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Phase I trial of droloxifene in patients with metastatic breast cancer

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Abstract. Droloxifene (3-hydroxytamoxifen) is a new, nonsteroidal antiestrogen. In comparison with tamoxifen, it has a 10- to 64-fold higher affinity for the estrogen receptor and has shown a lower estrogenic and higher antiestrogenic effect in experimental studies. The objective of this study was to determine the toxicity (and its reversibility) of droloxifene given at different doses to patients with advanced metastatic breast cancer refractory to conventional endocrine therapy and chemotherapy. In this study, 30 patients were treated in groups of 6 at 5 different doses (20, 40, 100, 200, and 300 mg) by mouth once a day. Toxic effects included hot flashes, nausea, and fatigue and were not dose-related. Toxicity did not require any dose reduction or discontinuation of therapy. There was one episode of deep venous thrombosis and pulmonary embolism. There was no complete or partial response in this study, but four patients showed a minor response (13%). These data illustrate that this drug is well tolerated and needs to be further evaluated in phase II and III studies.

Introduction

Approximately 25%–60% of breast cancer patients have tumors that are estrogen (ER)- and progesterone receptor (PR)-positive. The response to endocrine therapy correlates with the quantity of receptors. The antiestrogen tamoxifen has antitumor activity in 50%–55% of patients with metastatic breast cancer and an ER-positive tumor but in less than 10% of those with ER-negative tumors [1–3]. Tamoxifen accumulates in the organs, and after progression of the disease, a washout period is needed prior to a change to other therapies [4].

During the initial tamoxifen therapy, tumor flare occurs in 4%–13% of patients [5–8]. Although the mechanism of this tumor flare has not been elucidated, it is presumed that the estrogenicity of tamoxifen may play a significant role. Side effects such as thromboembolic complications, endometrial hyperplasia, endometrial polyps, and endometrial carcinoma may possibly be explained by the estrogenicity of the drug [7–9]. In isolated cases, tamoxifen causes peliosis, hepatitis, icterus, and increases in liver enzyme levels [7, 8, 10, 11]. In a few cases, cataracts, corneal changes, or retinopathy have been reported, especially in patients receiving higher doses over longer periods [12–19]. In premenopausal patients, menstrual disorders and ovarian cysts have been observed [20]. Although the overall frequency of these side effects is low, the search for an antiestrogen with a better therapeutic index and better pharmacological characteristics is ongoing.

Droloxifene, or 3-hydroxytamoxifen, is a new, nonsteroidal antiestrogen. Preclinical in vitro and in vivo studies have shown that this drug has the following advantages as compared with tamoxifen: a 10- to 64-fold higher affinity for the ER; lower estrogenic and higher antiestrogenic effects in rat uterus (better therapeutic index); greater inhibition of the growth of previously tested human ER-positive breast cancer cells; more effective reduction of the S-phase fraction; and more effective stimulation of the estrogen-independent, growth factor-stimulated proliferation of MCF-7 cells [21–24]. In addition, the drug blocks estrogen-activated *c-myc* expression more effectively than tamoxifen and induces a higher production of tumor growth factor β (TGF-β) in MCF-7 cells as well as lower growth of various experimental and transplanted tumors in animals more effectively (R3230, DMBA,T61) [23–25]. In contrast to tamoxifen, droloxifene itself is an active substance; therefore, metabolic activation is of no importance. In comparative animal toxicity trials, droloxifene had been qualitatively and quantitatively better tolerated than tamoxifen [26, 27]. In contrast to tamoxifen, in experimen-

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Table 1. Phase I study of droloxifene: patient's characteristics

Characteristics	Number
Total patients	30
Age:	
Median	59 (range, 31–75) years
< 50 years	9
≥50 years	21
Dominant site of disease:	
Soft tissue	4 (13%)
Viscera	12 (40%)
Bone	14 (47%)
Median performance status	1 (range, 0–2)
Estrogen receptor status:	
Positive	23 (77%)
Unknown	3 (10%)
Negative	4 (13%)
Prior chemotherapy:	
None	6 (20%)
1	10 (33%)
2	5 (17%)
≥3	9 (30%)
Prior endocrine therapy:	
1	2 (7%)
2	9 (30%)
≥3	19 (63%)

tal systems, droloxifene does not induce hepatic carcinoma and has no carcinogenic effect.

