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Droloxifene, a new antiestrogen: Its role in metastatic breast cancer

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Abstract

Droloxifene, a new antiestrogen, has theoretical advantages over tamoxifen based on preclinical data. These include higher affinity to the estrogen receptor, higher antiestrogenic to estrogenic ratio, and more effective inhibition of cell growth and division in ER positive cell lines, as well as less toxicity, including reduced carcinogenicity in animal models. Droloxifene also exhibits more rapid pharmacokinetics, reaching peak concentrations and being eliminated much more rapidly than tamoxifen. A phase II study compared droloxifene in dosages of 20, 40, and 100 mg daily in postmenopausal women with metastatic, or inoperable recurrent, or primary locoregional breast cancer who had not received prior hormonal therapy. Of 369 patients randomized, 292 were eligible and 268 evaluable for response. Response rates (CR + PR) were 30% in the 20 mg group, 47% in the 40 mg group, and 44% in the 100 mg group (40 mg vs 20 mg, $p = 0.02$; 100 mg vs 20 mg, $p = 0.04$; pooled 40 + 100 mg vs 20 mg, $p = 0.01$). Median response duration also favoured the higher dosages (20 mg group = 12 months; 40 mg group = 15 months; 100 mg group = 18 months). When adjusted for prognostic factors, time to progression was significantly better for the 100 mg ($p = 0.01$) and the 40 mg ($p = 0.02$) group compared to the 20 mg group. Droloxifene increased SHBG and suppressed FSH at all dosages and suppressed LH at the 40 and 100 mg dosages. These hormonal effects increased with increasing dosage. Short-term toxicity was generally mild, and similar to that seen with other antiestrogens. Droloxifene appears active and tolerable. It may have a particular role in situations in which rapid pharmacokinetics, or an increased antiestrogenic to estrogenic ratio, are required.

Introduction

Endocrine therapy remains a mainstay in the treatment of breast cancer, both in the adjuvant setting and for metastatic disease. The antiestrogen tamoxifen has become standard first-line therapy for metastatic disease in postmenopausal and frequently in premenopausal women. Tamoxifen is also increasingly used as standard adjuvant therapy for node-positive and node-negative postmenopausal women, although its role in the adjuvant therapy of premenopausal women remains less clear. Tamoxifen has become so widely used largely because of its very acceptable short-term toxicity profile in comparison to earlier antiestrogens and to historically standard hormones such as estrogen. Now that tamoxifen has been used for longer periods in adjuvant therapy and is being studied as a preventive in women at high risk of developing breast cancer, its short and long-term toxicity profiles are un-

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dergoing increasing scrutiny. Several recent reports suggest that tamoxifen may exert beneficial influences on both bone mineralization and lipid metabolism, perhaps because of its mild estrogenic effects. Some of tamoxifen's more serious, although infrequent, short-term complications such as hypercalcemia, deep venous thrombosis, and pulmonary embolism, as well as an increased incidence of endometrial cancer, however, are probably also related to this mild estrogenic effect. In addition, in animal models, tamoxifen has shown a probably non-hormonal hepatic carcinogenicity which has not, as yet, been demonstrated to occur in humans. Thus, the development over the last 5–10 years of a number of newer antiestrogens has raised considerable interest in the oncology community. Many of these antiestrogens are, however, very similar to tamoxifen, both in their estrogenic to antiestrogenic profiles and in their pharmacokinetic properties. Droloxifene (3-hydroxy-tamoxifen) is a new nonsteroidal antiestrogen of some particular interest, since preclinical *in vitro* and *in vivo* testing have shown a number of differences which represent potential advantages in comparison to tamoxifen.

