Bone Marrow Transplantation (2001) 28, 47–49

www.nature.com/bmt

Graft-versus-host disease

Treatment of severe steroid refractory acute graft-versus-host disease with infliximab, a chimeric human/mouse antiTNFα antibody

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Summary:

Acute graft-versus-host disease (aGVHD) is a serious complication of allogeneic peripheral blood stem cell transplantation (PBSCT). Patients with severe aGVHD not responding to treatment with steroids have a poor prognosis. We treated four patients with severe aGVHD refractory to steroids with infliximab, a chimeric human/mouse antiTNFα antibody. Patients (CML 2, MM 1, AML 1) developed grade III–IV GVHD at a median of 34 days (range 15–76) after myeloablative PBSCT (two), donor lymphocyte infusion for relapsed CML (one) or non-myeloablative PBSCT (one), respectively. All patients had severe intestinal involvement in addition to skin and/or liver disease and had received treatment with high-dose steroids (four) for a median of 11 days (range 5–17) in addition to CsA (four) and MMF (three). Infliximab (10 mg/kg) was given once a week until clinical improvement. In three of four patients a complete resolution of diarrhea and significant improvement of skin and liver disease were observed. Two patients received one, one patient two and one patient three infliximab infusions. At present two patients are alive >200 days after therapy, one with limited cGVHD. Two patients died, one of progressive malignant disease without GVHD and one of refractory GVHD. Infliximab is apparently an active drug for the treatment of aGVHD. *Bone Marrow Transplantation* (2001) **28,** 47–49.

Keywords: graft-versus-host disease; TNF-α; infliximab

Acute GVHD causes significant morbidity and mortality after allogeneic haematopoietic cell transplantation despite the use of effective prophylactic regimens. Following activation by recipient antigen-presenting cells, alloreactive donor-derived T cells expand and induce an inflammatory process that results in the clinical picture of aGVHD.[1] Steroids are the treatment of choice in aGVHD >II° and induce remissions in the majority of patients. Individuals who fail steroid therapy have been treated with a variety of agents including MMF, ATG, OKT3 and antibodies to the interleukin-2 receptor alone or in combination.[2,3] Response rates have varied between 15 and 60%, but, in part due to infectious complications and relapse of the underlying disease, survival has been low. Early studies have suggested a beneficial effect of treatment strategies that block the activity of TNFα, which is the key cytokine in the inflammatory cascade of aGVHD.[4] We treated four patients with severe steroid refractory GVHD with the chimeric anti-TNFα antibody infliximab (Remicade; Centocor, Leiden, The Netherlands), which is approved for the clinical use in rheumatoid arthritis and Crohn's disease.

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Received 23 February 2001; accepted 19 April 2001

Case 1

A 40-year-old male patient with CML in first chronic phase was given an allogeneic peripheral blood stem cell (PBSC) transplant (4.07×10^6 CD34$^+$ cells per kg) from his HLA-identical sister after conditioning with busulfan (16 mg/kg) and cytoxan (120 mg/kg). He received CsA and MMF for GVHD prophylaxis. The post-transplant clinical course was uneventful until at day 15, when the patient developed acute GVHD III–IV with cutaneous, hepatic and severe intestinal involvement. Steroid treatment was initiated, but the diarrhea continued. After 5 days with steroids >10 mg/kg/day without improvement he received a single dose of infliximab (10 mg/kg). Stool frequency started to decline after 4 days. Within 2 weeks the diarrhea disappeared completely. The patient later developed recurrent CMV antigenemia and pulmonary mycosis which was successfully treated with ganciclovir and liposomal amphotericin B. He experienced a second episode of GVHD 3 months later while on low dose CsA, which then resolved after treatment with steroids. He is alive at day 292, in molecular CR of his CML with limited chronic GVHD.

Case 2

A 48-year-old man with CML in first chronic phase received a T cell-depleted PBSC graft (3.32×10^6 CD34$^+$ cells per kg) from a matched unrelated donor. The

conditioning regimen consisted of melphalan (140 mg/m^2), thiotepa (10 mg/kg), cytoxan (120 mg/kg) and ATG (40 mg/kg). GVHD prophylaxis was CsA. On day 103 he experienced a cytogenetic relapse. Following repeated donor lymphocyte infusions with increasing cell numbers and three doses of interferon alpha the patient experienced acute cutaneous GVHD with involvement of the complete body surface which transiently improved with treatment with CsA, and steroids (5 mg/kg/day). During steroid taper at a dose of 3.5 mg/kg/day the skin worsened again and grade IV gastrointestinal GVHD occurred. The patient received two doses of infliximab (10 mg/kg, once a week). Skin and gastrointestinal involvement improved 5 days after the first dose and the diarrhea disappeared 2 weeks after the second dose. The patient developed multifocal pulmonary mycosis, CMV antigenemia, generalized seizures and severe wasting but was successfully treated with liposomal amphotericin B and ganciclovir. He is now alive, off steroids and amphotericin B, in molecular CR with limited chronic GVHD 275 days after treatment.