Droloxifene has been evaluated in a limited number of patients in phase I–II studies in Europe and Canada, and the response rates have been encouraging [28–32]. We designed this study to determine the drug's toxicity (and its reversibility) at different doses in patients with advanced metastatic breast cancer.

Patients and methods

This phase I study included patients with metastatic breast cancer who had failed conventional endocrine therapies and chemotherapy options and met the following eligibility criteria: evidence of a response to one prior endocrine therapy or of an ER-positive tumor, an International Union Against Cancer (IUCC) performance status of ≤2, and a life expectancy of >3 months. Patients were required to have been off all previous chemotherapy or radiotherapy for 3 weeks prior to entering on this study and to have recovered from the toxic effects of the therapy. Adequate bone marrow function was defined as a peripheral absolute granulocyte count of >1,500/mm^3 and a platelet count >100,000/mm^3; adequate liver function, as a bilirubin value of ≤1.5 mg/100 ml; and adequate renal function, as a creatinine level of ≤1.5 mg/100 ml. Patients with ER-negative tumors could be enrolled if they had previously responded to endocrine therapy. Patients with brain metastases who were symptomatic after receiving irradiation to the brain, those with previous malignancies except for in situ carcinoma of the cervix or basal-cell carcinoma of the skin, and those with a history of retinopathy or recurrent thromboembolic episodes were excluded.

In this study, six patients were evaluated at each dose level for acute and chronic toxicity. The drug was given orally once a day. After six patients had been entered at the first dose level and three patients had been observed for a minimum of 4 weeks and had no toxicity of greater than grade 2, additional patients were entered at the next dose level. We treated six patients on each planned dose level: 20, 40, 100, 200, and 300 mg. All patients were registered with our central data-management office. Each patient was informed regarding the investigational nature of this study, and a written informed consent was obtained prior to initiation of the therapy, in keeping with the institutional policy. Dose adjustment for individual patients was planned as follows: if the absolute granulocyte count was <500/mm^3, the platelet count was <50,000/mm^3, or >grade 2 nonhematological toxicity was observed, the dose was to be reduced by one level.

Table 2. Toxicity

Toxic reactions[a]	Grade			
	1	2	3	4
Hot flashes	12	6	1	0
Night sweats	1	0	0	0
Nausea	4	1	0	0
Anorexia	2	0	0	0
Headache	5	0	0	0
Fatigue	5	0	0	0
Dizziness	3	0	0	0
Leg cramps	4	0	0	0
Bone pain	0	1	2	0
Constipation	2	1	0	0
Diarrhea	1	0	0	0
Transient skin rash	1	0	0	0
Deep vein thrombosis and pulmonary embolus	0	0	0	1

[a] Not dose-related

Prior to entry on the study, each patient underwent a complete history and physical examination; documentation of all measurable disease, signs and symptoms of the disease, and performance status; a complete blood count (CBC) as well as a platelet and differential count; urinalysis; a systematic multiple analysis (SMA); a coagulation profile; and estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and hormone-binding globin (SHBG) determinations. Patients were evaluated weekly with SMA, urinalysis, CBC, and platelet and differential counts for the initial 4 weeks. If the results were normal, these tests were repeated first at 2-week intervals and then at 4-week intervals. Coagulation profiles and hormonal measurements of estradiol, LH, FSH, prolactin, and SHBG were obtained at 2-week intervals for 6 weeks and then at 8-week intervals. Changes in hormone levels and in the level of SHBG were evaluated using repeated measures and analysis of variance. A small number of cases were omitted from the analysis due to missing measurements, and changes in the estradiol level were not evaluated because the measurement technique could not detect low levels. Because many patients were removed from study after 6 weeks of therapy due to progressive disease, few measurements were available beyond 6 weeks; analyses were therefore limited to changes observed within the first 6 weeks of therapy. For purposes of presentation, the difference between week-0 and week-6 measurements for each of the hormones and SHBG at each dose were also considered. Tumor measurements were documented every 2 weeks for the first 6 weeks and then every 4 weeks. Appropriate radiology and radioisotope studies were repeated after 4 weeks and at 8 weeks of therapy or earlier to document response or progression of the disease.

