A Phase II Study of Etanercept (Enbrel), a Tumor Necrosis Factor α Inhibitor in Patients with Metastatic Breast Cancer

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ABSTRACT

Purpose: Tumor necrosis factor (TNF) α is a key player in the tumor microenvironment and is involved in the pathogenesis of breast cancer. Etanercept is a recombinant human soluble p75 TNF receptor that binds to TNF-α and renders it biologically unavailable. In the current study, we sought to determine the toxicity, biological activity, and therapeutic efficacy of Etanercept in metastatic breast cancer.

Experimental Design: We initiated a Phase II, nonrandomized, open-labeled study in patients with progressive metastatic breast cancer refractory to conventional therapy (Phase I toxicity data were available in patients with rheumatoid arthritis). Etanercept was administered subcutaneously at a dose of 25 mg twice weekly until disease progression.

Results: Sixteen patients were recruited [median age 53 years (range, 34 to 74)]. A total of 141.6 weeks of therapy was administered (median of 8.1 weeks). Seven patients received ≥12 weeks of therapy. The most common side effects were injection site reactions (6), fatigue (5), loss of appetite (2), nausea (1), headache (1), and dizziness (1). Brief period of disease stabilization was seen in 1 patient lasting for 16.4 weeks. Immunoreactive TNF-α was elevated within 24 hours of therapy and persisted until the end of treatment (days 7, 28, 56, and 84). Phytohemagglutinin stimulates the production of interleukin-6 and CCL2 in peripheral blood cells, and the ability of Etanercept to modulate this response was assessed in a cytokine release assay. A consistent decrease in interleukin-6 and CCL2 level was seen compared with pretreatment values in serial blood samples (days 1, 7, 28, 56, and 84).

Conclusions: Our study shows the safety and biological activity of Etanercept in breast cancer and provides data to assess pharmacodynamic endpoints of different schedules of Etanercept and combinations with chemotherapy or other biological therapies.

INTRODUCTION

Breast cancer is the commonest cancer and the second leading cause of cancer deaths in women (1). Although advances in adjuvant therapy have improved cure rates in early stage disease (2), metastatic breast cancer remains incurable (3). Thus new approaches are needed. Modulation of inflammation and tumor angiogenesis is a potential target with macrophage as a key component.

Convincing data now exists to support the link between inflammation and cancer (4). Tumor necrosis factor (TNF) α is a major mediator of inflammation (5). TNF-α is a M, 17,000 polypeptide and binds to p55 and p75 TNF receptors. These receptors exist both on the cell surface and as soluble receptors. The soluble forms are involved in the regulation and bioavailability of TNF-α (6). TNF-α plays a paradoxical role in the evolution of cancer. It can act as a tumor necrosis factor and also as a tumor promoting factor (7). Local administration of high-dose TNF-α is antiangiogenic and has a powerful antitumor effect (8). On the other hand, endogenous TNF-α chronically produced in tumor microenvironment enhances tumor development and spread. It may induce other cytokines/chemokines, proangiogenic factors (such as vascular endothelial growth factors, basic fibroblast growth factor, IL-8, and thymidine phosphorylase), and matrix metalloproteinases that promote cancer progression (9–13). Direct evidence for the role of TNF-α in malignancy comes from mice knockout studies (e.g., TNF-α knockout mice are resistant to skin carcinogenesis; ref. 14).

