Phase I Clinical Trial of Tamoxifen and Interferon Alpha in the Treatment of Solid Tumors

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ABSTRACT

Both tamoxifen and interferon-α exert many antitumor activities. The combination of these agents in the treatment of cancer warrants systematic evaluation. In this phase I clinical trial, tamoxifen was administered as a fixed daily dose of 20 mg orally with escalating doses of interferon-α 2b (Schering-Plough) of 3, 10, and 20 million units/m^2 given as subcutaneous injections three times a week. Twelve patients were enrolled in this study including 6 males and 6 females with a median age of 56 years (range, 33 to 70 years). The diagnoses included soft tissue sarcoma (7), renal cancer (3) and breast cancer (2). The median number of prior treatment regimens was 2 (range, 1 to 7 prior treatments). Tamoxifen and interferon-α were administered for a median duration of 10 weeks (range, 1 to 60 weeks). None of the 6 patients treated on the first dose level of interferon-α (3 million units/m^2) experienced higher than grade I toxicity. Hematologic toxicities included only grade 1 thrombocytopenia in 7 patients (3 in the first level and 4 in the second level) with a median nadir platelet count of 129 k/mm^3 (range, 89 to 234 k/mm^3). In 6 patients treated on the second dose level of interferon-α (10 million units/m^2), 3 patients experienced transient grade III and IV toxicities including thyrotoxicosis, hepatotoxicity, and neurotoxicity. Three of 7 patients with sarcoma had stable disease for 5, 6, and 10 months and one of three patients with renal cancer, who previously failed interferon-α therapy, had complete remission for over 24 months. As a result of this study, the recommended doses for phase II clinical trial are 20 mg daily of tamoxifen and 3 million units/m^2 of interferon-α subcutaneous injections three times a week. A phase II trial of this regime in soft tissue sarcoma is underway.

INTRODUCTION

Interferon-α has been used to treat various malignancies, including Kaposi's

sarcoma, renal carcinoma, melanoma, follicular lymphoma, central nervous system tumors, chronic myelogenous leukemia, hairy cell leukemia, and multiple myeloma. Interferon-α exerts pleiotropic effects, including general antiproliferative activity and immunomodulation. Interferon-α also shows anti-angiogenic activity that is reflected clinically by the good response of hemangiomas to interferon-α.[1,2] Several cases of sarcoma have been reported anecdotally to respond to interferon-α.[3,4] In addition, it has been shown that interferon-α down regulates the synthesis of basic fibroblast growth factor (bFGF).[5]

Anti-estrogens are agents known to exert anti-angiogenic activity.[6,7,8] Tamoxifen is an antiproliferative agent that in addition to antagonizing estrogen action, inhibits protein kinase C (PKC), which transduces mitogenic signals from both fibroblast and epidermal growth factors.[9]

In addition, tamoxifen increases the level of transforming growth factor-α (TGF-α), resulting in decreased endothelial mitosis, which would lead to additional inhibition of angiogenesis.[10, 11] Combining interferon-α and tamoxifen has been shown to have additive growth inhibition of tumor cell line growth independent of estrogen receptor expression.[12,13] This study combines two biologic agents, interferon-α and tamoxifen, that have generally non-overlapping toxicities. Both have more than one anti-tumor activity mechanism and they are expected to be active anti-cancer treatment when combined.

PATIENTS AND METHODS
Inclusion Criteria
Patients with a histologically proven diagnosis of solid tumor were included in this study. All patients had evidence of metastatic disease, unresectable tumor, or progressive disease after prior therapy. Appropriate radiographic studies must have been completed within 1 month of study registration and the most recent chemotherapy or radiotherapy must have been no less than 4 weeks prior to study registration. Patients must also have a Zuhord's performance status of 0 to 2, and a life expectancy of at least 8 weeks. Patients may not have biochemical evidence or clinical history of significant end organ dysfunction, as indicated by a white blood count (WBC) ≥ 4000, absolute neutrophil count (ANC) ≥ 1500/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin (Hgb) ≥ 10.0 gm %, blood urea nitrogen (BUN) ≤ 30 mg/dL, creatinine ≤ 1.5mg/dL, bilirubin ≤ 2.0 mg/dL, alkaline phosphatase <3.0 x upper limit of normal level. Patients must not have significant active infection, history of pulmonary embolus or current deep vein thrombosis, or symptomatic lung disease. If there is known chronic obstructive pulmonary disease, the patient must have a DLCO ≥ 50% and a FVC ≥ 60% of predicted normal values. All patients signed an Institutional Review Board-approved informed consent form.

TREATMENT PLAN
Tamoxifen was given at fixed daily dose of 20 mg. Interferon-α was given at an escalating dose at three treatment levels. Level I was 3 million units/m^2, level II was 10 million units/m^2, and level III was 20 million units/m^2. Interferon-α was given three times a week by subcutaneous injection. Interferon-α was administered at the level I dose for the first three consecutive patients, and if no grade III or IV toxicities were observed, then another cohort of three patients would be treated at the higher dose level. If one grade III or IV toxicity is encountered, then an additional 3 patients will be treated at the same dose level. If no more grade III or IV toxicity

Table 1. Patient Characteristics (N=12)

Male	6
Female	6
Race	
White	9
African American	3
Performance status	
0-1	5
2	7
Tumor Type	
Sarcoma	7
Renal cell	3
Breast	2

is encountered, then a new cohort will be started at the higher level. However, if there are two or more grade III or IV toxicities encountered at any level, the next 3 patients will be treated at lower level, which will be the maximum tolerated dose.

