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ORIGINAL ARTICLE

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Recombinant human soluble tumor necrosis factor (TNF) receptor (p75) fusion protein Enbrel in patients with refractory hematologic malignancies

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Abstract *Purpose:* Tumor necrosis factor-α (TNF-α) is an important effector and regulatory cytokine involved in the pathophysiology of hematologic malignancies, including hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL), agnogenic myeloid metaplasia (AMM) and Philadelphia-negative myeloproliferative disorders (MPD). We conducted a pilot study to assess the safety of the soluble TNF receptor, etanercept (p75 TNFR:Fc; Enbrel) in patients with refractory hematologic malignancies. *Methods:* Patients were eligible if they had refractory HCL, CLL, AMM, or Philadelphia-negative MPD. Enbrel was administered twice weekly at a dose of 25 mg subcutaneously for a minimum of eight doses, and was continued in patients without overt progression. *Results:* Among the 26 patients enrolled on study, 25 patients were evaluable. Nine patients had AMM, eight CLL, three HCL, and five Philadelphia-negative MPD. Their median age was 60 years (range 30–83 years). A total of 70 courses consisting of 486 doses of Enbrel were administered. Enbrel was well tolerated, without any overt increase in infectious episodes. Stable disease/no objective response was seen in 22 patients (88%) and progression in 3 patients (12%). Three patients with AMM improved (two showed hematologic improvement, and one showed a reduction in liver and spleen size), and two patients (one with CLL and one with Philadelphia-negative MPD) showed improvement in disease-related symptoms. *Conclusions:* Enbrel was well tolerated, but no responses were noted in these immunosuppressed patients with refractory hematologic malignancies.

Keywords Enbrel · Hematologic malignancies · Angiogenic myeloid metaplasia

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Introduction

Tumor necrosis factor-α (TNF-α) is a major effector and regulatory cytokine involved in the pathophysiology of lymphoproliferative and myeloproliferative disorders, including hairy cell leukemia (HCL) [31, 56, 59], chronic lymphocytic leukemia (CLL) [13, 14, 39, 44, 53, 57, 58, 59, 64], angiogenic myeloid metaplasia (AMM) and other myeloproliferative disorders (MPD) [5, 16, 22, 26, 28, 30, 51]. TNF has two distinct receptors, a 55-kDa (p55) and a 75-kDa (p75) protein, which are monomeric molecules on cell surfaces and in soluble forms [32, 54]. The biologic activity of TNF depends on binding to either cell surface TNF receptor. Soluble TNF receptors consist of the extracellular portion of the receptor, and serve as physiologic regulators of the inflammatory response by inhibiting TNF activity [27, 45, 50].

Therapeutic strategies targeting TNF-α include soluble TNF receptors, which inactivate TNF-α [1, 40], anti-TNF-α monoclonal antibodies [9, 12, 36], and agents modulating TNF-α signaling [7, 11, 23, 24, 41, 46, 47]. Two recombinant soluble TNF receptors are currently available: one of p75 (Enbrel, p75 TNFR:Fc; Immunex Corporation, Seattle, Wash.) [40] and one of p55 (Lenercept, p55 TNFR:Fc; F Hoffmann-La Roche, Basel, Switzerland) [1].

Enbrel (etanercept) is a dimeric form of the p75 TNF receptor, consisting of the fusion protein of the extracellular ligand-binding domain of the human p75 TNF receptor linked to the Fc portion of human IgG_1 [40],

which is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system [40, 42, 43]. Enbrel binds specifically to free TNF in the circulation, and acts as a competitive inhibitor, blocking its interaction with cell surface TNF receptors, and consequently, activation of target cells [40]. Enbrel can bind to two TNF molecules, and inhibit binding of both TNF-α and TNF-β or lymphotoxin-α to cell surface TNF receptors [40]. It has been extensively investigated in patients with inflammatory arthritides and in patients with sepsis. Enbrel is approved by the US Food and Drug Administration for patients with rheumatoid arthritis (RA) [4, 20, 42, 43, 63], juvenile RA [34], and psoriatic arthritis [38].

Enbrel has a very acceptable adverse event profile in these patients, many of whom are elderly and have significant comorbidity. However, in studies in patients with established shock, Enbrel treatment does not reduce mortality, and higher doses are associated with increased mortality rates [18]. While there is a clear rationale to investigate Enbrel for possible efficacy in patients with hematologic disorders, any resultant increase in infections would be a particularly serious problem in this patient population.