In breast cancer, infiltrating tumor-associated macrophages play an important role in tumor pathogenesis (12). Tumor-associated macrophages stimulate tumor-cell proliferation, angiogenesis, invasion, and metastasis of cancer (15–17). Tumor-associated macrophages have been shown to be of prognostic significance in breast cancer (18–20). Tumor-associated macrophages are a major source of TNF-α in breast cancer and may regulate thymidine phosphorylase, an important angiogenic enzyme in tumor epithelium (12, 21). Immunodetectable p75 and p55 TNF receptors have been detected on the cells of the mononuclear infiltrate and on the endothelium of invasive breast carcinomas (21, 22). TNF-α is a major inducer of chemokines in the tumor microenvironment (23), such as human monocyte...
evaluate toxicity, biological activity, and tumor response to volunteers, we directly proceeded to a Phase II, open-label, were available in rheumatoid arthritis patients and in healthy patients with metastatic breast cancer. As Phase I toxicity data dosing was selected on this basis. Bioavailability of 76% (31). So twice weekly subcutaneous after a single dose. The elimination half-life is 70 hours with a pharmacokinetics of Etanercept has been studied in 11 human trials involving. The pharmacokinetics of Etanercept has been studied in 11 human trials involving 285 subjects. It is slowly absorbed from a subcutaneous injection site achieving a maximum serum concentration ~48 hours after a single dose. The elimination half-life is 70 hours with a bioavailability of 76% (31). So twice weekly subcutaneous dosing was selected on this basis. We initiated a study to evaluate the role of Etanercept in patients with metastatic breast cancer. As Phase I toxicity data were available in rheumatoid arthritis patients and in healthy volunteers, we directly proceeded to a Phase II, open-label, nonrandomized study. The main objectives of the study were to evaluate toxicity, biological activity, and tumor response to Etanercept in patients with metastatic breast cancer.

MATERIALS AND METHODS

Patient Selection. This Phase II trial was conducted in compliance with the declaration at Helsinki, Tokyo, Venice, and Hong Kong (1989). Local research ethics committee approval was obtained. All of the patients provided written informed consent. Patients were eligible to participate in the study if they had advanced, histologically confirmed metastatic breast cancer with measurable or evaluable lesions, documented progression within two months before entry into the study and refractory to conventional therapy or for which no better therapy exists. Patients with a performance status (WHO) of 0, 1, or 2 and expected survival longer than three months were considered for the study. Absolute granulocyte count >1.5 × 10⁹/liter, platelet count greater >100 × 10⁹/liter, adequate renal function [serum creatinine ≤0.15 mmol/liter or EDTA clearance (≥40 ml/min)], hepatic function (bilirubin, alkaline phosphatase, transaminases ≤2 times the upper limit of normal) were essential.

Treatment Plan. The dose of Etanercept for the Phase II trial was 25 mg twice weekly given subcutaneously. Patients (or carer) were taught to self-administer Etanercept by the nursing staff. All patients were expected to receive at least 12 weeks of treatment, and responding patients continued therapy until disease progression.

Evaluation Protocol at Baseline and during Therapy. History, physical examination, and performance status assessments were done at baseline, days 1, 7, 28, and 4 weekly thereafter. Quality of life assessments with European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) pro forma was done on day 1 and 4 weekly from then on. Biochemical evaluation (serum Na, K, glucose, urea, creatinine, alkaline phosphatase, total bilirubin, AST, and GGT) and hematologic evaluation (hemoglobin, white cell count, and platelet count) were done at baseline, days 1, 7, 28, and 4 weekly thereafter. For the assessment of biological responses, blood samples were collected at baseline, 24 hours after Etanercept (day 1), day 7, 28, and 4 weekly thereafter. Radiologic evaluation (computed tomography scan and X-ray) was done at baseline and at 12 weekly intervals until disease progression. WHO response criteria was used for evaluation. Complete response was defined as disappearance of all clinical evidence of active tumors for a minimum of 4 weeks and tumor related biochemical abnormalities. Partial response was defined as 50% or greater decrease in the sum of the diameters of measured lesions. Stable disease was defined as <25% decrease or <25% increase in the sum of the longest perpendicular lesion diameter. An increase of >25% in the size of any measured lesion or appearance of new lesions was defined as progressive disease. Patients who achieved stable disease or showed regressions after 12 weeks of therapy were planned to receive additional courses of Etanercept with disease response assessments done at 12 weekly intervals. Therapy was terminated at disease progression with the occurrence of a serious adverse event.

We used the National Cancer Institute’s common toxicity criteria to evaluate toxicity. Toxicity was categorized as unrelated, possibly, probably, or definitely related to Etanercept. For patients who experienced grade 3 to 4 toxicity probably or definitely related to Etanercept, treatment was terminated. For patients developing grade 2 toxicity, treatment delay of up to 1 week was allowed, and treatment restarted once toxicity resolved to grade 1 or less.

