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Anti-tumor necrosis factor-α for the treatment of steroid-refractory acute graft-versus-host disease

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Abstract

Allogeneic stem cell transplantation has been increasingly performed for a variety of hematologic diseases. Clinically significant acute graft-versus-host disease (GVHD) occurs in 9 to 50% of patients who receive allogeneic grafts, resulting in high morbidity and mortality. There is no standard therapy for patients with acute GVHD who do not respond to steroids. Studies have shown a possible benefit of anti-TNF-α (infliximab) for the treatment of acute GVHD. We report here on the outcomes of 10 recipients of related or unrelated stem cell transplants who received 10 mg/kg infliximab, *iv*, once weekly for a median of 3.5 doses (range: 1-6) for the treatment of severe acute GVHD and who were not responsive to standard therapy. All patients had acute GVHD grades II to IV (II = 2, III = 3, IV = 5). Overall, 9 patients responded and 1 patient had progressive disease. Among the responders, 3 had complete responses and 6 partial responses. All patients with cutaneous or gastrointestinal involvement responded, while only 2 of 6 patients with liver disease showed any response. None of the 10 patients had any kind of immediate toxicity. Four patients died, all of them with sepsis. Six patients are still alive after a median follow-up time of 544 days (92-600) after transplantation. Considering the severity of the cases and the bad prognosis associated with advanced acute GVHD, we find our results encouraging. Anti-TNF-α seems to be a useful agent for the treatment of acute GVHD.

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Introduction

Transplantation with allogeneic bone marrow or peripheral blood has been increasingly performed for a variety of hematologic diseases. Clinically significant acute graft-versus-host disease (GVHD) occurs in 9 to 50% of patients who receive allogeneic grafts, and remains an important cause of morbidity and mortality. Patients with severe, grades III to IV, acute GVHD are usually treated with intensification of their im-

munosuppressive regimen, typically with high-dose steroids. However, there is no standard therapy for patients with acute GVHD who fail to respond to an initial course of corticosteroids (1).

Tumor necrosis factor alpha (TNF-α) is an important cytokine involved in the pathophysiology of acute GVHD (2-5). Infliximab is a chimeric human anti-TNF-α IgG1 monoclonal antibody (6). Studies have shown a possible benefit of anti-TNF-α antibody as treatment for acute GVHD (7-10).

We report here on the outcomes of 10 patients treated with infliximab against severe acute GVHD at our institution.

Patients and Methods

Patients

Between July 2003 and January 2006, 10 patients with a median age of 13 years (range: 4-36 years) with steroid-refractory acute GVHD received infliximab at our institution. These patients were retrospectively analyzed. The characteristics of the patients and transplants are shown in Table 1.

Transplants

GVHD prophylaxis was done with cyclosporine and prednisone in all patients who received cord blood, and with cyclosporine and methotrexate in those who received either bone marrow or peripheral blood stem cells. The characteristics of the transplants are shown in Table 1.

Graft-versus-host disease

Acute GVHD was diagnosed within 100 days of allogeneic transplantation or donor lymphocyte infusion. Acute GVHD was staged and graded according to modified Glucksberg criteria (11). GVHD that developed 100 days after allogeneic transplantation was considered to be chronic GVHD. At the start of infliximab treatment, 2 patients had developed grade II acute GVHD, while 8 had developed either grade III or IV acute GVHD. The liver was compromised in 6 (grades 1-4; median = 2), the gastrointestinal tract (GIT) in 8 (grades 1-4; median = 3.5), and the skin in all (grades 1-4; median = 3). Sicca syndrome was present in one

Table 1. Characteristics of patients and transplants.

No.	Sex	Age (years)	Diagnosis	Type of donor	HLA-identical	Loci of mismatch	Cell source	Conditioning	GVHD prophylaxis
1	F	36	AML	R	Yes		BM	Bu/Flu	CSP/MTX
2	M	21	CML-BC	U	Yes		PB	ATG/Cy/TBI	CSP/MTX
3	M	13	ALL	R	Yes		BM	Cy/TBI	CSP/MTX
4	M	6	Krabbe disease	U	No	DR	CB	Flu/TBI	CSP/Pred
5	M	4	ALL	U	No	B, DR	CB	ATG/Cy/TBI	CSP/Pred
6	M	21	CML-CP	U	Yes		BM	ATG/Cy/TBI	CSP/MTX
7	M	6	ALL	U	Yes		BM	ATG/Cy/TBI	CSP/MTX
8	F	13	AML	U	No	B	PB	ATG/Cy/TBI	CSP/MTX
9	M	8	ALL	U	No	A, B	CB	ATG/Cy/TBI	CSP/Pred
10	F	35	CML-CP	R	Yes		BM	Bu/Cy	CSP/MTX

