EUR. J. ONCOL., vol. 18, n. 1, pp. 25-29, 2013

Etanercept in the second-line treatment of acute graft-versus-host disease: a case series

Fernando do Pazo-Oubiña[1], Natàlia Creus-Baró[1], Carmen Martínez-Muñoz[2], Montserrat Rovira-Tarrats[2]

[1] Pharmacy Department, Hospital Clinic, Barcelona, Spain; [2] Institute of Hematology and Oncology, Hematology Department, Hematopoietic Transplantation Unit, Hospital Clinic, Barcelona, Spain

Summary. *Aim:* Acute graft-versus-host disease is a major complication of allogeneic hematopoietic stem cell transplantation. First-line treatment is with corticosteroids, but there is no standard second-line treatment, although etanercept is an option. In this case series, we present the efficacy and safety profile of etanercept in the second-line treatment of acute graft-versus-host disease. *Patients and Methods:* Ten patients received at least 1 dose of etanercept for treatment of acute graft-versus-host disease between January 2009 and February 2011. We assessed response to treatment and associated toxicity. *Results:* Diagnosis of acute graft-versus-host disease was histologically confirmed in all but 1 patient. A clinical response was obtained in 3 patients (2 complete responses and 1 partial response). Etanercept was well tolerated, and no cases of associated secondary toxicity were observed. *Conclusions:* The efficacy results of this study were slightly worse than those reported in the literature. The poorer response obtained may be explained by the more severe acute graft-versus-host disease at diagnosis: all the patients had intestinal grade ≥ II (7 with grade IV disease).

Key words: graft-versus-host disease, hematopoietic stem cell transplantation, etanercept

«Etanercept nel trattamento di seconda linea della malattia del trapianto contro l'ospite: serie di casi»

Riassunto. *Finalità:* La malattia acuta del trapianto contro l'ospite è la complicazione maggiore legata al trapianto di cellule staminali allogeniche ematopoietiche. Il trattamento di prima scelta è con corticosteroidi e non esistono trattamenti di seconda scelta, sebbene etanercept sia una opzione possibile. Nei casi di seguito riportati presentiamo l'efficacia e la sicurezza di etanercept come trattamento di seconda scelta della malattia acuta del trapianto contro l'ospite. *Pazienti e Metodi:* Dieci pazienti hanno ricevuto almeno 1 dose di etanercept per il trattamento della malattia del trapianto contro l'ospite tra gennaio 2009 e febbraio 2011. Abbiamo in seguito valutato la risposta al trattamento e la relativa tossicità. *Risultati:* La diagnosi di malattia del trapianto contro l'ospite è stata confermata istologicamente in tutti i pazienti tranne 1. Una risposta clinica è stata ottenuta in 3 pazienti (2 risposte complete ed 1 parziale). L'etanercept è stato ben tollerato e non ci sono stati casi di tossicità secondaria associata. *Conclusioni:* I risultati riguardanti l'efficacia in questo studio sono leggermente peggiori rispetto a quelli riportati in letteratura. La scarsa risposta ottenuta può essere dovuta al fatto che la malattia acuta del trapianto contro l'ospite al momento della diagnosi era più severa: tutti i pazienti avevano grado intestinale ≥ II (7 con grado IV della malattia).

Parole chiave: malattia del trapianto contro l'ospite, trapianto di cellule staminali ematopoietiche, etanercept

Presented in part as an abstract at 53rd National Meeting of the Spanish Society of Haematology and Hemotherapy (SEHH) – 27th Spanish Society of Thrombosis and Hemostasis (SETH), Zaragoza, Spain, October 27-29, 2011

Introduction

Acute graft-versus-host disease (aGVHD) is an immune disorder that results from the action of donor T-cells against the tissues of allogeneic hematopoietic stem cell transplant (HSCT) recipients. It is the most important complication of HSCT and mainly affects the skin, gastrointestinal tract, and liver (1).

The main risk factors for aGVHD are the degree of mismatch of human leukocyte antigen (HLA) proteins, patient age and opposite-sex donor. Other factors include type of conditioning, donor age, prior cytomegalovirus (CMV) infection in the recipient, and the use of peripheral blood stem cells (2). The prevalence of aGVHD is around 40% in patients undergoing HSCT with a full-matched sibling donor. This proportion increases to 60-80% in the case of unrelated HLA-mismatched donor grafts (3).

GVHD prophylaxis is usually based on the combination of a calcineurin inhibitor with methotrexate or mycophenolate mofetil (4). First-line treatment is with corticosteroids (5, 6), with or without calcineurin inhibitors, while evidence on second-line treatment is scarce, and there is no standard treatment (6, 7).