We thus conducted a pilot study of Enbrel in patients with refractory HCL, CLL, AMM, and Philadelphia-negative MPD in order to assess the safety of this TNF-α-inactivating agent in patients with refractory hematologic malignancies.

Patients and methods

Study group

Patients with refractory hematologic malignancies were entered into the study between June 2000 and March 2001, after written informed consent was obtained according to institutional guidelines. Patients were eligible if they had refractory HCL, CLL, AMM, or Philadelphia-negative MPD, without overt infection, hypotension, concurrent chemotherapy, systemic radiotherapy or surgery, pregnancy or overt psychosis.

Pretreatment evaluation included complete history and physical examination; documentation of all measurable disease, signs and symptoms, performance status (PS), and details of prior chemotherapy and/or radiation therapy, complete blood count, differential, and platelet count; serum chemistries, including liver and renal function studies; bone marrow aspiration with or without biopsy; cytogenetic analysis, immunophenotyping, and molecular studies as indicated.

Therapy

Treatment consisted of Enbrel 25 mg twice weekly subcutaneously (s.c.) for a minimum of eight doses (4 weeks, one cycle). Supportive care, including transfusion of blood and blood products, antibiotics, antiemetics, antidiarrheals, and analgesics were administered as needed.

Course timing

Enbrel was given for one course of treatment (4 weeks). If patients responded or had no signs of progression, treatment was continued for 16 additional doses (two courses) of Enbrel without interruption, at the same dose. Further courses were given in patients without overt progression.

Endpoints and statistical methods

In patients with HCL and CLL complete response (CR) was defined as an absolute lymphocyte count (ALC) $<4\times10^9$/l, hemoglobin (Hgb) 11 g/dl, absolute neutrophil count (ANC) 1.5×10^9/l, and platelet count $>100\times10^9$/l, disappearance of all palpable lymph node, spleen, and liver without the appearance of new lesions, and $<30\%$ lymphocytes in the bone marrow. Partial response (PR) was defined as an ALC reduction of $>50\%$, Hgb >11 g/dl, or 50% improvement in deviation from normal and platelet count $>100\times10^9$/l or 50% improvement in deviation from normal, and a $>50\%$ reduction in the sum of the products of two perpendicular diameters of all measurable lesions without the appearance of new lesions. Progressive disease (PD) was defined as a 50% increase in ALC, and a $>50\%$ increase in the sum of the products of two perpendicular diameters of all measurable lesions, and/or appearance of new lesions. Failure to meet the criteria for response or progression was categorized as stable disease.

For patients with AMM and MPD, CR was defined as absence of signs or symptoms of the disease, WBC between 1 and 10×10^9/l with no peripheral blasts, promyelocytes, or myelocytes, and with $<5\%$ blasts in a normocellular or hypocellular bone marrow for at least 4 weeks; resolution of pretreatment cytopenias (ANC 1.5×10^9/l without granulocyte-colony stimulation factor or granulocyte macrophage-colony stimulation factor support, Hgb 12 g/dl for males and 11 g/dl for females without erythropoietin or transfusion support, and a platelet count 100×10^9/l without growth factor or transfusion support); and resolution of pretreatment leukocytosis and/or thrombocytosis with a leukocyte count of 10×10^9/l without circulating blasts, promyelocytes, or myelocytes, and a platelet count of 100×10^9/l but $<450\times10^9$/l. PR was defined as improvement of at least two of the following parameters: (1) increase by 100% in neutrophil count, and $>1\times10^9$/l for neutropenia, WBC between 1 and 10×10^9/l with persistence of immature cells for pretreatment leukocytosis, (2) increase by 2 g/dl in Hgb if baseline value was <10 g/dl, and decrease in transfusion requirements by at least 50%, (3) increase by 100% in platelet count and increase to $>50\times10^9$/l if baseline value was below that level or persistent thrombocytosis $>450\times10^9$/l but $<50\%$ of pretreatment value, (4) reduction in marrow blasts to 5% or less if baseline value was $>10\%$ in normocellular or hypercellular marrow, and (5) reduction in splenomegaly and/or hepatomegaly by 50% of pretreatment dimensions, measured as length below the left costal margin on palpation. All other responses were considered failures.