GVHD = graft-versus-host disease; F = female; M = male; AML = acute myelocytic leukemia; CML-BC = chronic myelogenous leukemia-blast crisis; ALL = acute lymphocytic leukemia; CML-CP = chronic myelogenous leukemia-chronic phase; R = related; U = unrelated; BM = bone marrow; PB = peripheral blood; CB = cord blood; Bu = busulphan; Flu = fludarabine; ATG = anti-thymocyte globulin; Cy = cyclophosphamide; TBI = total-body irradiation; CSP = cyclosporine; MTX = methotrexate; Pred = methylprednisolone.

patient, and isolated xerophthalmia in another. The data about GVHD are shown in Table 2.

Treatment of graft-versus-host disease

Before starting infliximab, all 10 patients were receiving a combination of methylprednisolone, 2 mg kg^{-1} day^{-1}, *iv*, with a calcineurin inhibitor (9 on cyclosporine, 1 on tacrolimus). Patients 1, 3, and 10 were also on mycophenolate mofetil, which is the drug of choice in our service, once steroid refractory acute GVHD occurs. Patient number 3 also received basiliximab and was started on extracorporeal photopheresis for severe cutaneous involvement. Patients 5, 6, 7, 8, and 9 were switched from cyclosporine to tacrolimus in view of the reports of better results in unrelated bone marrow transplants with the latter drug. Since patient number 6 had developed hemolytic-uremic syndrome attributed to tacrolimus and was not able to start mycophenolate mofetil because of pancytopenia, he was started on thalidomide. All 10 patients received infliximab, 10 mg/kg, *iv*, once weekly for a median of 3.5 doses (range: 1-6).

After the start of infliximab, all patients continued to receive methylprednisolone, 2 mg kg^{-1} day^{-1}, *iv*, in divided doses. Corticosteroids were progressively tapered and discontinued as GVHD improved. The median time between the introduction of corticosteroids and the start of infliximab was 20.5 days (10-33) (Table 2). Details are shown in Table 3.

Response

The overall response represented the responses of the skin, GIT and liver. Complete response was defined as resolution of GVHD in all evaluable organs, partial response as any improvement in at least one evaluable organ without deterioration of others, and no response as the absence of any change or any situation other than complete or partial response, or progressive disease (7).

Results

Evaluation of the response

Overall, 9 patients responded and one patient had progressive disease. Among the responders, 3 had a complete response and 6 had a partial response. Only 2 of 6 patients with liver disease showed any grade of liver improvement, while all patients with either cutaneous or GIT involvement had responses

Table 2. Graft-versus-host disease (GVHD) characteristics and response to infliximab.

No.	Grading of GVHD				No. of doses of infliximab	Days of corticosteroid before infliximab was started	Response to infliximab				Chronic GVHD	Death	
	Overall	Liver	GIT	Skin			Overall	Liver	GIT	Skin		Y/N	Cause
1	IV	2	4	1	3	28	PD	No	No	No	Yes	Yes	Sepsis
2	IV	0	2	4	1	13	CR	NA	Yes	Yes	Yes	No	NA
3	II	0	1	3	1	33	PR	NA	Yes	Yes	Yes	No	NA
4	IV	4	4	3	4	20	CR	Yes	Yes	Yes	Yes	No	NA
5	II	0	0	3	2	16	CR	NA	NA	Yes	Yes	No	NA
6	III	2	0	3	4	32	PR	No	NA	Yes	Yes	No	NA
7	III	1	1	3	6	10	PR	No	Yes	Yes	Yes	Yes	Sepsis
8	III	0	3	3	3	16	PR	NA	Yes	Yes	NE	Yes	Sepsis
9	IV	2	4	3	4	29	PR	No	Yes	Yes	NE	Yes	Sepsis
10	IV	2	4	2	4	21	PR	Yes	Yes	Yes	NE	No	NA

GIT = gastrointestinal tract; PD = progressive disease; CR = complete response; PR = partial response; NA = not applicable; NE = not evaluated.

in these organs. Seven patients had progressive chronic GVHD, 3 were not evaluable (2 died before day 100, and 1 was on day 92 by the time of the analysis). The data are summarized in Table 2.