One of the options for corticosteroid-refractory aGVHD are inhibitors of tumor necrosis factor α (TNF-α). Both infliximab and etanercept have shown similar efficacy in this setting, but etanercept seems to have less infectious complications and its subcutaneous route of administration makes it a more convenient option (8).

The aim of this case series is to present our experience of etanercept for the second-line treatment of aGVHD.

General data on cases

We describe the efficacy and safety profile of etanercept as second-line treatment in patients with aGVHD.

All patients admitted to the Hematology Department who were administered etanercept between January 2009 and February 2011 for the treatment of corticosteroid-refractory aGVHD were identified through the computerized order entry system.

As this is an off-label indication, all treatments needed the informed consent of the patient or a family member according to Spanish law. The study was approved by the local Clinical Research Ethics Committee and authorized by the Spanish Agency for Medicines and Health Care Products (AEMPS).

Once patients were identified, medical records were reviewed to collect the following variables: patient demographics (sex, diagnosis, age, and disease status at transplantation), donor characteristics (sex, sibling, HLA compatibility, and previous transfusions), source of hematopoietic progenitor cells (peripheral blood, bone marrow, umbilical cord), number of infused CD34+ cells, conditioning regimens (myeloablative or reduced intensity), aGVHD prophylaxis administered, etanercept dose and administration (number of doses and time from diagnosis of aGVHD to administration of etanercept), and aGVHD clinical grade and confirmation by biopsy.

Response was classified according to data from the medical record in complete response (resolution of all manifestations of GVHD in all organs affected after treatment with etanercept), partial response (resolution of more than 50% of signs and symptoms in at least 1 organ without worsening the others) and no response or progression (worsening of GVHD or third-line treatment). Clinical response is the set of complete responses and partial responses.

Toxicity associated with etanercept was classified according to the *Common Terminology Criteria for Adverse Events, version 4.0* (9).

Results were analyzed using descriptive statistics.

Illustration of cases

Ten patients received at least 1 dose of etanercept. Table 1 shows patient characteristics and the main features of the HSCT performed.

All patients received nebulized pentamidine, oral levofloxacin and fluconazole, and oral or intravenous acyclovir as anti-infective prophylaxis during the conditioning regimen and during the first and second months after transplantation. Three patients underwent a reduced-intensity conditioning regimen (1 was

Table 1. Patient and HSCT[a] characteristics

Number of patients	10
Median age at transplantation (range)	47 (23 - 66)
Diagnosis	
CLL[b]	3
AML[c]	3
Aggressive lymphoma	3
ALL[d]	1
Disease stage at transplantation	
Complete remission	3
Partial remission	1
Disease progression	6
Sex mismatch	
None	3
MTF[e]	4
FTM[f]	3
Source of stem cells	
Peripheral blood	9
Bone marrow	1
Conditioning regimen	
Myeloablative	7
Reduced intensity	3
GVHD[g] prophylaxis	
CsA[h] + MTX[i]	6
CsA + MMF[j]	3
CsA + MMF + ATG[k]	1

[a] = HSCT: hematopoietic stem cell transplantation. [b] = CLL: chronic lymphocytic leukemia. [c] = AML: acute myelogenous leukemia. [d] = ALL: acute lymphocytic leukemia. [e] = MTF: male-to-female. [f] = FTM: female-to-male. [g] = GVHD: graft-versus-host disease. [h] = CsA: cyclosporin A. [i] = MTX: methotrexate. [j] = MMF: mycophenolate mofetil. [k] = ATG: rabbit antithymocyte globulin

aged over 50 years, 1 for pre-orthotopic liver transplantation, and 1 was undergoing a second HSCT). One patient received rabbit antithymocyte immunoglobulin prophylaxis for GVHD because of an HLA-B mismatch. All patients received unmanipulated hematopoietic stem cells.

Table 2 shows the age at transplantation, type of donor, the number of infused CD34+ cells, the location, stage, and diagnosis of aGVHD, and the results of treatment with etanercept.

Patient number 4 presented with a 15-day history of watery diarrhea that was originally thought to be intestinal aGVHD. Second-line treatment with etanercept was started and mycophenolate mofetil was progressively withdrawn. The patient's condition improved, a biopsy was performed and the patient was diagnosed with mycophenolate-induced gastrointestinal toxicity, so treatment with etanercept was stopped. Only 1 patient was diagnosed with late-onset aGVHD (234 days after HSCT).

First-line treatment for GVHD was always intravenous methylprednisolone at 1 mg/kg/12 h. Eight patients received oral beclomethasone or budesonide as part of the treatment for intestinal GVHD, and 3 patients received third-line treatment, which comprised antithymocyte immunoglobulin in 1 case and infusion of mesenchymal cells in 2 cases.