Overall survival was measured from the date of entry into this trial until date of death from any cause or date of last follow-up. Survival curves were calculated according to the method of Kaplan and Meier. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.

Results

Study group

A total of 26 patients were enrolled on study, of whom 25 were evaluable. One patient withdrew consent prior to initiation of Enbrel. The clinical characteristics of the patients treated with Enbrel are summarized in Table 1. Three patients had HCL, eight patients had CLL, nine patients had AMM, and five patients had Philadelphia-negative MPD. Their median age was 60 years (range 30–83 years), and 18 (72%) were male. Three patients (12%) had a PS score of 0, 21 (84%) a PS score of 1, and

Table 1. Patient characteristics, adverse events, and responses on study

		No.	%
Diagnosis			
HCL		3	12
CLL		8	32
AMM		9	36
Philadelphia-negative MPD		5	20
Age (years)			
Median	60		
Range	30–83		
Patients >60 years		12	48
Male		18	72
PS >1		1	4
Prior regimens			
0–2		13	42
3–8		12	48
Hgb <10 g/dl		11	44
WBC $<4\times10^9$/l		11	44
PLT $<100\times10^9$/l		14	56
Grade III/IV adverse event		0	
Grade II adverse event			
Fatigue		5	20
Headache		2	8
Fever		2	8
Muscle pain		1	4
Gastric reflux		1	4
Nausea		1	4
Objective response		0	

1 (4%) a PS score of 2. The median number of prior treatments was two (range one to eight). Maximum response to prior treatment was: CR in 12%, PR in 20%, progressive disease in 36%, and no response in the remaining patients.

Six patients (one with HCL, two with CLL, one with AMM, and two with Philadelphia-negative MPD) had a history of splenectomy. Of the remaining patients, 12 had palpable splenomegaly with a median spleen size of 7 cm below the left costal margin (range 5–21 cm) and 4 had hepatomegaly with a median liver size of 5 cm (range 4–14 cm). Seven patients (28%) had palpable lymphadenopathy. The median pretreatment Hgb value was 10.4 g/dl (range 5.7–14.8 g/dl), the median WBC count was 4.7×10^9/l (range 1.5–113.7×10^9/l), and the median platelet count was 95×10^9/l (range 24–394×10^9/l). Cytogenetic analysis was successful in 19 patients. Of these, 15 (79%) had diploid cytogenetics (one with HCL, four with CLL, seven with AMM, and three with Philadelphia-negative MPD). Two patients with CLL had cytogenetic abnormalities (one had hyperdiploid metaphases 47–48, XY, +11, –14, +16, add (17)(p13), +1–2 markers, and one had pseudodiploid metaphases 44, XX, del (5)(q21), add (19)(q13). One patient with AMM had pseudodiploid clone 46, XX, +1, der (1; 13)(q10; q10). Finally, one patient with Philadelphia-negative MPD had a pseudodiploid clone 46,XX, del (20)(q12) and a hypodiploid clone 45, XX, dup (1)(q21q32), -7, del (20)(q12).

Treatment results

The 25 evaluable patients received a total of 70 courses. The median number of cycles administered was two (range one to nine). The median number of doses was 16 (range 3–72), and the total number of doses was 486.

Toxicity

No grade 3 or 4 adverse events occurred. Grade 2 possibly attributable adverse events included: fatigue in five patients, headache in two patients, fever in two patients, muscle pain in one patient, gastric reflux in one patient, nausea in one patient, and diarrhea/constipation in one patient. No patient was withdrawn from study because of toxicity.

Response

No patient had an objective response to Enbrel. However, three patients with AMM improved: one had a 50% reduction in spleen and liver size; one with a baseline thrombocytopenia had a twofold increase in platelet count; and one had a 50% reduction in red blood cell transfusion requirements. One patient with CLL had a significant improvement in constitutional symptoms, and one patient with Philadelphia-negative MPD had an improvement in energy level and in disease-related bone pain. A total of three patients (12%) had progressive disease: two with CLL (including one in prolymphocytic transformation removed after two doses of Enbrel), and one with myelofibrosis.