Laboratory Procedures. TNF-α mediates the production of IL-6 and CCL2 in the whole blood when stimulated by phytohemagglutinin (PHA) in vitro. The ability of Etanercept to alter this response was assessed in sequential samples at baseline, 24 hours after the first dose of Etanercept (day 1), day 7, day 28, and 4 weekly thereafter with the whole blood cytokine release assay as reported previously (32). Briefly, whole blood from patients was stimulated with PHA, and release of cytokines IL-6 and CCL2 was measured after 24 hours incubation at 37°C in 5% CO₂. Fifteen milliliters sterile, pyrogen-free Falcon tubes were spiked with sterilized, pyrogen-free heparin (30 units/ml whole blood from CP Pharmaceuticals, Wexham, United Kingdom). One tube of each pair was additionally spiked with PHA (2 μg/ml whole blood from Bio-stat Diagnostic Systems, Stockport, United Kingdom). Twenty milliliters of blood were collected from the patient and split equally into a pair of prepared
Falcon tubes labeled either heparin + PHA or heparin (control). Bloods were incubated at 37°C for 24 hours, then the tubes centrifuged at 1,500 rpm for 10 minutes at 4°C, plasma aspirated, frozen, and stored at −80°C until assayed. Ten milliliters of blood were also collected and processed immediately for measuring TNF-α levels in unstimulated samples, IL-6, CCL2, and TNF-α were measured in plasma, in duplicates, following the protocols provided by the manufacturer [human IL-6 ELISA kit (D6050, R&D Systems, Minneapolis, MN), human CCL2 ELISA kit (DCP00, R&D Systems), and human TNF-α ELISA kit (DTA50, R&D Systems)]. All results were expressed in pg/ml.

Statistical Considerations. This was a Phase II study with a primary end point of efficacy. Therefore, it was planned that the study would be discontinued if no responses were observed in the first 14 patients. Wilcoxon-matched pairs signed-ranks test was done to analyze the serial changes in blood TNF-α, IL-6, and CCL2 levels.

RESULTS

Baseline Data (Table 1)

Fourteen patients were initially recruited. An additional 2 patients were later recruited as 2 patients in the initial cohort progressed rapidly having received <4 weeks of Etanercept therapy. The characteristics of the 16 patients recruited are shown in Table 1. Median age at diagnosis was 53 years (range, 34 to 74). A total of 141.6 weeks of Etanercept therapy was administered with a median duration of 8.1 weeks (range, 1.5 to 16.4 weeks). Seven patients received ≥12 weeks of therapy.

<table>
<thead>
<tr>
<th>Table 1 Baseline data</th>
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<tbody>
<tr>
<td>Total number of patients</td>
</tr>
<tr>
<td>Median age at diagnosis (range)</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
</tr>
<tr>
<td>Initial surgery</td>
</tr>
<tr>
<td>WLE + ANC/ANS</td>
</tr>
<tr>
<td>Mastectomy + ANC/ANS</td>
</tr>
<tr>
<td>Biopsy only</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
</tr>
<tr>
<td>Adjuvant endocrine therapy</td>
</tr>
<tr>
<td>Systemic therapy at relapse prior to Etanercept</td>
</tr>
<tr>
<td>(Chemotherapy (anthracycline based, Taxotere/taxol ± herceptin, capecitabine, cisplatin and etoposide, and others) ± endocrine therapy (tamoxifen, arimidex, exemestane, megestride, aminoglutethamide and hydrocortisone))</td>
</tr>
<tr>
<td>&lt;2 lines of therapy</td>
</tr>
<tr>
<td>≥2 lines of therapy</td>
</tr>
<tr>
<td>Radiotherapy for metastatic or recurrent disease</td>
</tr>
<tr>
<td>Surgery for local recurrence</td>
</tr>
<tr>
<td>Sites of metastatic disease at baseline (skin ± liver ± lung ± bone ± other sites)</td>
</tr>
<tr>
<td>&lt;2 sites*</td>
</tr>
<tr>
<td>≥2 sites</td>
</tr>
<tr>
<td>Baseline WHO performance status</td>
</tr>
<tr>
<td>Zero</td>
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<tr>
<td>One</td>
</tr>
</tbody>
</table>

Abbreviations: pts, patients; ANC, axillary node clearance; ANS, axillary node sampling; CMF, .

