the stage of GVHD for each organ group, and overall clinical grade was assigned using the IBMTR Severity Index. Complete response (CR) was defined as resolution of GVHD in all organ systems. Partial response (PR) signified improvement in at least one organ system by at least one grade without deterioration in another. A mixed response was used to describe improvement in one organ system with worsening of another organ system, and progression of disease describes worsening of at least one organ system without improvement in others. Patients without improvement or deterioration during treatment with daclizumab and infliximab were described as no change. Patients were considered refractory to corticosteroids if they did not have a CR or PR. Cause of death was assessed in all patients based on chart review. Infectious complications during treatment with daclizumab and infliximab were noted.

Statistical Analysis—The Kaplan-Meier method (18) was used to estimate overall survival from the time of transplant, DLI or onset of GVHD. Fisher exact test (19) was used to determine the impact on response and survival of several outcomes including GVHD severity, and the number of doses of therapy. The threshold for significance was a p value of 0.05.

RESULTS

Patient characteristics

Between June 2001 and May 2008, 354 patients underwent allogeneic HSCT. During this time period, 55% of patients developed acute GVHD. Grade I–II acute GVHD developed in 29% of patients and grade III–IV aGVHD developed in 26% of patients. Among this group we identified 22 patients who received a combination of daclizumab and infliximab for steroid-refractory aGVHD; sufficient data was available for 17 of these patients for a detailed review of outcomes. GVHD grade in these patients was reassigned using the IBMTR severity index. Patient characteristics are summarized in Table 1. All patients underwent allogeneic HSCT for hematologic malignancies with bone marrow (n=7), peripheral blood stem cell (n=9) or cord blood grafts (n=1) from matched siblings (n=5), unrelated donors (n=11) or umbilical cord blood (n=1). Except for one patient who received cyclosporine and prednisone, all received primary GVHD prophylaxis with calcineurin inhibitors and methotrexate. The majority of patients developed aGVHD following initial transplantation (n= 12, 71%) at a median of 49 days after transplant (range 21–231 days). Five additional patients developed aGVHD a median of 46 days after donor lymphocyte infusions (DLI) (range 25–119 days).

Graft-vs-Host Disease and Treatment

Patients were treated with corticosteroids at an initial dose 1–2 mg/kg/day for a median of 7 days (range 2–26 days) before initiation of daclizumab and infliximab. Two patients were escalated to 3mg/kg/day of corticosteroids upon initiation of daclizumab and infliximab. All other patients' steroids were tapered as their clinical response allowed. One patient was treated with daclizumab and infliximab two days after initiation of high-dose steroids for progression to stage 4 GI GVHD with a life-threatening gastrointestinal bleed. All other patients had received at least 4 days of high dose steroids. The aGVHD severity and organ involvement on initiation of daclizumab and infliximab is detailed in Table 2. Most patients had severity index C/D disease (n=14, 82%). Skin was involved in 9 patients, liver in 9 patients, and GI tract in 15 patients. Multiple organs were involved in 11 patients. All 5 planned doses of daclizumab were given to 53% of patients (median 5 doses, range 2–5) and all 4 planned doses of infliximab were given to 53% of patients (median 4, range 1–4). Reasons for failure to deliver the full treatment course included death, sepsis, or due to lack of response. Seven patients were given additional therapies for aGVHD, including alemtuzumab, mycophenolate mofetil, rituximab, and pentostatin at a median of 27 days after starting daclizumab and infliximab (range 6 to 43).

Response and Survival

Of the 17 patients analyzed, 8 (47%) responded to treatment with daclizumab and infliximab (Table 2). Complete remission occurred at a median of 11 days after treatment in 4 patients. Three of these four patients had severity index B disease. One patient with a CR went on to develop recurrent aGVHD two weeks after completing therapy with daclizumab and infliximab, and died as a result of GVHD. The other 3 patients who achieved CR died of infections either during or 3 to 6 weeks following initiation of daclizumab and infliximab therapy. The 4 patients who achieved a PR all died 22–35 days after initiation of therapy for SR-GVHD from infection or GVHD. The majority of infections were bacterial, although viral reactivation was common (Table 3); we did not observe any documented mycobacterial infections.