Monitoring

Pretreatment evaluations included physical examination, complete blood count and differential, urinalysis, BUN, creatinine, electrolytes, transaminase, alkaline phosphatase, total bilirubin, chest roentgenogram, and CT scan of the involved organs.

Patients had CBC, electrolytes, liver function test, and toxicity notation on a weekly basis and a physical examination every other week. The tumor response was evaluated at week number 8, and then at week 26. If a patient has stable disease or tumor response, then treatment will be resumed. However, if there is progression of the disease or unacceptable toxicity, the patient will be taken off the study.

RESULTS

Twelve patients were enrolled on this study including 6 males and 6 females with a median age of 56 years (range, 33 to 70 years). Patient characteristics are depicted in Table 1. The diagnoses included soft tissue sarcoma (7), renal cancer (3) and breast cancer (2). The median number of prior treatment regimens was 2 (range, 1 to 7 prior treatments). Tamoxifen and interferon-α were administered for a median duration of 10 weeks (range, 1 to 60 weeks). The first 3 patients at level I did not experience serious toxicity, therefore, the interferon-α dose was escalated to level II. In the first 3 patients, one patient had thryotoxicosis. Three additional patients were enrolled in Level II, and two additional toxicities were encountered including grade III hepatotoxicity and neurotoxicity (Table 2). Both toxicities were reversible.

The fourth cohort of patients was treated on the level I dose of interferon-α. No additional grade III or IV toxicity was encountered. None of the 6 patients treated on the first dose level of interferon-α (3 million units/m^2) experienced higher than grade I toxicity. Hematologic toxicities included only grade 1 thrombocytopenia in 7 patients (3 in the first level and 4 in the second level) with a median nadir platelet count of 129 k/mm^3 (range, 89 to 234 k/mm^3). In 6 patients treated on the second dose level of interferon-α (10 million units/m^2), 3 patients experienced transient grade III and IV toxicities including thyrotoxicosis, hepatotoxicity, and neurotoxicity. There were no treatment-related deaths. The maximum tolerated

Table 2. Therapy-related Toxicity by Grade and Dose Level

	Dose Level I N= 6		Dose Level II N= 6	
	Grade I/II	Grade III/IV	Grade I/II	Grade III/IV
Leukopenia	2	0	2	0
Thrombocytopenia	1	1	2	0
Anemia	3	0	3	0
Renal	1	1	2	0
Hepatotoxicity	0	0	0	1
Hyperthyroidism	0	0	0	1
Neurotoxicity	0	0	0	1

dose was determined to be 3 million units/m^2 of interferon-α 3 times weekly, and tamoxifen 20 mg daily. Three of 7 patients with sarcoma had stable disease for 5, 6, and 10 months and one of 3 patients with renal cancer had complete remission for over 24 months. As a result of this study, the recommended doses for phase II clinical trial are tamoxifen 20 mg daily and interferon-α 3 million /M^2 three times a week subcutaneously. Phase II trials using these doses are underway in patients with advanced soft tissue sarcoma.

DISCUSSION

Combining both interferon-α and tamoxifen as biologic agents with anti-cancer activities is a very promising approach that could be further potentiated by additional anticancer therapy, such as chemotherapeutic agents.

Anti-angiogenic agents form an emerging modality of cancer therapy.[14] The rationale is that for the tumor to grow, adequate blood supply must be available locally to deliver nutrients and oxygen to tumor cells. This is accomplished by neovascularization (angiogenesis). The formation of new vessels may also play a role in transporting tumor cells to distant sites. For example, several studies have correlated the increase of microvessel density with worse outcome of the disease.[15-19]

Our study determined the maximum tolerated dose of interferon-α to be 3 million units/m^2, three times a week, in combination with 20 mg of tamoxifen, daily. The higher dose of interferon-α was associated with severe toxicities. Although these toxicities are expected side effects of interferon-α therapy alone, one cannot rule out the potentiating effect of tamoxifen on interferon-α. A smaller increment of interferon-α dose (between 3-10 million) may have resulted in a higher maximum tolerated dose. However, we attempted in this regimen, to push the dose of interferon-α to a higher level similar to its use in melanoma.

There are different mechanisms of action for tamoxifen, including estrogen receptors-independent anti-angiogenesis activities. Tamoxifen inhibits protein

kinase C, which transduces mitogenic signals from both fibroblast and epidermal growth factors. [20]   In addition, tamoxifen enhances transforming growth factor beta results in decreased endothelial mitosis, leading to angiogenesis inhibition.[21]   Other mechanisms of action include inhibition calmodulin and phospholipase C. It has antioxidant activity, enhances apoptosis, and stimulates phosphoinositide kinase. Finally, tamoxifen may inhibit multidrug resistance p glycoprotein.[22]

Tamoxifen potentiates the interferon-α activity through enhancement of interferon-stimulated gene expression (ISG) in interferon-resistant cells. [23] These genes have antiviral, anti-angiogenic, immunomodulatory and cell cycle inhibiting effects, and apoptotic effects. [24]

There is conflicting data of whether or not interferon-α affects the quantity estrogen receptor with both increase and decrease in the receptor expression.[25-28]   Studies of patients with sequential treatment of interferon-α and tamoxifen showed an increase in hormone receptors and P24 protein (estrogen-regulated protein) with interferon.[29] Both interferon-α and tamoxifen are anti-angiogenic agents that may enhance each other's activity.[30] The observation of some efficacy of this combination in patients with sarcoma lead to an ongoing phase II trial in this disease.

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