Etanercept was the second-line treatment in all patients, administered as follows: 0.4 mg/kg up to 25 mg subcutaneously, 2 days a week for 4 weeks, followed by 1 dose weekly for 4 weeks for up to 12 doses. The median time from diagnosis of aGVHD and start of treatment was 8 days (range, 3 to 23 days).

A clinical response was obtained in 3 of the 9 patients diagnosed with aGVHD (2 complete responses and 1 partial response). Four patients received 12 doses. Among the remaining 6 patients, 2 died after 5 and 6 doses, 1 patient stopped treatment after 4 doses because of mycophenolate mofetil-induced toxicity, and in 3 cases due to progression or non-response after 1, 3, and 9 doses.

Administration was well tolerated, and toxicity was not associated with etanercept in any cases. Two patients showed no infections. CMV reactivation occurred in 6 cases, and adenovirus was isolated in 3 patients, although infection resolved with antiviral therapy (ganciclovir, foscarnet, or cidofovir). Four patients presented bacterial infections that responded to antibiotic treatment (1 with positive blood culture for *Enterococcus faecium*, *Stenotrophomonas maltophilia*, and *Klebsiella pneumoniae*; 1 with positive blood and urine culture for *Klebsiella pneumoniae*; 1 with positive blood culture for methicillin-sensitive *Staphylococcus aureus*; and 1 with a positive urine culture for extended-spectrum beta-lactamase-producing *Escherichia coli*). In 1 case, *Clostridium difficile* toxin was detected in feces, and digestive symptoms persisted despite treatment with oral vancomycin and metronidazole. Only 1 case of invasive aspergillosis was detected; the patient was treated with amphotericin B but died 15 days later.

Table 2. Donor type, infused CD34+ cells, aGVHD[a] grade and diagnosis, and results of etanercept treatment.

Patient no.	Age at transplant	Donor	Infused CD34+ (x10^6/kg)	aGVHD grade			Time to diagnosis[b]	Time to etanercept[c]	Doses	Response	Death	Cause	Overall survival[d]
				Skin	Gut	Liver							
1	58	MSD[e]	7.38	0	IV*	II	33	8	5	NR[i]	Yes	GVHD[l]	22
2	66	MSD	5.9	0	IV*	0	30	5	12	NR	Yes	PML[m]	65
3	51	MSD	7.01	II*	IV*	0	18	14	12	PR[j]	Yes	Infection	37
4	43	PMUD[f] HLAg 9/10	2.55	-	-	-	55	8	4	-	No	-	-
5	47	MSD	2.75	IV	IV	0	41	3	1	NR	Yes	PAE[n]	12
6	41	MSD	1.83	0	IV*	0	46	6	3	CR[k]	Yes	ALP[o]	35
7	60	MSD	4.18	III*	III*	0	86	8	9	NR	Yes	MOF[p]	112
8	23	PMUD HLA 9/10	7.5	III	IV*	II	234	9	12	CR	No	-	-
9	35	MSD	2.42	III	IV*	III	45	10	12	NR	Yes	MOF	86
10	34	MUD[h] HLA 10/10	9.78	0	II-III	IV	33	23	6	NR	Yes	MOF	23

[a] = aGVHD: acute graft-versus-host disease. [b] = Days from stem cell transplantation to diagnosis of aGVHD. [c] = Days from diagnosis of aGVHD to initiation of etanercept. [d] = Days from initiation of etanercept to death/last follow-up. [e] = MSD: matched sibling donor. [f] = PMUD: partially matched unrelated donor. [g] = HLA: human leukocyte antigen. [h] = MUD: matched unrelated donor. [i] = NR: no response. [j] = PR: partial response. [k] = CR: complete response. [l] = GVHD: graft-versus-host disease. [m] = PML: progressive multifocal leukoencephalopathy. [n] = PAE: pulmonary acute edema. [o] = ALP: aggressive lymphoma progression. [p] = MOF: multiple organ failure. * = designates histologically confirmed diagnosis

Discussion

We observed a clinical response in 3 of the 9 patients who received etanercept for second-line treatment of corticosteroid-refractory aGVHD.

Only 2 of the 9 patients had an unrelated donor, and only 3 cases of male recipient/female donor were observed. Seven patients presented an active disease at the time of transplantation, and 7 patients underwent myeloablative conditioning regimens, both of which factors contributed to the development of aGVHD. Peripheral blood stem cells were used in 9 patients; this seems to confer greater risk for developing chronic graft-versus-host disease (cGVHD), but no aGVHD.

