TNF-α inhibitor etanercept and hematologic malignancies: Report of a case and review of the literature

Bijay Nair, Girindra Raval, and Paulette Mehta*

Division of Hematology/Oncology, Department of Internal Medicine, University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System, Little Rock, Arkansas

We report here a 57-year-old man treated with etanercept for 6 months for psoriasis who developed myelodysplasia with acute myeloid leukemia. Leukemia cells had distinct karyotype associated with poor prognosis. The patient did not respond to cytosine arabinoside 100 mg/m^2 continuous infusion over 7 days with daunorubicin 45 mg/m^2 daily for 3 days. He also did not respond to salvage induction therapy with gemtuzumab (6 mg/m^2 on day 1 and 4 mg/m^2 on day 8) and intravenous continuous infusion cytosine arabinoside 200 mg/m^2. We review other cases of lymphoma and leukemia associated with tumor necrosis factor inhibitors and suggest mechanisms by which inhibition of the TNF-α family may predispose to cancer. We also suggest that all patients being considered for TNF-α treatment be screened for hematologic malignancies or premalignancies with blood counts and bone marrow aspirates/biopsies if indicated. Am. J. Hematol. 82:1022–1024, 2007. © 2007 Wiley-Liss, Inc.

Introduction

Tumor necrosis factor alpha (TNF-α) receptor blockers are a class of drugs that have brought about major advances in the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. Etanercept (Enbrel) is an injectable drug belonging to this category. Although these drugs have been noted to have relatively good safety profiles, some important side effects have been reported in literature including infections, injection-site reactions, lupus-like syndrome, induction of auto-antibodies, congestive heart failure, demyelinating diseases, lymphoma [1–3], leukemia [4], and solid tumors [5–6].

We report here a 57-year-old man with psoriatic arthritis who developed acute myelogenous leukemia several months after having been treated with etanercept for 6 months. His course of disease and the temporal relationship with the TNF-α inhibitor resembles that of a previously reported patient who had also received TNF-α inhibitor prior to developing acute myeloid leukemia [4].

Case Report

MH was a 57-year-old lawyer with psoriatic arthritis and deafness since childhood. He was treated with acitretin, and topical calcipotriene, tar and steroids for psoriatic arthritis for many years and maintained partial control of disease. In March 2004, he was started on etanercept 50 mg SQ per week for a total of 9 months. Although no blood counts were available from the time of starting treatment, labs from a year earlier showed WBC count of 9,000/mm^3 (normal differential), hemoglobin of 15.7 g/dL, hematocrit of 45.1, MCV 92.5 fL, and platelet count of 184,000/uL. Treatment was discontinued in November 2004 because of stabilization of disease and cost of the drug. In April 2005, 5 months after discontinuation of etanercept, he developed progressive fatigue and shortness of breath for which he sought medical attention. Further evaluation revealed severe anemia and thrombocytopenia (hemoglobin 3.7 g/dL, hematocrit 10.7%, MCV 114 fL, platelet count of 36,000/mm^3, WBC count 6,300/mm^3 with peripheral blood smear showing blasts) and he was subsequently admitted to the hospital. At that time, he was afebrile with stable blood pressure, heart rate, and respiratory rate. Physical examination showed significant pallor, heart and chest exam were normal. There was no evidence of hepatosplenomegaly or lymphadenoapthy. There were significant psoriatic lesions on bilateral lower extremities. Bone marrow aspirate and biopsy were done which showed blasts with prominent nucleoli, cytoplasmic granules, and dysplastic features in erythroid, myeloid, and megakaryocytic lines. Flow cytometry showed 20% bone marrow cells in the blast region with expression of CD45, CD4, CD7, HLA-DR, CD13, CD33, CD34, CD117. TdT and B cell markers were negative. Myeloperoxidase expression was dim. Chromosome analysis revealed: 46,XY,del(5)(q13q21),−13,−17,add(17)(p11.1),?19,−21,+r[3]/46,idem +8, del(9)(q34),−19[cp18]. The diagnosis of acute myeloid leukemia, therapy related (WHO Criteria) was made based on these findings.

After initiating prophylactic treatment for tumor lysis syndrome, he was given induction chemotherapy consisting of cytosine arabinoside 100 mg/m^2 for 7 days and daunorubicin 45 mg/m^2 for 3 days by continuous infusion. Blood was taken from him and from family members for HLA typing in anticipation of possible need for stem cell transplantation.

Following induction chemotherapy, patient developed numerous infectious complications including febrile neutropenia, pneumonia, mandibular abscess, and typhlitis, which responded slowly to antibiotics. He also developed pulmonary edema, which responded appropriately to diuretics. Evaluation with echocardiogram showed normal ejection fraction with concentric LVH and impaired filling.

