

## Phase I trial of droloxifene in patients with metastatic breast cancer

Aman U. Buzdar<sup>1</sup>, Shu Kau<sup>1</sup>, Gabriel N. Hortobagyi<sup>1</sup>, Richard L. Theriault<sup>1</sup>, Daniel Booser<sup>1</sup>, Frankie A. Holmes<sup>1</sup>, Ronald Walters<sup>1</sup>, Irwin H. Krakoff<sup>2</sup>

<sup>1</sup> Department of Medical Oncology/Medical Breast Service, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA

<sup>2</sup> Division of Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA

Received: 20 March 1993/Accepted: 4 August 1993

**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.

sion 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  $\beta$  (TGF- $\beta$ ) 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-

### 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 progres-

This study was supported by a research grant from Fujisawa Pharmaceutical (USA)

Correspondence to: Aman U. Buzdar, M.D., Department of Medical Oncology, Box 56, M.D. Anderson Cancer Center, 1515 Holcombe, Houston, TX 77030, USA

**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 (IUC) 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<sup>3</sup> and a platelet count >100,000/mm<sup>3</sup>; 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.

**Table 2.** Toxicity

Toxic reactions <sup>a</sup>	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

<sup>a</sup> Not dose-related

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<sup>3</sup>, the platelet count was <50,000/mm<sup>3</sup>, or >grade 2 nonhematological toxicity was observed, the dose was to be reduced by one level.

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),

**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 <sup>a</sup>	-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

<sup>a</sup> 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  $\geq 2$  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.

## References

1. Wittliff JL (1984) Steroid hormone receptors in breast cancer. *Cancer* 53:630–643
2. Taylor SG, Gelman RS, Falkson G, et al (1986) Combination chemotherapy compared to tamoxifen as initial therapy for stage IV breast cancer in elderly women. *Ann Intern Med* 104:455–461
3. Allan SG, Rodger A, Smyth JF, et al (1985) Tamoxifen as primary treatment of breast cancer in elderly or frail patients: a practical management. *BMJ* 290:358–362
4. Riippa P, Kauppila A, Sundstrom H, et al (1984) Hepatic impairment during simultaneous administration of medroxyprogesterone-acetate and tamoxifen in the treatment of endometrial and ovarian carcinoma. *Anticancer Res* 4:109–112
5. Arnold DJ, Markham MJ, Hacker S (1979) Tamoxifen flare. *JAMA* 241:2506
6. Plotkin D, Lechner JJ, Jung WE, et al (1978) Tamoxifen flare in advanced breast cancer. *JAMA* 240:2644–2646
7. Loomus GN, Aneja P, Bota RA (1983) A case of peliosis hepatitis in association with tamoxifen therapy. *Am J Clin Pathol* 80:881–883
8. Agrawal BL, Zelkowitz L (1981) Bone “flare”, hypercalcemia, and jaundice after tamoxifen therapy. *Arch Intern Med* 141:1240
9. Blackburn AM, Amiel SA, Millis RR, et al (1984) Tamoxifen and liver damage. *BMJ* 289:288
10. Gockerman JP, Spremulli EN, Raney M, et al (1986) Randomized comparison of tamoxifen versus diethylstilbestrol in estrogen receptor-positive or -unknown metastatic breast cancer: a Southeastern Cancer Study Group trial. *Cancer Treat Rep* 70:1199–1203
11. Nomura Y, Tashiro H, Hisamatsu K, et al (1988) A randomized trial of adjuvant endocrine therapy, chemotherapy and chemoendocrine therapy for operable breast cancer stratified by estrogen receptors. *Cancer* 61:2168–2175
12. Pavlidis NA, Petris C, Briassoulis E, et al (1992) Clear evidence that long-term, low-dose tamoxifen treatment can induce ocular toxicity. A prospective study of 63 patients. *Cancer* 69:2961–2964
13. Chang T, Gonder JR, Ventresca MR (1992) Low-dose tamoxifen retinopathy. *Can J Ophthalmol* 27:148–149
14. Bentley CR, Davies G, Aclimandos WA (1992) Tamoxifen reti-