Although limited by the small number of patients and its retrospective design, our results are slightly poorer than those reported in the literature.

The first published study to assess the efficacy and toxicity of etanercept in second-line treatment of GVHD was a retrospective review by Busca et al (10), who recorded a clinical response in 6 out of 13 patients with aGVHD (46%) and in 5 of 8 patients with cGVHD (62%). The main findings were as follows: greater efficacy in patients with a gastrointestinal and/or skin location; a statistically significant difference in response depending on the interval between diagnosis and the start of treatment; and a greater efficacy in grade II disease than in grades III-IV disease.

A recent work, reporting long-term follow-up of 100 steroid-refractory aGVHD patients managed either with MMF (52 patients), inolimomab (22 patients) or etanercept (23 patients), has been published (11). Overall response rate was 45% (complete response 28%) and 2-year survival was 30%. Risk factors significantly associated with overall survival were disease status at transplantation, grade III-IV aGVHD and liver involvement. No impact of second-line therapy in this poor outcome was found. When focusing in etanercept treated patients, clinical response was seen in 6 of 21 patients.

Both in our study and in Xhaard et al. work, the poorer response may be explained by the presence of

more severe aGVHD at diagnosis. In our study, all patients presented intestinal aGVHD grade ≥ II (7 with grade IV), and 15 of 21 patients presented intestinal aGVHD grade ≥ II (11 with grade IV) in Xhaard et al. work, while only 6 of the 13 patients with aGVHD in the study by Busca et al (10) were diagnosed with intestinal aGVHD ≥ grade II, and only 1 patient was diagnosed with GVHD grade IV (liver).

We observed that efficacy does not seem to differ depending on the time from diagnosis to the start of treatment. The 3 patients with a clinical response started treatment 6, 9, and 14 days after diagnosis, and the 6 patients with no response started treatment a median of 8 days (range 3 to 23) after diagnosis.

Although a potential contribution to toxicity cannot be excluded, the infections that occurred in patients on treatment cannot be attributed exclusively to etanercept. Busca et al detected reactivation of CMV infection in 10 of 21 patients, bacterial infection in 3, and fungal infection in 4. These rates are lower than those found in our study, in which 6 of 9 patients developed reactivation of CMV infection, 3 presented adenovirus infection, 4 a bacterial infection, and 1 a fungal infection. Xhaard et al found no differences in viral and fungal infections between the three treatment options, but an increased bacterial infections risk in patients treated with anticytokines (inlimomab and etanercept). No patient presented toxicity directly related to etanercept.

Conclusions

In conclusion, the efficacy results of this study were slightly worse than those reported in previous studies, but almost comparable with recent published data, considering patients with very poor prognosis. The grim outcomes of current treatment options highlight the need for alternative strategies to treat steroid-refractory aGVHD to be explored.

References

1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006; 354: 1813-26.
2. Flowers ME, Inamoto Y, Carpenter PA, *et al.* Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood 2011; 117: 3214-9.
3. Ferrara JL, Levine JE, Reddy P, *et al.* Graft-versus-host disease. Lancet 2009; 373: 1550-61.
4. Bacigalupo A. Management of acute graft-versus-host disease. Br J Haematol 2007; 137: 87-98.
5. Wolff D, Gerbitz A, Ayuk F, *et al.* Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. Biol Blood Marrow Transplant 2010; 16: 1611-28.
6. Kim SS. Treatment options in steroid-refractory acute graft-versus-host disease following hematopoietic stem cell transplantation. Ann Pharmacother 2007; 41: 1436-44.
7. Wolff D, Schleuning M, von Harsdorf S, *et al.* Consensus Conference on Clinical Practice in Chronic GVHD: second-line treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2011; 17: 1-17.
8. Busca A. The use of monoclonal antibodies for the treatment of graft-versus-host disease following allogeneic stem cell transplantation. Expert Opin Biol Ther 2011; 11: 687-97.
9. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed: 2012 November 2).
10. Busca A, Locatelli F, Marmont F, *et al.* Recombinant human soluble tumor necrosis factor receptor fusion protein as treatment for steroid refractory graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. Am J Hematol 2007; 82: 45-52.
11. Xhaard A, Rocha V, Bueno B, *et al.* Steroid-refractory acute GVHD: lack of long-term improved survival using new generation anticytokine treatment. Biol Blood Marrow Transplant 2012; 18: 406-13.

Received: 12.12.2012
Accepted: 4.2.2013
Address: Fernando do Pazo-Oubiña,
Pharmacy Department, Hospital Clinic de Barcelona,
Villarroel 170, 08036 Barcelona, Spain
E-mail address: fdopazo@clinic.ub.es