Bone marrow aspirate and biopsy were done 28 days after the first induction treatment, which showed cellularity close to 100% with sheets of blasts throughout the medullary cavity. Myelodysplastic features were still present.

*Correspondence to: Paulette Mehta, MD, Hematology Oncology, UAMS/CAVHS, 4301 W 7th Street, Slot 111-K, Little Rock, AR 72205.
E-mail: mehtapaulette@uams.edu

Received for publication 27 June 2006; Revised 19 January 2007; Accepted 23 January 2007

Am. J. Hematol. 82:1022–1024, 2007.

Published online 24 July 2007 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20926

The patient was then given a second cycle of induction chemotherapy with anti-CD33 molecule Gemtuzumab (Mylotarg) 6 mg/m^2 on day 1, followed by Ara-C 200 mg/m^2 daily continuous infusion for 7 days, and then Mylotarg again at 4 mg/m^2 on day 8, according to a regimen in a SWOG protocol no. 0117 and prior experience elsewhere [7].

The patient again suffered severe myelosuppression and required red blood cell and platelet transfusions for anemia and thrombocytopenia, respectively. He developed pneumonia and septicemia with vancomycin resistant *enterococcus faecium*. He was treated with daptomycin, in addition to empiric treatment with aztreonam, ciprofloxacin, flagyl, and caspofungin. The management of complications following both the induction regimens was done in the intensive care unit.

A bone marrow aspirate/biopsy was repeated at 28 days after the initiation of his second induction chemotherapy that showed 70% replacement of marrow with myeloblasts and the same underlying myelodysplastic changes.

The patient continued to deteriorate with fever spikes in spite of coverage with multiple antibiotic and antifungal drugs. Pancytopenia continued and patient developed abnormal liver function tests and coagulation abnormalities consistent with disseminated intravascular coagulation. The patient refused further chemotherapy in view of his debilitated condition, overwhelming sepsis, and resistance of his disease. After long discussions, the patient was discharged from the intensive care unit to the ward for palliative care, and subsequently to hospice care.

Discussion

We report this patient to add to the growing literature of patients who develop hematologic malignancies after TNF-α inhibitor treatment [1–6].

A review of the MedWatch postmarket adverse event surveillance system run by the US Food and Drug Administration identified 26 cases of lymphoproliferative disorders following treatment with etanercept (18 cases) or infliximab (8 cases). The majority of cases (81%) were non-Hodgkin's lymphomas. The median interval between initiation of therapy with etanercept or infliximab and the development of lymphoma in this review was 8 weeks [3]. In this patient the interval was almost 20 weeks. In a prospective study of 18,572 patients with rheumatoid arthritis enrolled in National Data Bank for Rheumatoid Diseases compared with controls in the Surveillance, Epidemiology End Results (SEER) database, the relative risk for developing lymphoma was 3.8 for patients receiving etanercept and 2.6 for patients receiving infliximab (both TNF-α inhibitors) compared with control subjects [2].

A study by the South Swedish Arthritis Treatment Group register (SSATG) showed that patients with rheumatoid arthritis treated with anti-TNF agents had a possible increased risk for lymphomas [8]. A recent meta-analysis by Bongartz et al. showed that the incidence of malignancy was 0.8% in patients receiving anti-TNFα medications for rheumatoid arthritis as against 0.2% in the controls who received only methotrexate +/− placebo, and the odd ratio was calculated as 7.91 for patients receiving anti-TNF-α medications [5].

TNF-α inhibitors have also been associated with development of acute myeloid leukemia. A case report by Bakland et al. described a 31-year-old woman with ankylosing spondylitis who developed AML-M2 4 months after treatment with etanercept [4]. She went on to attain complete remission after a second course of induction chemotherapy with Cytosar and Cerubidin.

The mechanism by which TNF-α protects against cancer, and thereby how its inhibition may promote cancer, is not well understood. TNF-α is a family of factors consisting of more than 20 individual molecules with affinity for at least 21 different receptors [9]. TNF-α promotes killing of tumor cells through apoptosis via interaction with death-domain regions in tumor cells [10,11], by stimulating natural killer cells, and by inducing CD-8 killer cells [12,13].

In the in vitro setting, TNF-α has shown potent antitumor and proapoptotic activity in mammary carcinoma, multiple myeloma, lymphoma, leukemia, and other cell lines [10,14]. TNFα synergizes the antitumor activity of camptothecan and etoposide [14], and potentiate destruction of colony forming units in cell lines of acute myeloid leukemia or of chronic myeloid leukemia in blast crisis, after pretreatment with interferon or IL-2 [15,16].

