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European Early Phase II Dose-Finding Study of Droloxifene in Advanced Breast Cancer

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Preliminary results from clinical phase II studies with droloxifene demonstrated efficacy and good tolerability. One hundred ninety-six female, postmenopausal patients with advanced breast cancer were treated with 20, 40, or 100 mg of droloxifene daily. Exclusion criteria were as follows: negative ER/PR status, tamoxifen treatment within the preceding three months, chemotherapy within the preceding three weeks, and performance grade of four. Seventeen percent of the patients treated with 20 mg daily responded to treatment, exhibiting complete or partial responses according to World Health Organization criteria. In the 40-mg group, 30% responded and in the 100-mg group, 31% responded. Adverse symptoms generally were mild.
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The data presented in this paper were obtained from a variety of European clinical dose-finding studies designed as part of the phase II development of droloxifene. The studies were performed in collaboration, between investigators in several European countries (see *Note*).

PATIENT SELECTION AND METHODS

Two types of studies are included in this article. The majority of the data comes from open dose-finding studies in which either one, two, or all three of the three possible dosage levels were investigated in each center. The rest of the data come from droloxifene-treated patients from open, comparative studies with droloxifene versus other systemic treatment. In all of these studies, treatments were assigned in an alternating fashion, rather than by random allocation.

All studies included postmenopausal women with advanced breast cancer and positive or unknown hormone receptor levels. Patients with negative hormone receptors, who had received tamoxifen therapy during the last three months, chemotherapy during the last three weeks, or who had poor performance status, grade four (1), were excluded. Patients were treated with 20, 40, or 100 mg of droloxifene once daily until disease progression. Treatment could also be stopped for medical or personal reasons. No other systemic tumor active treatment was allowed. Radiotherapy could be applied, provided not all target lesions were irradiated.

Tumor measurements were obtained by means of ultrasound examinations, radiographs, radionuclide scans, or computer tomography—radionuclide scans could not be used for measurements alone but had to be interpreted together with appropriate radiographs. Target lesions had to be staged by the same technical method at each visit. Response was assessed according to World Health Organization (WHO)/Union Internationale Contre le Cancer (UICC) criteria (1). The

data obtained were thoroughly validated against hospital records; for example, all tumor measurements were checked against original sources. Data not yet verified in this way have been omitted from this collation. A total of 196 patients were treated as part of the trials described above. For a patient to be regarded as evaluable for efficacy, it was required that the inclusion criteria be fulfilled, that the protocol be properly adhered to, and that full tumor assessments be obtained. Data from 18 of the patients were, therefore, excluded because of protocol violations or insufficient data. Of the remaining 178 patients, 44 received 20 mg of droloxifene daily, 53 received 40 mg daily, and 81 received 100 mg. The entire group of 178 patients is included in describing tolerability. In reporting toxicity, all reported symptoms as collected in checklist questionnaires were included regardless of causality. Fifty-four of the 178 patients could not be evaluated for efficacy because of inadequate tumor assessment. Therefore, 124 patients were evaluable for efficacy. Thirty patients received 20 mg daily, 33 patients received 40 mg daily, and 61 patients received 100 mg daily.

RESULTS

The median age for the 178 patients was 64 years, ranging from 34 to 87 years. In the 20 mg group the median age was 68 years, in the 40 mg group, 61 years, and in the 100 mg group, 64 years. There is no difference among the three groups according to this parameter. Only 32% of the patients had positive hormone receptors in the primary tumor, and 9% in the secondary tumor. Three percent had negative receptors in the primary tumor and <1% negative in the secondary tumor. No patients had negative receptors in both primary and secondary tumors. It appears that the receptor state for the majority of the patients, 65%, was unknown for the primary tumor. For the secondary tumor, this proportion was ~91%. The three dosage groups were similar with regard to receptor status. Eighty-one percent of patients had a disease-free interval longer than 2 years. The mean ranged from 46.4 months in the 100-mg treatment group to 51.3 months in the 20-mg group.

Bone, soft tissue, and lung metastases were the most frequently occurring metastatic sites. Fifty-eight percent of all the patients had bone metastases, 34% had soft tissue metastases, and 31% had lung metastases. At least one-half of the patients presented with metastases at more than one location. Nineteen percent of patients had metastatic pleural effusions. Metastases in liver and peripheral lymph nodes were each present in 10%. Locations that were less frequently involved were the mediastinal lymph nodes in 6% of the patients, the central nervous system in 5% of the patients, and malignant ascites, which were reported in 1% of patients. In summary, the patients studied had extensive metastatic involvement with metastases that often respond poorly to hormonal therapy.

Only 32% of the patients had not received any previous therapy, 28% had received one previous course of treatment, 19% had received two previous treatments, 14% had received three, and 7% had received four to six. Thus, many of these patients were intensively treated prior to study entry. The patients may be unevenly distributed with regard to previous therapy in the different dosage groups. It is, however, not possible to show whether or not this may influence treatment results. With regard to type of previous therapy, 30% received both previous endocrine- and chemotherapy, 19% received previous endocrine treatment only, and 20% of the patients received only previous chemotherapy.

The mean duration of droloxifene treatment was 8.3 months in the 20-mg group, 8.9 months in the 40-mg group, and 11.6 months in the 100-mg group. These figures represent all the 178 evaluable patients. The 44 patients still receiving treatment are included. All patients are included, even those who were not evaluable for efficacy. This means that early dropouts as well as patients with early progression are included, and this, of course, will shorten the mean duration of treatment. The duration of treatment ranged from <2 weeks to 39.4 months in the 20-mg group, 41.9 months in the 40-mg group, and 31.5 months in the 100-mg group.