15. Costa RH, Dhooge MR, Van-Wing F, et al (1990) Tamoxifen retinopathy. A case report. *Bull Soc Belge Ophthalmol* 238:161-168
16. Gerner EW (1989) Ocular toxicity of tamoxifen. *Ann Ophthalmol* 21:420-423
17. Griffiths MF (1987) Tamoxifen retinopathy at low dosage. *Am J Ophthalmol* 104:185-186
18. Pugesgaard PT, Von Eyben FE (1980) Bilateral optic neuritis evolved during tamoxifen treatment. *Cancer* 58:383-386
19. Ashford AR, Doner I, Tiwari RP, et al (1985) Reversible ocular toxicity related to tamoxifen. *Cancer* 61:33-35
20. Sawka CA, Pritchard IC, Paterson et al (1986) Role and mechanism of action of tamoxifen in premenopausal women with metastatic breast carcinoma. *Cancer Res* 46:3152-3156
21. Roos WK, Oeze L, Loser R, et al (1983) Antiestrogenic action of 3-hydroxytamoxifen in the human breast cancer cell line MCF-7. *J Natl Cancer Inst* 71:55-59
22. Loser R, Seibel K, Roos W, et al (1985) In vivo and in vitro antiestrogenic action of 3-hydroxy-tamoxifen, tamoxifen and 4-hydroxy-tamoxifen. *Eur J Cancer Clin Oncol* 21(8):985-990
23. Kawamura I, Mizota T, Mukumoto S, et al (1989) Antiestrogenic and antitumor effects of droloxifene in experimental breast carcinoma. *Arzneimittelforschung* 39:889-893
24. Eppenberger U, Wosikowski K, Kung W (1991) Pharmacologic and biologic properties of droloxifene, a new antiestrogen. *Am J Clin Oncol* 14 [Suppl 2]:5-14
25. Knabbe C, Zugmaier G, Schmahl M, et al (1991) Induction of transforming growth factor  $\beta$  by the antiestrogens droloxifene, tamoxifen, and toremifene in MCF-7 cells. *Am J Clin Oncol* 14 [Suppl 2]:15-20
26. Loser R, Hasmann M, Seibel K, et al (1989) Pharmacological activity of the metabolites of the antiestrogen droloxifene (abstract 89). *Breast Cancer Res Treat* 14:155
27. Lien EA, Solheim E, Lea OA, et al (1989) Distribution of 4-hydroxy-N-desmethyltamoxifen and other tamoxifen metabolites in human biological fluids during tamoxifen treatment. *Cancer Res* 49:2175-2183
28. Abe O (1991) Japanese early phase II study of droloxifene in the treatment of advanced breast cancer. *Am J Clin Oncol* 14 [Suppl 2]:40-45
29. Stamm H, Roth R, Huber HJ, et al (1986) Preliminary data on a phase I trial of the new antiestrogen droloxifene: tolerance, pharmacokinetics and metabolism. In: Eckhardt S, Holzner JH, Nagel GA (eds) *Contributions to Oncology*, vol 23. Karger, Basel, pp 73-78
30. Deschenes L (1991) Droloxifene, a new antiestrogen, in advanced breast cancer. A double-blind dose-finding study. *Am J Clin Oncol* 14 [Suppl 2]:52-55
31. Bellmunt J, Sole L (1991) European early phase II dose-finding study of droloxifene in advanced breast cancer. *Am J Clin Oncol* 14 [Suppl 2]:36-39
32. Osahiko A, et al (1991) Japanese early phase II study of droloxifene in the treatment of advanced breast cancer. Preliminary dose-finding study. *Am J Clin Oncol* 14 [Suppl 2]:40-45