Given the pivotal role of TNF-α in apoptosis, it is possible that loss of such activity predisposes to tumor growth, although the exact mechanisms have not been elucidated. It is also not known how long the antitumor surveillance and killing activities would be inhibited after discontinuation of the tumor factor inhibiting drug.

A confounding problem in interpreting malignancy after treatment with TNF-α inhibitors is that the underlying disease for which TNF-α inhibitors are used are themselves sometimes associated with malignancy. On the basis of the study by Askling et al. the patients with rheumatoid arthritis were at increased risk of lymphoma and leukemia with a standardized incidence ratio of 2.0 and 2.2, respectively [17]. In this study, patients with rheumatoid arthritis had a threefold risk for lymphoma (SIR = 2.9) compared with the general population. Similarly, patients with psoriasis also have increased risk of malignancy [18].

The most compelling factor linking development of acute myeloid leukemia in this patient to TNF-α blocker treatment is the temporal association and the fact that similar malignancies have been reported in literature. Another piece of evidence in support of a drug-induced malignancy in this man is the rare cytogenetics of his leukemia cells, which is also occasionally seen in other forms of therapy-related leukemia, resistance to therapy, and rapid demise. In particular, deletion of the long arm of chromosome 5 is known to be associated with drug-induced leukemia and is often seen in conjunction with other karyotypic abnormalities (as in the present case) and is usually associated with a poor prognosis.

It is unclear as to whether myelodysplasia was present at the time that he was initially treated with etanercept since no blood count was done at the onset of treatment. It is possible that he may have had myelodysplasia at that time and that etancercept accelerated the evolution of myelodysplasia to acute myeloid leukemia. Since myelodysplasia is a premalignancy with predelection for evolution to acute myeloid leukemia, blood counts should be done prior to initiating therapy. If blood counts suggest bone marrow disease (e.g. anemia, megaloblastosis, etc.) then bone marrow aspirates/biopsies should be done to exclude malignancy or premalignancy prior to starting tumor necrosis inhibitors.

References

1. Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. [see comment]. J Dermatol Treat 2004;15:280–294.
2. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: The effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. [see comment]. Arthritis Rheum 2004;50:1740–1751.
3. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: Twenty-six cases reported to the Food and Drug Administration. [see comment]. Arthritis Rheum 2002;46:3151–3158.

4. Bakland G, Nossent H. Acute myelogenous leukaemia following etanercept therapy. Rheumatology 2003;42:900–901.
5. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–2285.
6. Burge D. Etanercept and squamous cell carcinoma. J Am Acad Dermatol 2003;49:358–359.
7. Durrant S, Schuster MW, Linkesch W, et al. Preliminary report of the safety and efficacy of gemtuzumab ozogamicin (Mylotarg) given in combination with cytarabine in patients with acute myeloid leukemia (AML). Proc Am Soc Clin Oncol 2002;21:271a (abstract).
8. Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005;64:699–703.
9. Younes A, Aggarwall BB. Clinical implications of the tumor necrosis factor family in benign and malignant hematologic disorders. Cancer 2003;98:458–467.
10. Katschinski DM, Robins HI, Schad M, Frede S, Fandrey J. Role of tumor necrosis factor alpha in hyperthermia-induced apoptosis of human leukemia cells. Cancer Res 1999;59:3404–3410.
11. Screaton G, Xu XN. T cell life and death signalling via TNF-receptor family members. Curr Opin Immunol 2000;12:316–322.
12. van Kooten C, Banchereau J. CD40-CD40 ligand. J Leukocyte Biol 2000;67: 2–17.
13. Kashii Y, Giorda R, Herberman RB, Whiteside TL, Vujanovic NL. Constitutive expression and role of the TNF family ligands in apoptotic killing of tumor cells by human NK cells. J Immunol 1999;163:5358–5366.
14. Bergeron S, Beauchemin M, Bertrand R. Camptothecin- and etoposide-induced apoptosis in human leukemia cells is independent of cell death receptor-3 and -4 aggregation but accelerates tumor necrosis factor-related apoptosis-inducing ligand-mediated cell death. Mol Cancer Ther 2004;3: 1659–1669.
15. Geissler K, Tricot G, Leemhuis T, Walker E, Broxmeyer HE. Differentiation-inducing effect of recombinant human tumor necrosis factor α and γ-interferon in vitro on blast cells from patients with acute myeloid leukemia and myeloid blast crisis of chronic myeloid leukemia. Cancer Res 1989;49: 3057–3062.
16. Lee NS, Cheong HJ, Kim SJ, et al. Ex vivo purging of leukemia cells using tumor-necrosis-factor-related apoptosis-inducing ligand in hematopoietic stem cell transplantation. Leukemia 2003;17:1375–1383.
17. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: Lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1414–1420.
18. Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. Arch Dermatol 2001;137:778–783.