In reporting efficacy, only those patients in whom proper tumor assessments were carried out are included. This group comprises 124 patients. The number of responding patients—complete and partial—were 5 in the 20-mg group (17%), 10 in the 40-mg group (30%) and 19 in the 100-mg group (31%). One of 33 (3%) in the 40-mg group and 6 of 61 (10%) in the 100-mg group obtained complete responses. Responses by site showed 14 of 69 (20%) in bone, and 6 of 22 (27%) in patients with pleural effusion. In four, the effusion completely disappeared and two further patients had a marked decrease. In one patient with ascites, the ascites completely disappeared.

Adverse symptoms are shown in Table 1. As one patient may have reported a symptom several times during the trial and in different grades of severity, only the most severe report is shown. This means that if a patient, for example, reported mild nausea several times during the treatment and moderate nausea once, the patient contributes to this diagram with moderate nausea only. No dose relations are prominent, though vomiting may be less frequent in the

TABLE 1. *Adverse symptoms with droloxifene*

Symptom	Severity level[a] 1 (20 mg group, n = 44)	2	3	1 (40 mg group, n = 53)	2	3	1 (100 mg group, n = 81)	2	3
Gastrointestinal	3	4	1	4	4	2	8	4	2
Nausea	5	5	1	5	4	2	9	7	1
Gastrointestinal pain	1	2	—	6	—	—	5	1	1
Headache	4	1	—	4	1	1	3	3	—
Dizziness	7	2	1	5	2	—	4	3	1
Lassitude	5	4	—	6	5	—	9	1	1
Flush	5	2	—	2	1	1	6	3	—
Vomiting	2	1	1	4	3	1	8	4	2
Vaginal bleeding	3	—	—	—	1	—	1	1	1
Pulmonary toxicity	—	—	—	—	1	—	3	—	1
Neurotoxicity	—	1	—	—	—	—	5	3	—
Depression	2	—	—	1	1	1	6	5	—
Skin allergy	—	—	—	1	—	—	2	1	—
Renal toxicity	1	1	—	—	1	—	—	1	—
Hepatotoxicity	—	—	—	—	—	1	2	—	1
Hypercalcemia	1	—	—	1	1	1	1	—	1
Hot flushes	2	3	—	—	3	—	11	7	—
Euphoria	—	—	—	1	—	—	—	—	—
Thromb./Phlebit.	—	—	—	—	—	—	1	1	2
Edema	1	2	—	4	4	1	3	2	—
Lymphedema	—	2	—	1	3	—	1	—	—
Weight gain	3	1	—	6	1	—	10	1	—
Eye disorders	1	—	—	—	—	—	2	—	1
Joint pain	2	1	1	1	3	—	2	1	1
Anorexia	5	2	—	2	7	2	4	—	2
Other	5	4	—	3	5	3	10	12	2

[a] Severity 1 = mild, 2 = moderate, 3 = severe.

20-mg group than in the two other groups and possibly hot flushes with more than 20% in the 100-mg group. Severe symptoms occurred in <5% of the patients in each treatment group. The most common adverse symptoms in all groups were nausea 22%, gastrointestinal discomfort 18%, lassitude 17%, hot flushes 15%, vomiting 15%, dizziness 14%, and anorexia 13%. The largest proportion of these reports were of mild symptoms. Other symptoms reported in smaller proportions of the patients included depression, weight gain, lymphoedema, hypercalcemia, joint pain, and skin rash.

During these trials, 18 serious adverse events were noted, in most cases by source evaluation. In nine of the cases, droloxifene was eliminated as a possible cause. The remainder included three instances of hypercalcemia, two of which were successfully treated and one that was associated with a fatal outcome. However, it could not be established if this patient could possibly have died from a suspected brain metastasis. In two patients, leucocytopenia was reported. Thrombophlebitis followed by pulmonary embolism was seen in one patient. Severe dizziness, psychologically provoked disturbances of the autonomic nervous system, and deep venous thrombosis have been reported, each for one patient.

DISCUSSION

In these studies, response rates of 17% in patients receiving 20 mg daily, 30% in those receiving 40 mg, and 31% in those receiving 100 mg daily were obtained. We regard the results as most satisfactory for a collection of patients in such relatively poor condition. In general, we had the impression that the response to droloxifene was quite rapid and perhaps occurred sooner than we might normally expect from hormonal therapy. A further 36–40% disease stabilizations were obtained. This means that only 31–33% of patients in the two best groups, 40 and 100 mg, and 43% in the 20-mg group, had progressive disease while receiving droloxifene.

Not many studies exist with a patient population so extensively pretreated as ours, as 68% of our patients had been pretreated and of those, 40% had had more than one pretreatment. However, one study that obtained some results with tamoxifen under similar study conditions was published by Muss and coworkers in 1985 (2). The patient population of that study differed in some aspects from ours: only 35% of the patients had been pretreated, and 66% of the patients had positive receptor state; the rest had unknown receptor state. With this population of pa-

tients with relatively better prognosis, the same response rate was obtained as in our 40- and 100-mg group, namely 31%. An additional 30% obtained disease stabilization. A quantitative comparison of side-effect profile between droloxifene and tamoxifen cannot really be done outside the frame of a comparative, randomized study. However, qualitatively, the profiles of the two drugs are comparable. Gastrointestinal disturbances, hot flushes and tumor flare are the most common symptoms with tamoxifen, according to the product description (3).

On the basis of comparison of two independent studies, no firm conclusion can be drawn. However, it seems likely that in other studies with patients of better prognosis, the treatment results with droloxifene will be even better than those presented here. These favorable response rates in combination with the good tolerability we have observed with droloxifene, bring positive expectations for upcoming reports. ₡

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