Toxicity and infections

None of the 10 patients had any kind of infusion-related, immediate toxicity. Nevertheless, all of them had a diagnosis of infection. Four had febrile neutropenia, 4 had cutaneous infections, 3 had a clinical diagnosis of sinusitis confirmed by computed tomographic scan, 3 had pneumonia, 1 had hemorrhagic cystitis, 1 had encephalitis, and 1 had oral candidiasis. Seven bacterial infections were microbiologically documented in four patients: *Pseudomonas* sp (N = 1), *Streptococcus* sp (N = 2), *Staphylococcus* sp (N = 2), and *Enterococcus* sp (N = 2). One patient had pneumonia, with *Pneumocystis carinii* identified in the sputum. Eight patients developed cytomegalovirus infection detected by antigenemia, but none progressed to cytomegalovirus disease. Fungal infections occurred in 3 patients: 1 patient had a subcutaneous abscess due to *Aspergillus* sp, which resolved after surgical drainage and specific antifungal therapy. The other 2 patients died of sepsis due to *Fusarium* sp; 1 had only cutaneous lesions and the other had cutaneous as well as cerebral involvement. Data about infectious complications are summarized in Tables 4 and 5.

Outcomes

Four patients died. Two of them, who had controlled GVHD, died of fungal infections. One patient whose GVHD had also been controlled died with bacterial sepsis. The last one had progressive GVHD and also died due to bacterial sepsis. Six patients are still alive, with chronic GVHD, at a median of 544 days (92-600) after the transplant. All 6 had either a partial or complete response to infliximab.

Table 3. Immunosuppressive treatments.

No.	Immunosuppression before the introduction of infliximab					Immunosuppression after the introduction of infliximab				
	CSP serum level (ng/mL)	Pred (mg kg^{-1} day^{-1})	MMF (g/day)	FK506 (mg kg^{-1} day^{-1})	Other	CSP serum level (ng/mL)	Pred (mg kg^{-1} day^{-1})	MMF (g/day)	FK506 (mg kg^{-1} day^{-1})	Other
1	No	2	1.5	0.03	No	No	2	No	0.03	No
2	478	2	No	No	No	589	2	No	No	No
3	289	2	1.5	No	Basiliximab	339	2	1.5	No	ECP
4	332	2	No	No	No	432	2	No	No	No
5	405	2	No	No	No	80	2	No	0.03	No
6	229	2	No	No	No	274	2	No	0.03	Thal
7	297	2	No	No	No	429	2	No	0.03	No
8	308	2	No	No	No	NA	2	No	0.03	No
9	228	2	No	No	No	278	2	No	0.03	No
10	459	2	2	No	No	93	2	2	No	No

CSP = cyclosporine; Pred = methylprednisolone; MMF = mycophenolate mofetil; FK506 = tacrolimus; ECP = extracorporeal photopheresis; Thal = thalidomide; NA = not available. Serum levels of CSP were measured twice weekly. The values shown reflect the nearest measurements to the day of infliximab start. Patient 1 was unresponsive to CSP/Pred and was switched to FK506. Patient 3 had severe cutaneous involvement and received basiliximab and ECP in view of the good results already reported in the literature. Patient 5 developed microangiopathic hemolysis that was attributed to CSP toxicity and was switched to FK506. Patient 6 developed microangiopathic hemolysis that was attributed to CSP toxicity and was first switched to FK506 without improvement of hemolysis; thalidomide was then substituted. Patients 7, 8 and 9 were unresponsive to CSP/Pred and were switched to FK506 in view of the good results reported for GVHD in unrelated transplants with this drug. Patient 10 developed microangiopathic hemolysis and acute renal failure that were attributed to CSP toxicity and was switched to MMF.

Discussion

Despite the use of prophylactic immunosuppressive regimens, grades II-IV acute GVHD occur in 30 to 80% of allogeneic transplant recipients, with greater frequency after transplantation from HLA non-identical or unrelated donors (12-14).

The pathophysiology of acute GVHD is triphasic (15,16). The initial phase results from the damage induced by the conditioning regimen in host tissues. Damaged tissues secrete inflammatory cytokines, including interleukin-1, TNF-α, and interferon-gamma. In the second phase, recipient antigen-presenting cells trigger the activation of donor-derived T cells, which expand and differentiate into effector cells (17,18). In the third phase, the effector phase, activated donor T cells mediate cytotoxicity against target host cells through Fas-Fas ligand interactions, perforin-granzyme B and cytokine production, including production of TNF-α (19,20). This sequence of events leads to the tissue damage that is characteristic of acute GVHD.