These include a 20–60 fold higher affinity to the estrogen receptor [1], lower estrogenic and higher antiestrogenic effects on the rat uterus (higher therapeutic index) [2], more effective inhibition of the growth of ER-positive human breast cancer cell lines [3–5], more effective reduction of S-phase proportion in a variety of cell lines [6], complete suppression of growth factor (IGF-1) stimulated proliferation of MCF-7 cells when a therapeutic concentration is achieved [3], more effective blockade of estrogen-activated c-myc-expression [5], higher production of TGF-β in MCF-7 cells [6, 7], and more effective growth reduction of various experimental and transplanted tumors in animals (R 3230, DMBA, T61)[3, 5, 8, 9]. In addition, in comparative animal toxicity trials droloxifene is qualitatively and quantitatively better tolerated than tamoxifen [10–15]. Furthermore, droloxifene does not transform Syrian hamster embryo fibroblasts as tamoxifen does, nor produce ovarian or Leydig cell tumors in mice [16], suggesting that it may not have the same potential to increase the incidence of endometrial carcinoma in women that tamoxifen does. It is also notable that droloxifene, in contrast to tamoxifen, does not induce hepatic carcinomas in rats [17], suggesting a lack of hepato-carcinogenic potential in humans.

In addition, several pharmacokinetic properties of droloxifene are of potential clinical advantage in comparison to those of tamoxifen. First, droloxifene is itself the active anticancer compound [18, 19], in comparison to tamoxifen, which must be metabolized in order to form the active product, 4-OH-tamoxifen [20]. As a result, the concentration of droloxifene necessary for antitumor activity is reached within the first day of therapy [18, 19], in contrast to tamoxifen, for which effective concentrations are attained only from the 11th day onwards [20]. Furthermore, extensive accumulation of tamoxifen takes place, extending over 4 weeks [20], the wash-out time of tamoxifen being 7 times longer than that of droloxifene, which has a serum elimination half life of one to one and a half-days [19].

Because of these encouraging preclinical characteristics, and following several phase I-II studies in which droloxifene demonstrated safety, good tolerability, and some efficacy in women who had previously received tamoxifen and/or other endocrine therapy [21, 22], this new antiestrogen was then tested as first line therapy in the study described below, a multicentre, double-blind, randomized, dose finding study comparing 20, 40, and 100 mg of droloxifene given daily in postmenopausal women who had received no previous hormonal therapy for metastatic breast cancer. Early results from a preliminary analysis of some of the women entered on this study have been previously described [23].

Patient selection and methods

Study design

The study described was carried out by investigators from Austria, Belgium, Brazil, Canada, France, Germany, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom. The trial was designed to determine the optimal daily dose of droloxifene in postmenopausal women not previously exposed to systemic anti-tumor hormonal

therapy. Patients were randomized to receive 20, 40, or 100 mg of droloxifene given in double-blind fashion. Each centre was supplied with numbered medications in three doses. The randomization was done in groups of six patients. There was no stratification other than by centre.

Patient selection

Patients included were postmenopausal women with histologically proven breast cancer who, at the time of study entry, had advanced disease which could include distant metastatic cancer, inoperable recurrent loco-regional cancer, or inoperable primary local or loco-regional cancer. All patients were required to have at least one lesion that was evaluable or measurable according to the World Health Organization (WHO) criteria [24]. Study candidates were required to have positive estrogen or progesterone receptor status in either the primary tumor specimen or subsequently obtained specimens, or to have unknown receptor status. Patients with prior chemotherapy were eligible only if such chemotherapy had been given as adjuvant treatment and was terminated at least a year prior to study. Patients were not permitted to have received any type of systemic endocrine therapy either with adjuvant intent or as treatment for metastatic disease.

Exclusion criteria included a performance status of grade four, previous malignancy of other organs except adequately treated *in situ* carcinoma of the cervix uteri or basal or squamous cell carcinoma of the skin, a history of retinopathy, a history of severe liver disease, acute severe infectious disease, current thrombophlebitis or thrombosis, a history of leukocytopenia or thrombocytopenia not related to previous chemotherapy, and elevated calcium levels. Patients whose only lesions were malignant effusions, lymphangitis carcinomatosis, osteoblastic bone lesions, or lesion(s) that had been recently irradiated were not considered eligible. Patients with inflammatory breast cancer or with brain metastases were not eligible for study. Patients felt to be at very high risk because of rapid progression of disease or extensive disease in liver or lung were not considered eligible for this trial of a hormonal agent.