Toxicity

All of the 16 patients were evaluable for toxicity. Treatment was well tolerated in all patients. There were no treatment-related deaths. There were no serious infections in any patient during therapy. The most common side effects probably, possibly, or definitely related to Etanercept were injection site reactions (including skin rash, swelling, pain, and injection site bruise) [6 patients (grade 1; 4 patients, grade 2; 2 patients)], fatigue [5 patients (grade 1; 2 patients; grade 2; 3 patients)], loss of appetite [2 patients (grade 1)], nausea [1 patient (grade 1)], headache [1 patient (grade 1)], and dizziness [1 patient (grade 1)]. One patient had grade 1 chest wall and back pain thought to be related Etanercept. One patient with grade 2 skin rash had her treatment withheld for 1 week. As the skin rash completely disappeared after one week, Etanercept was restarted without any additional problems.

Disease Response

Seven patients who had at least 12 weeks of therapy were available for disease response evaluation. No complete responses or partial responses were seen. One patient achieved a brief period of radiologic disease stabilization (patient Br 2). She presented at the age of 45 with node negative, estrogen receptor-positive lobular carcinoma. She had surgery (wide local excision + axillary node sampling), adjuvant radiotherapy, and tamoxifen. Patient had local recurrence 4 years later and was treated with mastectomy. Three years later, she relapsed systemically and received two lines of chemotherapy (Epirubicin, Taxol+LY335979) and palliative radiotherapy. She had...
bone, peritoneal, serosal, and subcapsular liver secondaries before starting Etanercept. Twelve weeks into her therapy, she achieved stable disease with minor radiologic regression in the subcapsular liver lesion. She later progressed after 16 weeks of therapy. Another patient (patient Br 9) who presented at the age of 68 with node positive, estrogen receptor-positive lobular carcinoma was treated with surgery (WLE + ANS), adjuvant radiotherapy, and tamoxifen. Two years later, she relapsed and received four lines of systemic therapy (Arimidex, Megace, MMM chemotherapy, and Exemestane). Before initiating Etanercept therapy she had metastatic disease in bones, infiltration of mesentry, gastric antrum, and head of pancreas. She presented with gastric outlet obstruction 11.5 weeks into Etanercept therapy. She had metastatic disease in bones, infiltration of mesentry, gastric antrum, and head of pancreas. She presented with gastric outlet obstruction 11.5 weeks into Etanercept therapy.

Biological Response

Plasma TNF-α Levels with Therapy. Serial blood samples were available for biological response analysis in patients (pretreatment, days 1, 7, 28, and 4 weekly thereafter). The plasma TNF-α was measured. No measurable immunoreactive TNF-α was detected in pretreatment plasma. However, within 24 hours of Etanercept treatment, immunoreactive TNF-α was detected in blood (Table 2). Wilcoxon-matched pairs signed-ranks test was done comparing day 1 level with all of the other time points. TNF-α level increased and reached statistical significance (compared with day 1) at all of the subsequent time points as follows: day 1 versus day 7 (P = 0.003); day 1 versus day 28 (P = 0.01); day 1 versus day 56 (P = 0.01); and day 1 versus day 84 (P = 0.002). Interestingly, there was a steep increase in immunoreactive TNF-α over the whole time course in one patient, Br 9 described above (see Fig. 1), compared with all of the others. This outlier was removed and the data reanalyzed for changes in TNF-α levels. All results were significant as described previously.

Cytokine Release Assay (IL-6; Fig. 2)

Whole blood cytokine release assay was done to assess the effect of Etanercept on the release of IL-6 in the whole blood when stimulated by PHA. Mean levels of IL-6 production over the whole time course are summarized in Table 2. There was considerable variation in the response throughout treatment, with a detectable decrease only in those treated for the longest period (D84).