The standard of primary therapy for acute GVHD is considered to be methylprednisolone for 14 days, followed by a steroid taper (21). However, reports from the 1990's indicated that 80% of responses to corticosteroids, incomplete or complete, were not sustained. Failure was associated with a 75% non-relapse mortality rate (22,23). When steroid therapy fails to control the manifestations of acute GVHD, there is no standard approach to secondary GVHD therapy.

TNF-α is a key cytotoxic and proinflammatory cytokine involved in the pathogenesis of GVHD. TNF-α induces apoptosis, activates macrophages, granulocytes and lymphocytes, and produces a cascade of other inflammatory cytokines. TNF-α also increases the expression of HLA molecules and facilitates cytolysis mediated by T-lymphocytes (24). High levels of TNF-α have been correlated with the occurrence of acute and chronic GVHD (3,24).

Infliximab is a chimeric monoclonal IgG1 antibody that inhibits TNF-α activity and triggers complement-mediated lysis of TNF-α-expressing cells *in vitro* (25-29). The drug binds to the soluble and transmembrane forms of TNF-α (6,28). Intravenous infusions of infliximab are FDA-approved for the management of Crohn's disease and rheumatoid arthritis.

In our series, 9 of 10 patients responded to infliximab, 3 with complete and 6 with partial responses. When considering organ involvement, 9 of 10 patients with cutaneous involvement responded, 7 of 8 with intestinal GVHD, and only 2 of 6 with liver disease. Couriel et al. (7) reported a 67% overall response rate. These were primarily complete responses, and the highest response rates were observed in the GIT and skin. In the study of Patriarca et al. (9) there was a 59% response rate to infliximab, with 19% complete and 40% partial responses. Ac-

Table 4. Microbiologically documented infections.

Infectious agent	No. of isolates
Bacterial	
Gram-positive	6
Gram-negative	1
Fungal	
Fusarium sp	2
Aspergillus sp	1
Viral	
Cytomegalovirus	8
Pneumocystis carinii	1
Total	19

Table 5. Sites of infection.

Infection	No. of cases
Sinusitis	3
Pneumonia	3
Cutaneous	4
Encephalitis	1
Cystitis	1
Total	12

cordingly, the best responses were also observed in the GIT. In the case series of Kobbe et al. (10), 3 of 4 patients responded to infliximab.

None of our patients had any kind of toxicity attributable to infliximab. Some studies have described adverse events, which include acute infusional toxicity, serum sickness, development of autoantibodies (21), and neurological (30) or hepatic complications (31), but most of the series do not report adverse events (7,9,10).

Fungal infections, which were severe, occurred in 3 of our patients. TNF-α is essential for immune defense, playing a major role in the recruitment of inflammatory cells to the site of infection and in the formation and maintenance of granulomas (32). Marty et al. (1) reported on 5 cases of fungal infection in 11 patients who had received infliximab for the treatment of acute GVHD. In other studies, the incidence of fungal infections ranged from approximately 6% (2 of 32 patients) (9) to 28% (6 of 21 patients) (7). The possibility that infliximab contributed to a higher risk of lethal infections cannot be ruled out; however, acute GVHD and its immunosuppressive treatment already put these patients at higher risk for these complications. Tuberculosis has also been described after the use of infliximab (32), but none of our patients developed this complication.

Our study has important limitations. First, the number of patients is small and the distribution of strong risk factors for GVHD such as the use of unrelated donors is not homogeneous. There was no consensus on the choice of different immunosuppressive agents once resistance to corticosteroids was recognized. Second, the rationale for the introduction of infliximab was not the same in every patient. Third, it is only a retrospective, uncontrolled study. Although the response to infliximab appeared to be significant, one cannot exclude the possibility of a late response to corticosteroids or any of the other immunosuppressive treatments simultaneously employed. Nevertheless, in view of the high morbidity and mortality of steroid-resistant GVHD, we believe that these results may help justify the design of controlled, randomized clinical trials to investigate the subject further.

In summary, infliximab was well tolerated and appears to have a role in the treatment of acute GVHD, especially when the gastrointestinal tract is compromised. Randomized studies on the use of infliximab for the treatment of acute GVHD are underway (7) and the results are eagerly awaited.

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