Patient assessment and follow up

At entry, all patients were required to be staged with a chest radiograph, bone scan, radiographs of all suspicious bone scan lesions, an ultrasound or computer tomographic scan of the liver, liver function tests including an SGOT, SGPT and γ-GT, an LDH, alkaline phosphatase, serum glucose, bilirubin, creatinine, BUN, and calcium as well as a hemoglobin, sodium, potassium level, white blood cell count with differential, and a platelet count. Target metastases were required to be determined and measured on entry, and remeasured every two months for the first six months, then every three months. The technical method for measuring the tumor was not to be changed during the trial. Complete restaging as described above was required every six months.

Response assessment

The quality of the data obtained was assured by two methods. All data in the case record forms were checked against hospital records of the patients by monitors of the two sponsoring companies, Rhone-Poulenc and Klinge Pharma. Furthermore, in response evaluation meetings, the investigators jointly evaluated the sources used for tumor response for all patients. As a result of these response evaluation meetings, the tumor status of all patients was peer reviewed.

The criteria used to determine objective response (according to WHO) were:

a) complete remission: disappearance of all known disease determined by two observations made not less than four weeks apart;
b) partial remission: a decrease of 50% or more in total tumor load; no lesion should have progressed (≥ 25%); no new lesion(s) should have occurred;
c) no change: decrease of less than 50% or in-

crease of less than 25% in the tumor size; no new lesions;

d) progressive disease: increase of the tumor size by 25% or more, or appearance of new lesions.

Results

Patient characteristics

Between June of 1988 and March of 1991, 369 patients were randomized from 29 centres in Europe, 9 centres in Canada and 4 centres in Brazil. Of 369 patients randomized, 268 are evaluable for response. Seventy seven were ineligible for reasons including primary operable breast cancer (24), no WHO evaluable lesion (16), prior hormonal therapy (6), incomplete baseline staging (6), negative hormone receptor status (5), high risk status (4), inflammatory breast cancer (3), not post-menopausal (3), palliative chemotherapy :(3), hypercalcemia (2), previous other cancer (2), no proof of breast cancer (1), adjuvant chemotherapy not terminated at least one year prior to study enrollment (1), history of retinopathy (1). Twenty-three patients were inevaluable, largely because early withdrawals or deaths, loss to follow-up or failure to repeat the investigations required to determine response. Table 1 illustrates the reasons for ineligibility and inevaluability by treatment group, and in total.

The distribution of demographic data and risk factors for all evaluable patients is displayed in Table 2. The three groups did not differ with respect to age distribution (mean = 64), disease-free interval or hormone receptor status. If anything, patients with unfavourable prognostic factors were slightly overrepresented in the higher dose groups, in that 32% of the 20 mg group had an unfavourable prog-

Table 1. Patients enrolled and evaluated.

Patients	Treatment group 20 mg		40 mg		100 mg		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Patients enrolled	112	(30.4)	124	(33.6)	133	(36.0)	369	(100)
Ineligible:	21	(18.8)	27	(21.8)	29	(21.8)	77	(20.9)
no UICC lesions	6	(5.4)	4	(3.2)	6	(4.5)	16	(4.3)
neg. hormone receptor status	3	(2.6)	2	(1.6)	–		5	(1.4)
no proof of breast cancer	–		1	(0.8)	–		1	(0.3)
inflammatory breast cancer	–		2	(1.6)	1	(0.8)	3	(0.8)
high risk patients	–		4	(3.2)	–		4	(1.1)
not postmenopausal	1	(0.9)	–		2	(1.5)	3	(0.8)
prior palliative chemo	–		–		3	(2.3)	3	(0.8)
prior hormonal treatment	2	(1.8)	2	(1.6)	2	(1.5)	6	(1.6)
adj chemo not terminated at least one year prior to study enrollment	–		–		1	(0.8)	1	(0.3)
incomplete baseline staging	3	(2.6)	2	(1.6)	1	(0.8)	6	(1.6)
history of retinopathy	–		–		1	(0.8)	1	(0.3)
hypercalcemia on entry	–		–		2	(1.5)	2	(0.5)
previous other cancer	–		–		2	(1.5)	2	(0.5)
primary operable	6	(5.4)	10	(8.1)	8	(6.0)	24	(6.5)
Not evaluable	7	(6.3)	9	(7.3)	7	(5.3)	23	(6.2)
early withdrawals	4	(3.5)	3	(2.4)	1	(0.8)	8	(2.1)
early deaths	2	(1.8)	1	(0.8)	1	(0.8)	4	(1.7)
lost to follow-up	–		3	(2.4)	–		3	(0.8)
target lesions not followed according to protocol	1	(0.9)	2	(1.6)	4	(3.0)	7	(1.9)
insufficient treatment compliance	–		–		1	(0.8)	1	(0.3)
Open	–		–		1	(0.8)	1	(0.3)
Evaluable	84	(75.0)	88	(71.0)	96	(72.2)	268	(72.6)