Cytokine Release Assay (CCL2; Fig. 3)

Whole blood cytokine release assay was done to assess the effect of Etanercept on the release of CCL2 in the whole blood when stimulated by PHA. Mean levels over the whole time course are summarized in Table 2. In contrast to IL-6, there was

Table 2 Biological response data

<table>
<thead>
<tr>
<th></th>
<th>Mean TNF-α level* (n = patients)</th>
<th>Mean IL-6 level† (n = patients)</th>
<th>Mean CCL2 level† (n = patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>Undetectable (n = 11)</td>
<td>707 (range 21–5314) [SD 1409]</td>
<td>2,759 (range 318–7652) [SD 2383]</td>
</tr>
<tr>
<td>Day 1</td>
<td>56 (range 18–99) [SD 22.9]</td>
<td>498 (range 1–2094) [SD 587]</td>
<td>2,000 (range 565–7652) [SD 1240]</td>
</tr>
<tr>
<td>Day 7</td>
<td>207 (range 110–416) [SD 19.28]</td>
<td>225 (range 1–552) [SD 208]</td>
<td>1,789 (range 157–9100) [SD 2517]</td>
</tr>
<tr>
<td>Day 28</td>
<td>157 (range 44–484) [SD 121.08]</td>
<td>316 (range 1–928) [SD 295]</td>
<td>1,828 (range 240–4475) [SD 1401]</td>
</tr>
<tr>
<td></td>
<td>(n = 11; P = 0.003)</td>
<td>(n = 11; P = 0.17)</td>
<td>(n = 12; P = 0.07)</td>
</tr>
<tr>
<td>Day 56</td>
<td>240 (range 133–670) [SD 176.59]</td>
<td>662 (range 1–4614) [SD 1492]</td>
<td>1,585 (range 215–5189) [SD 1598]</td>
</tr>
<tr>
<td></td>
<td>(n = 8; P = 0.01)</td>
<td>(n = 9; P = 0.05)</td>
<td>(n = 9; P = 0.01)</td>
</tr>
<tr>
<td>Day 84</td>
<td>192 (range 188–200) [SD 5.74]</td>
<td>154 (range 7–588) [SD 220]</td>
<td>1,290 (range 277–2350) [SD 827]</td>
</tr>
<tr>
<td></td>
<td>(n = 4; P = 0.002)</td>
<td>(n = 6; P = 0.35)</td>
<td>(n = 6; P = 0.01)</td>
</tr>
</tbody>
</table>

Note. All values were expressed as pg/ml. Wilcoxon-matched pairs signed-ranks test was performed comparing day 1 level with all other time points (days 7, 28, 56, and 84) for TNF-α and pretreatment level with all other time points (days 1, 7, 28, 56, and 84) for IL-6 and CCL2. The Ps are shown in the table.

* Unstimulated.
† PHA stimulated.
a clear trend of decrease in CCL2 response in those on treatment for a month or longer. Although in most patients CCL2 decreased, in some patients during the first month there was an initial transient increase. There were no obvious causes for this (e.g., infection or rapid progression). A statistically significant decrease in mean CCL2 was seen (compared pretreatment values) on day 56 \( (P = 0.01) \) and day 84 \( (P = 0.01) \), respectively. Two patients, Br 2 and Br 9, had marked reduction in PHA stimulated IL-6 and CCL2 levels when compared with pretreatment values.

![Graph of Mean IL-6 Level](image)

**Fig. 2** PHA stimulated whole blood cytokine release assay (IL-6). The mean PHA-stimulated IL-6 levels showed a gradual decrease from pretreatment to day 84 \( (A); \) bars, \( \pm \) SEM. The percentage difference in IL-6 level was calculated (compared with pretreatment value), and \( B \) and \( C \) show the trend in individual patients.