Results

A total of 30 patients were entered, and 6 patients were studied at each dose level. As shown in Table 1, the median age of the patients was 59 years (range, 31–75 years). The median performance status was 1 (range, 0–2), the median number of prior endocrine treatments was 3 (range, 1–5), and the median number of prior chemotherapy regimens

Table 3. Summary of hormonal measurement changes from 0 to 6 weeks with droloxifene therapy

Dose (mg)	Estradiol	FSH	LH	Prolactin	SHBG
20	–8.0[a]	–47.0	–12.3	–3.0	12.0
40	–77.6	–1.3	17.0	3.5	29.0
100	100.8	–0.1	–15.3	6.6	46.4
200	–5.8	3.1	3.9	–2.0	43.5
300	–5.6	0	–7.7	0.1	36.0
Totals	0.8	–10.9	–3.5	1.1	35.4

[a] Entries represent the mean of the week-6 value minus the week-0 value

was 2 (range, 1–5). The median duration of prior endocrine therapies was 29 months (range, 3–97 months), and the median duration of prior chemotherapy was 14 months (range, 2–30 months). The median duration of droloxifene therapy was 3 months (range, 1–16 months). All patients were off therapy at the time of this report.

Toxic reactions included hot flashes, nausea, and fatigue. The grade of toxicity, shown in Table 2, was not dose-related. Toxicity was in no case severe enough to require dose reduction or discontinuation of therapy. There was one episode of deep venous thrombosis and pulmonary embolism, but no hematological, hepatic, or renal toxicity occurred. The data regarding estradiol, LH, FSH, prolactin, and SHBG are summarized in Table 3. With the exception of SHBG, there was no clear pattern of change over time at any of the dose levels examined. Testing for a time effect over the first 6 weeks (using measurements taken at 0, 2, 4, and 6 weeks) for SHBG indicated a statistically significant increase ($P<0.01$). No change in any of the other factors approached statistical significance.

There was no complete or partial response in this study, but four patients showed a minor response (13%). For the patients who showed a minor response, the median time to progression from the initiation of therapy was 9 months (range, 8–12 months). In all, 16 patients showed no change in disease status for ≥ 2 months, and the median time to progression from the start of therapy was 4 months (range, 2–16 months). Ten patients developed progressive disease within 1–3 months on the study.

Discussion

The objective of this study was to determine the safety of droloxifene at five different dose levels. Considering that this patient population was heavily treated, the treatment was well tolerated. Increasing the dose produced no evidence of increased toxicity. The major toxic reactions were hot flashes and nausea; these were mostly of grade 1 and did not result in discontinuation of the treatment in any patient. One patient experienced deep vein thrombosis.

No complete or partial response was observed, but a few patients showed a minor response and a large number of patients had stabilization of their disease. In a phase I–II European trial, the drug showed significant antitumor activity when given at 20, 40, and 100 mg on a once-a-day schedule [30]. In this study there was suggestive evidence that a higher response rate occurred at 40 and 100 mg/day than at 20 mg/day, but this suggestion was inconsistent with the experience with tamoxifen, which had no dose-dependent antitumor activity.

From European trial data, there is enough evidence of the significant antitumor activity of droloxifene. To see some antitumor activity in our heavily treated patient population was also encouraging and may suggest at least a partial lack of cross-resistance with other endocrine treatments. Phase II studies are needed to determine the role of droloxifene as a second-line therapy in patients treated with tamoxifen, and comparative trials are needed to determine its antitumor and toxicity profile relative to that of other antiestrogens.

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