Survival

The median follow-up was 6 months (range 2–13 months). One patient died. This was a male 64 years of age with a history of CLL, refractory to prior therapy with fludarabine and cyclophosphamide; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); rituximab; and Campath. The patient received a total of two courses of Enbrel and had progressive disease with pleural effusion bilaterally, developed septic shock and expired 1 month after discontinuation of Enbrel therapy.

The median survival had not been reached at the time of this report and at 12 months the estimated overall survival rate was 96%. The majority of patients received post-Enbrel salvage regimens.

Discussion

The results of this study suggest that Enbrel is not associated with increased infections, or increased mortality rates, in the setting of immunocompromised patients

with refractory lymphoproliferative or myeloproliferative disorders. Using standard response criteria, no responses were seen. However, signs of clinical improvement were noted in some patients, particularly in those with AMM.

In terms of tolerability, the current trial corroborated our prior experience with the use of Enbrel in immunosuppressed patients with multiple myeloma [60]. The safety of Enbrel in hematologic malignancies has also been investigated by others, and generally good tolerability has been reported [55, 61]. In a study by Steensma et al., although the same Enbrel regimen as in our study was administered to 20 patients with AMM, four patients (20%) developed injection-site reactions and one patient developed pancytopenia, reversible after discontinuation of Enbrel [55]. Minor infections occurred in two patients, which was in keeping with the pre-study infection history of the cohort, consistent with our finding that in patients with hematologic malignancies, Enbrel is not associated with an increased incidence of infections. However, concerns have been expressed about infectious toxicities [17, 42, 43, 63], and increased mortality rates in the setting of established sepsis [18]. In contrast to our results in patients with hematologic malignancies, injection-site reactions are well documented in patients with RA, juvenile RA, psoriatic arthritis, and inflammatory bowel disease [43, 65].

Current treatment options other than allogeneic stem cell transplantation [21], including hydroxyurea [33], α-interferon [19, 37], androgens [6], thalidomide [3, 8], and splenectomy [2] are ultimately ineffective in patients with AMM and novel agents are required. Our results are in accordance with those reported by Steensma et al., who found that Enbrel resulted in improvement in erythropoiesis in 3 of 20 patients with AMM (15%), normalization in platelet count in one patient (5%), and reduction in spleen size in one patient (5%) [55]. Notably, in the same study, Enbrel was associated with improvement in constitutional symptoms in 12 patients (60%).

TNF is considered to contribute to organ fibrosis formation in several diseases [10, 29, 62], and to mediate hypercatabolic constitutional symptoms [49]. These pathophysiologic properties of TNF may, at least partially, explain the improvement in some patients with AMM treated with Enbrel. In addition, they may explain the improvement in constitutional symptoms of the patient with CLL, and of the patient with Philadelphia-negative MPD in our study.

In patients with myelodysplastic syndromes, Enbrel as a single agent [46], or in combination with thalidomide [48] is also well tolerated and has demonstrated some activity. The safety data from the currently reported study is very similar to those reported recently by Maciejewski et al. in a National Institutes of Health pilot study of Enbrel in a cohort of 16 patients with MDS [35]. These patients received Enbrel 25 mg twice weekly s.c. for a minimum of 3 months. Of 16 patients, 14 completed all 3 months of therapy. No patient discontinued Enbrel because of toxicity. No patient experienced Enbrel-attributable grade III or IV toxicity (one patient reported skin erythema at the injection site). Two minor upper respiratory infections, a grade III thrombocytopenia, a febrile neutropenic episode requiring intravenous hospitalization, and a septic death were noted and considered to be attributable to underlying disease. Although one patient became temporarily (for 14 weeks) independent of red cell transfusion and there was a transient increase in ANC in a second, no objective responses were seen. These investigators came to the conclusion that Enbrel in patients with MDS was well tolerated, but associated with little efficacy [35].

Enbrel may also be effective in patients with AL amyloidosis, resulting in stabilization of cardiac amyloid accumulation [52], in nephrotic syndrome with AA amyloidosis [15], and in Langerhans cell histiocytosis [25].

In conclusion, our study indicates that Enbrel at a dosage of 25 mg twice weekly was well tolerated in patients with refractory hematologic malignancies, without an overt increase in infectious episodes. Although no objective responses were seen in this study, longer term administration may be worthy of investigation, particularly in patients with AMM.

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