![Graph of Mean CCL2 Level](image)

**Fig. 3** PHA stimulated whole blood cytokine release assay (CCL2). The mean PHA-stimulated CCL2 levels showed a gradual decline from pretreatment to day 84 \( (A); \) bars, \( \pm \) SEM. The percentage difference in CCL2 level was calculated (compared with pretreatment value), and \( B \) and \( C \) show the trend in individual patients.
DISCUSSION

Etanercept was found to be safe and well tolerated. No objective disease responses were documented in this Phase II trial that recruited heavily pretreated patients with advanced breast cancer. However, a substantial effect of Etanercept on the TNF-α pathway was shown for the first time in breast cancer patients in our study at this dose level.

A statistically significant increase in immunoreactive TNF-α was seen in patients within 24 hours of initiation of Etanercept therapy. This increase continued (compared with day 1) at all of the subsequent time points (days 7, 28, 56, and 84). Given the long half-life of Etanercept (70 hours, ~3 days), it would be expected to take 15 days (5 × half-life) to reach steady state level of immunoreactive TNF-α in patients. This was shown with a substantial increase in plasma TNF-α levels from day 1 to day 7 after start of treatment. In contrast to all of the others, one patient (patient Br 9) showed continued rising levels of TNF-α. She remained on therapy for 11.5 weeks and was withdrawn because of gastric outlet obstruction. The marked elevation shows, however, that for most patients, there is spare capacity of the soluble-TNF receptor and that the dose was reasonable for the first trial of this agent in breast cancer.

Diminished cytokine (TNF-α, IL-1, IL-6, and chemokines) production in joints has been shown in rheumatoid arthritis patients receiving anti-TNF-α therapy, and a decrease in serum levels of several cytokines and chemokines has also been shown in rheumatoid arthritis (30). The decrease in TNF-α seen at day 28 and maintenance of a lower steady state level subsequently may reflect equilibrium of tissue production versus depletion of TNF-α.

We also evaluated whether the depletion of biologically active TNF-α could have a functional effect on target cells. The whole blood cytokine release assay showed reduction in CCL2 and IL-6 levels in response to PHA. This reduction is consistent with those seen in rheumatoid arthritis patients who show reduction in serum levels of IL-6, chemokines, and acute phase proteins (30). For IL-6 levels, with therapy, no statistical significance was reached and there was marked fluctuation of release, although in patients on most chronic treatment there was a decrease.

For CCL2, there was a clear decrease overall from the first month of therapy onwards. The reasons for fluctuations in these downstream markers compared with the steady trapping of TNF-α are not clear but could reflect adaptive responses or changes in successive generations of lymphocytes. Clearly, there is variability between patients, but considering variable amounts of chemotherapy and radiotherapy and bone involvement that could affect lymphocyte function, there was a pattern of response in the majority of patients, indicating a functional blockade of pathways known to be activated by TNF-α. Only patients thought not to have progressive disease in month 2 would have stayed on therapy, so this may reflect biological differences between patients, with those having some effect of TNF-α depletion showing slower tumor growth and cellular effects of therapy. There was no relation of TNF-α plasma level to the effects on cytokine release.

There is substantial biological evidence for the success of anti-TNF-α therapy in rheumatoid arthritis joints [including diminished cytokine/chemokine (TNF-α, IL-6, and CCL2) production, reduced levels of vascular endothelial growth factor and angiogenesis, and restoration of depressed T-cell immune responses]. We have shown similar effects in peripheral blood mononuclear cells. However, the potential for Etanercept to modulate breast tumor biology in tumor microenvironment needs to be substantiated by analyzing serial tumor tissue sample obtained by sequential biopsy in future studies.

A key issue for future analysis is whether higher doses of Etanercept could produce more tissue depletion in cancer patients and whether blockade with other anti-TNF-α approaches (some with longer half-lives) could enhance biological effectiveness [e.g., Infliximab (a chimeric IgG1 monoclonal antibody targeted against TNF-α)]. Other potential roles of TNF-α blockade include its use in antiangiogenic combinations to block multiple pathways.

Our study shows the safety and biological activity of Etanercept in breast cancer and provides data to assess pharmacodynamic endpoints of different schedules of Etanercept and combinations with chemotherapy or other biological therapies, for which there are several candidates as indicated above.

REFERENCES

Clinical Cancer Research

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