The median survival was 44 days (range 14–77) after the development of aGVHD and 35 days (range 9–72) after the initiation of daclizumab and infliximab. Median survival was 39 days (range 33–74) after onset of aGVHD in responding patients and 45 days (14–77) after aGVHD onset in patients without a response (p=NS).

Cause of death is outlined in Table 2 and included infection in 8 patients, progressive GVHD in 5 patients, disease relapse in 2 patients, hypoxic respiratory failure in 1 patient and marrow failure and bleeding in 1 patient. Infections occurring after start of therapy are listed in Table 3.

Patients with severity index B SR-GVHD were more likely to achieve a CR (3/3) compared to patients with severity index C/D (1/14) (p=0.006). There was no significant association with all responses (PR plus CR) and severity index B (3/3) vs C/D (5/14, (p=0.08). There was no association of overall survival with achieving a CR (p=0.34) or any response (PR

plus CR) ($p=0.68$) though the numbers of patients analyzed are quite small and survival was limited in all cases.

DISCUSSION

Graft-vs-host disease remains a major cause of morbidity and mortality after allogeneic HSCT. The prognosis for patients who fail to respond to corticosteroids is historically poor and there is no standard or consistently effective therapy for SR GVHD (20). Given the importance of inflammatory cytokines to the pathogenesis of GVHD (9), agents that interfere with cytokines such as IL-2 and TNF- α have been studied to treat SR-GVHD with variable results (10–14, 21–27). Complete responses have been reported in 15–100% of patients and appear to depend on severity of GVHD, specific organ involvement, timing of therapy, previous and concurrent therapy, and other patient-specific factors that cannot be controlled for in small phase II or retrospective studies (23). Despite reasonable response rates that demonstrate clear activity from this approach, most of these studies confirm a poor overall prognosis particularly for patients with the most severe GVHD.

We have analyzed outcomes of 17 patients treated with a combination of daclizumab and infliximab to block both IL-2 and TNF- α activity as therapy for SR-GVHD. We demonstrate a significant response rate of 47% with 4 patients achieving CR. This is similar to response rates noted in other reports using daclizumab and/or infliximab (11, 12, 25).

We found that severity index B aGVHD was associated with increased probability of CR to daclizumab and infliximab compared to severity index C/D ($p=0.008$) in keeping with other reports using infliximab alone in SR-GVHD (10, 12). Some reports have identified younger age (13, 23), specific organ involvement and time from HSCT to initiation of therapy as predictors of GVHD response (23)). While only approximately one half of our patients received all planned doses of therapy; treatment was stopped in most cases because of infection or death. There was no correlation with the number of doses with response or survival. Other studies using infliximab to treat SR-GVHD also report that many patients do not receive all planned doses of therapy typically because of infection or death (10, 12, 23). Given the small number of patients in our cohort, and most with advanced disease (14 with severity index C/D), it was not possible to identify other predictors of response.

Despite these significant response rates, overall survival was poor in our series. In a similar study of 18 adult patients with SR-GVHD, Srinivasan et al reported on 12 patients treated with daclizumab +/- ATG and/or infliximab (14). These patients had a 100% CR rate, a 73% day 200 survival and a median survival of 453 days. However, only 34% of their patients had grade III/IV acute GVHD and patients were treated for GVHD after predominantly non-myeloablative allogeneic HSCT. Of the 5 surviving patients, 2 had received ATG in addition to daclizumab. Furthermore, of the 5 recipients of combination daclizumab/infliximab, only 2 were still alive at publication (at 82 and 170 days). Rao et al reported a very high response rate with this combination (19/22 patients) in pediatric patients and 68% overall survival, with a median follow up of 31 months (28)). All patients had grade III/IV acute GVHD. The median age was 5.6 and only 4 patients received a myeloablative conditioning regimen and most patients had non-malignant disorders. In our

series, the median age was 49 (range 35–63), 76% of patients were treated with myeloablative conditioning regimens, and all but 3 patients had IBMTR severity index C/D GVHD, three factors that may account for the observed differences in outcomes. Unlike some reports (12, 23), but consistent with others (10), we did not find a survival advantage for patients who achieved a CR. Taken together, our results are consistent with other reports of SR-GVHD (11, 12, 25), and different outcomes compared to other studies of cytokine-specific therapy may be related to the heterogeneity of patients studied, particularly with respect to important GVHD prognostic factors of age, conditioning regimen, and severity of disease.