Case 3

A 41-year-old female with multiple myeloma IgA lambda received an autologous PBSC transplant after conditioning with melphalan (200 mg/m^2). For consolidation she was treated with an allogeneic PBSC transplant from her HLA-identical sister after conditioning with fludarabin (90 mg/m^2) and 2 Gy TBI followed by CsA and MMF. The patient engrafted but suffered from an early relapse of the myeloma with multiple extramedular tumors. Following withdrawal of immunosuppression she developed complete donor chimerism and acute GVHD with liver (grade 3) and gastrointestinal (grade 4) involvement which was refractory to treatment with high-dose steroids (>10 mg/kg/day), CsA and MMF. After 11 days on steroids she received one dose of infliximab (10 mg/kg). The diarrhea improved after 5 days and completely disappeared within 3 weeks. Bilirubin and liver enzymes declined 26 days after treatment. Unfortunately the myeloma progressed rapidly and the patient died 99 days after transplantation without signs of GVHD.

Case 4

A 49-year-old female was treated with an allogeneic peripheral blood stem cell transplant (7.7×10^6 CD34$^+$ cells/kg) from her HLA-identical brother for secondary AML in first remission. She received conditioning with busulfan (16 mg/kg) and cyclophosphamide (120 mg/kg) followed by CsA and MMF for GVHD prophylaxis. On day 76 the patient developed aGVHD with cutaneous (grade 2), hepatic (grade 1) and intestinal (grade 4) involvement. After 11 days on high-dose steroids without substantial improvement she received the first dose of infliximab. A total of three doses (5 mg/kg, 10 mg/kg and 10 mg/kg) were given without improvement. The patient then received salvage treatment with ATG (75 mg/kg) and later pentostatin but died of progressive GVHD 125 days after transplantation.

Discussion

Infliximab (Remicade; Centocor) is a chimeric mouse/human IgG_{1kappa} antibody that binds with high affin-

Table 1 Summary for four patients with severe steroid refractory acute GVHD treated with infliximab

	Case 1	*Case 2*	*Case 3*	*Case 4*
Age/Sex	40/M	48/M	41/F	49/F
Diagnosis	CML	CML	MM	AML
Acute GVHD (grade)	IV	IV	IV	IV
Organ involvement (grade)	skin (2) liver (3) intestinal (4)	skin (3) — intestinal (4)	— liver (3) intestinal (4)	skin (2) liver (4) intestinal (4)
Diarrhea at the start of steroids (ml)	>2000	[a]	>1500	>1000 bloody
Bilirubin at the start of steroids (mg/dl)	2.9	0.7	1.5	1.6
Steroid treatment before infliximab (days)	5	17	11	11
Additional treatment	CsA/MMF	CsA	CsA/MMF	CsA/MMF
Number of infliximab doses	1	2	1	3
Side-effects during infliximab infusion	—	—	—	—
Diarrhea at the start of infliximab (ml)	>2000	>2000	>2000	>1000 bloody
Interval to intestinal improvement (days)	4	5	5	—
Interval to stool normalization (days)	8	17	20	—
Bilirubin at the start of infliximab (mg/dl)	1.4	0.4	4.5	0.7
Maximal bilirubin (mg/dl)	6.8	—	11.6	34.6
Interval to bilirubin normalization (days)	29	—	39	—
Response	CR	CR	CR	PD
Additional salvage treatment	—	—	—	ATG, Pentostatin
Response to salvage treatment	—	—	—	PD
Chronic GVHD	limited	limited	—	—
Outcome (day)	alive (+292)	alive (+275)	dead[b]	dead[c]

[a]Patient developed grade 4 intestinal GVHD while on steroids for cutaneous GVHD.
[b]Patient died of progressive myeloma without signs of GVHD.
[c]Patient died of GVHD.

ity to soluble and transmembrane forms of human TNFα. Binding to soluble TNFα results in the neutralization of its activity, whereas binding to the transmembrane form of TNFα causes lysis of the affected cell by activation of complement and induction of antibody-mediated cellular toxicity.[5] Both mechanisms may have contributed to the clinical response observed in the three patients described above. Very likely depletion of TNFα producing cells is the main reason for the long-lasting clinical effects of infliximab in Crohn's disease and rheumatoid arthritis. In both diseases a single dose of infliximab can induce clinical remissions in patients with disease refractory to standard treatment.[6,7] A significant number of patients experience a relapse of their autoimmune disease about 2 months after the first infusion. Patient 1 in our series also suffered from recurrent GVHD 3 months after the first episode which then improved with steroids. Couriel *et al*[8] observed a response rate of 70% in patients receiving infliximab for the treatment of steroid-refractory aGVHD. Patients with involvement of the gastrointestinal tract had the greatest benefit (85% response). As a limitation of the study of Couriel *et al*, patients were treated with ATG and/or daclizumab, in addition to infliximab. Therefore clinical improvement may be attributed to one of these substances or a combination of all. The responses observed in the patients treated in our institution demonstrate that infliximab alone has a significant activity in severe steroid-resistant aGVHD.

Two of the four patients in our group developed serious infectious complications including CMV antigenemia and aspergillosis. How far suppression of TNFα activity contributed to the development of these infections is not clear. Reactivation of CMV is closely linked to the development of aGVHD, and aspergillosis also occurs frequently in patients receiving intensive immunosuppression for aGVHD. However, randomized placebo-controlled studies in rheumatoid arthritis and Crohn's disease have suggested an increased incidence of infections in patients treated with infliximab. Other side-effects included the development of autoantibodies and possibly an increased incidence of lymphoma. Animal studies with neutralization of TNFα after allogeneic stem cell transplantation have shown an increased risk of leukemic relapse. In contrast both patients with CML in our series entered molecular remission despite immunosuppressive therapy and treatment with infliximab suggesting a persistence of the graft-versus-leukemia effect at least in patients with CML. We conclude that infliximab is a promising new agent for the treatment of aGVHD especially in cases with gastrointestinal involvement.

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