nosis (Possinger score ≥ 7), while 39% in the 40 mg and 43% in the 100 mg group scored unfavourably (see Table 3 for calculation of Possinger score) [25]. Similarly, 33% of the 20 mg group had visceral metastases, while 40% of the 40 mg group and 45% of the 100 mg group had this generally acknowledged poor prognostic factor. These differences in the distribution of prognostic factors were not statistically significant.

Response to droloxifene

Response rates for all patients evaluated are shown on Table 4. Response rates (CR + PR) were 30% in the 20 mg group, 47% in the 40 mg group, and 44% in the 100 mg group. Median duration of response was 12 months in the 20 mg group, 15 months in the 40 mg group, and 18 months in the 100 mg group. When the three groups were compared, adjusting for prognostic factors using logistic regression, both the 40 mg ($p = 0.02$) and 100 mg ($p = 0.04$) groups had significantly higher response rates than the 20 mg group. The pooled 40 and 100 mg groups also had a higher response rate than the 20 mg group ($p = 0.01$).

Time to response was relatively short. In all three groups, 50% of the remissions were obtained in the first two months (see Fig. 1). Patients who responded later were generally those with bone metastases. The median pain score of patients on study decreased by nearly half within the first two weeks. (20 mg group 1.4 (± 0.8) to 0.7 (± 0.9); 40 mg group 1.2 (± 0.8) to 0.7 (± 0.9); 100 mg group 1.6 (± 0.8) to 0.9 (± 0.9).

Time to progression was 5.6 months in the 20 mg group, 8.3 months in the 40 mg group, and 6.4 months in the 100 mg group (see Fig. 2). When ana-

Table 2. Demographic data of patients evaluated for efficacy (n = 268), (percentage of patients in relation to size of treatment group).

Variable	Treatment group 20 mg (n = 84) No.	(%)	40 mg (n = 88) No.	(%)	100 mg (n = 96) No.	(%)
Age (yrs, mean ± std.dev.)		64.2 ±9.2		64.6 ±9.1		64.2 ±9.9
Performance status (WHO) on entry						
Grade 0	39	(46.4)	34	(38.6)	36	(37.5)
Grade I	35	(41.7)	45	(51.1)	38	(39.6)
Grade II	10	(11.9)	5	(5.7)	14	(14.6)
Grade III	0	(0.0)	3	(3.4)	6	(6.3)
no data	0	(0.0)	1	(1.1)	2	(2.1)
Disease free interval						
DW 2 years	34	(40.5)	34	(38.6)	43	(44.8)
> 2 years	43	(51.2)	43	(48.9)	46	(47.9)
no data	7	(8.3)	11	(12.5)	7	(7.3)
Receptor status (primary)*						
positive	43	(51.2)	51	(58.0)	49	(51.0)
unknown	41	(48.8)	37	(42.0)	47	(49.0)
Prior adjuvant chemotherapy						
Yes	19	(22.6)	16	(18.2)	19	(19.8)
No	65	(77.4)	72	(81.8)	77	(80.2)
Risk factor (Possinger Score)**						
0–6	57	(67.9)	54	(61.4)	54	(56.3)
≥ 7	27	(32.1)	34	(38.6)	42	(43.8)
Dominant site of disease						
soft tissue	25	(29.8)	28	(31.8)	26	(27.1)
bone	31	(36.9)	25	(28.4)	26	(27.1)
visceral	28	(33.3)	35	(39.8)	44	(45.8)

* $p = 0.573$, Chi^2 test.
** $p = 0.112$, Mantel Haenszel test.

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