The majority of deaths in our patients were related to GVHD and infection. It has been our standard during the time period of this study to use prophylactic anti-fungal therapy for all transplant recipients and for all patients treated with corticosteroids for GVHD. Agents used for antifungal prophylaxis in this time period have varied based on evolving clinical practice and clinical trials open at our institution but have included fluconazole, voriconazole and caspofungin. For patients initially on empiric fluconazole, we have a low threshold to broaden this empiric coverage in the event of persistent fever or radiographic suggestion of invasive fungal infection. All transplant recipients and patients on high dose steroids receive prophylaxis for PCP with either trimethoprim/sulfamethoxazole or dapsone. It has not been our practice to use prophylactic anti-bacterial antibiotics, but when indicated for fevers or suspected or documented clinical infection, broad spectrum empiric and targeted antibiotics (a third or fourth generation cephalosporin, a carbapenem, or a fluoroquinolone with an aminoglycoside) would be started. Since this is a retrospective analysis, we reviewed antibiotic use in our recipients of daclizumab and infliximab and found that these guidelines were followed in this cohort of patients. The high rate of deaths related to bacterial infections raises the controversial issue of the need for prophylactic antibacterial therapy.

During the same time period, our center performed 354 allogeneic SCTs and 26% of patients developed grade III/IV aGVHD. Patients with grade 3/4 acute GVHD who did not receive daclizumab and infliximab had a 2 year overall survival of 25%. This was not statistically different than overall survival of recipients of daclizumab/infliximab ($p=0.42$) though it may be clinically relevant. A detailed retrospective review of response outcomes for these patients was not performed for the current analysis. However, since our institutional practice during this timeframe was to use daclizumab and infliximab for SR-GVHD, we assume that most of these patients had at least an initial response to steroids.

A major limitation to these observations is the retrospective nature of this report. Combination treatment with daclizumab/infliximab was likely selected for patients with the most severe cases of GVHD, and it is not possible to compare outcomes from this approach to other therapies. In addition, 7 patients received other immunosuppressive therapy during or after administration of daclizumab/infliximab, complicating the ability to assess response to these drugs alone, though additional therapy was added because of lack of response. Finally, 5 additional patients received daclizumab/infliximab for SR-GVHD during the time period of this report, but there was insufficient data for complete evaluation of presentation or response and these subjects were excluded from the analysis. While response data is limited for these patients, all 5 patients died, and it seems unlikely that inclusion of these

patients would alter the conclusions of this study. Regardless of these issues, our report confirms the poor prognosis associated with SR-GVHD treated with combination anti-cytokine therapy despite high response rates. This was because of both progression of GVHD and infection despite the use of standard prophylactic and empiric antibiotics, similar to other reports (10, 12, 29).

Targeting IL-2 and TNF with daclizumab and infliximab may continue to have an important role in GVHD management, though is likely to be most effective earlier in the course of the disease. The utility of anti-cytokine therapy as prevention or initial therapy of GVHD (30, 31) remains to be determined. Since the addition of agents to further inhibit T cells, and the use of anti-cytokine therapy reported in this study result in poor outcomes for SR-GVHD, future efforts should include earlier and more intensive treatment of advanced GVHD before it becomes steroid-refractory. Given the conflicting outcomes reported by different trials using anti-cytokine therapy for SR-GVHD, further studies will need to determine the impact of age, underlying disease, and conditioning regimen intensity on management and prognosis of GVHD. The identification of biomarkers or other clinical characteristics that predict poor response to steroids will be particularly important to allow trials of earlier intervention in the highest risk patients. In addition, using aggressive anti-fungal prophylaxis resulted in no deaths in this cohort from fungal infection and the majority of infectious-related deaths were from bacterial infection. This raises the controversial issue of using prophylactic anti-bacterial agents for patients with SR-GVHD. Prospective studies would be needed to determine if this would effect outcome or just lead to acquired antibiotic resistance without improvement in survival. Given our current findings, we do not recommend combination daclizumab and infliximab for advanced SR-GVHD.

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Table 1

Characteristics of Patients Treated with Combined Daclizumab and Infliximab

Characteristic	
Median age, years (range)	47 (35–63)
Male: n (%)	10 (59%)
Female: n (%)	7 (41%)
Diagnosis: n (%)	
Acute leukemia	9 (53%)
Chronic leukemia	2 (12%)
Lymphoma	5 (29%)
Multiple Myeloma	1 (6%)
Stem cell source: n (%)	
BM	7 (41%)
PBSC	9 (53%)
Cord	1 (6%)
Conditioning regimen intensity: n (%)	
Myeloablative	13 (76%)
Reduced intensity	4 (24%)
Therapy prior to GVHD: n (%)	
Transplantation	12 (71%)
DLI	5 (29%)
Donor Source: n (%)	
HLA-identical, sibling	5 (29%)
HLA-matched, unrelated	9 (53%)
HLA-mismatched, unrelated	2 (12%)
Cord blood	1 (6%)
GVHD Prophylaxis: n (%)	
MTX/Tacrolimus	14 (82%)
MTX/CSA	2 (12%)
CSA/Steroids	1 (6%)
IBMTR Severity Index Grade Acute GVHD: n (%)	
B	3 (18%)
C	10 (59%)
D	4 (24%)
Organs involved: n (%)	
Skin	9 (53%)
Liver	9 (53%)

Characteristic	
Gut	15 (88%)
Days treatment to aGVHD: median (range)	
From transplant (n=12 pts)	49 (21–231)
From DLI (n=5 pts)	46 (25–119)
Days of steroids to dac/inf: median (range)	7 (2–26)
Number of doses daclizumab: median (range)	5 (2–5)
Number of doses infliximab: median (range)	4 (1–4)

Abbreviations: n= number of patients, BM = bone marrow, CSA=cyclosporine, DLI = donor lymphocyte infusion, MTX=methotrexate, PBSC = peripheral blood stem cell,

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Table 2

Results of Daclizumab and Infliximab Treatment

Pt #	Donor	Days of steroid treatment before D/I	aGVHD Grade	Skin	Liver	GI	Response	Cause of Death	Survival (days) ¹
1	Sibling match	5	C	0	0	3	P	Infection	9
2	MUD	9	D	1	0	4	MR	Infection	35
3	UCB	9	C	0	3	0	PR	Infection	35
4	MUD	8	D	4	0	2	P	Respiratory failure	17
5	Sibling match	5	D	0	0	4	P	GVHD	40
6	MUD	7	C	2	1	3	MR	Disease	36
7	MUD	5	C	2	3	0	MR	GVHD	72
8	Sibling match	6	C	3	0	1	CR	Infection	50
9	MUD	4	C	0	0	3	PR	GVHD	22
10	mmURD	11	D	3	4	2	PR	Infection	26
11	Sibling match	7	C	3	1	2	MR	Disease	52
12	mmURD	2	B	0	2	1	CR	GVHD	58
13	MUD	7	B	0	0	2	CR	Infection	34
14	MUD	11	C	0	2	3	MR	GVHD	65
15	MUD	26	C	3	3	2	MR	Marrow failure	37
16	MUD	9	C	1	2	3	PR	Infection	24
17	Sibling match	7	B	0	0	1	CR	Infection	31

¹ Overall Survival from initiation of daclizumab and infliximab

Abbreviations: CR = complete remission, D/I = daclizumab/infliximab, mmURD= mismatch unrelated donor, MR = mixed response, MUD = matched unrelated donor, P = progression, PR = partial response., UCB = umbilical cord blood

Table 3

Infectious complications

Infection Type	N=	Days to infection from dac & inf median (range)
Bacterial Infection		
Gram-negative	10	23 (3–80)
Gram-positive	9	24 (1–67)
Other	1	49
Viral Infections		
CMV	2	25 (12–39)
HSV	1	23
VZV	1	28

Abbreviations: N = number of patients with infections, dac = daclizumab, inf= infliximab, CMV = cytomegalovirus, HSV = herpes simplex virus, VZV = varicella zoster virus

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