Influence of Droloxifene on Metastatic Breast Cancer as First-Line Endocrine Treatment

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The effect of droloxifene (3-hydroxytamoxifen) given as first-line endocrine treatment was evaluated in 39 postmenopausal women with advanced receptor-positive or receptor-unknown breast cancer. The patients had not received any previous anticancer therapy apart from adjuvant treatment. The overall response rate (CR + PR) was 51% (8% CR, 43% PR), 95% confidence interval ± 15.7%. Median time to progression (all patients) was 8 months, the median time to response 2 months, while the median duration of response was 10 months. The drug was well tolerated with no major side effects recorded; 16% of the patients experienced hot flushes. The response to droloxifene recorded in the present study is in accordance with the response rates to tamoxifen as first-line treatment in identical groups of patients.

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Endocrine therapy is considered to be the most important systemic treatment in patients with advanced breast cancer (1). While the response rate to different endocrine treatment alternatives seems to be similar, the drugs may vary somewhat with respect to their side effect profile (2). Owing to well-documented effects and an advantageous side-effect profile, endocrine treatment options such as antiestrogens are the therapies of choice in situations where the intention of the treatment is palliation. Because of its favorable toxicity profile, the antiestrogen tamoxifen has become first-line treatment in pre- as well as postmenopausal breast cancer patients (3). Droloxifene (3-hydroxytamoxifen) is a novel antiestrogen with a chemical structure resembling that of tamoxifen. However, preclinical studies have shown droloxifene to have a shorter serum elimination half-life, a higher affinity to estrogen receptors, a higher antiestrogenic and a lower estrogen agonistic effect and to be less carcinogenic to the rat liver compared with tamoxifen (4). Expectations of an increased efficacy and a better tolerability of droloxifene have thus initiated clinical investigations.

In a previous phase II study we investigated the effect of droloxifene in patients with advanced breast cancer previously exposed to different forms of endocrine treatment (5). A partial remission was seen in 15% of the patients, some of whom were resistant to tamoxifen when treatment with droloxifene was started. The purpose of the present study was to evaluate the effect of droloxifene as first-line endocrine treatment in patients with metastatic breast cancer.

MATERIAL AND METHODS

Patients

Postmenopausal patients (> 50 years or oophorectomized patients) with advanced breast cancer (distant metastatic, locoregional recurrences not subject to local therapy, or inoperable primary tumors) with measurable lesions were eligible for inclusion in the study. Tumors were receptor (estrogen and/or progesterone) positive or unknown. Previous systemic anticancer treatment was not allowed, with the exception of adjuvant tamoxifen therapy for up to 2 years which should have been terminated at least 3 months before inclusion in the study, adjuvant oophorectomy (≥ 1 year ago), or adjuvant chemotherapy for up to 6 months terminated at least 3 months earlier. Performance status was WHO grade 3 or better. Patients with a history of thromboembolism, high serum calcium levels, subnormal WBC or platelet count, brain or leptomeningial metastasis were not eligible.

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Table 1

Patient pretreatment characteristics

No. of evaluable patients	39
Age, median (range)	68 years (51–78)
WHO performance status, median (range)	0 (0–2)
Mastectomy (operated/not operated)	26/13
Disease-free interval, median (range)*	6.6 years (0.9–12.6)
Receptor status**	
ER positive/unknown/negative	31/7/1
PgR positive/unknown/negative	20/9/10
Both ER and PgR positive	19
Previous treatment	
No previous treatment	25 (64%)
Perioperative chemotherapy	8 (21%)
Adjuvant tamoxifen	3 (8%)
Adjuvant oophorectomy	3 (8%)
Adjuvant chemotherapy	3 (8%)
Main metastatic locations	
Cutaneous/subcutaneous	23 (59%)
Superficial lymph nodes	17 (44%)
Bone	8 (21%)
Lung	7 (18%)
Liver	2 (5%)
Metastatic locations	
1 location	24 (62%)
2 locations	13 (33%)
>2 locations	2 (5%)

*Time from primary operation to relapse (n = 25).
**ER = estrogen receptors; PgR = progesterone receptors.

Pretreatment staging

Prior to treatment, an anamnestic and physical examination was performed, as well as a complete tumor assessment and a search for occult metastases (bone scan, chest x-ray and ultrasound of the abdomen). The pretreatment characteristics of the patients are presented in Table 1.

Drug schedule

All patients received droloxifene as a single daily tablet of 100 mg.

Follow-up

During the trial, patients were clinically examined at weeks 2, 4, 8, 12, 16, 20, 24, and then at 12-week intervals. Up until week 24 a full tumor assessment was carried out at 8-week intervals. Every 24 weeks a complete staging was performed for detection of occult metastases.

Evaluation

Tumor response was evaluated according to the criteria of the WHO (6). Throughout the study each patient was monitored for possible adverse reactions, which were classified according to severity as mild, moderate or severe. Parameters for evaluation of the efficacy of droloxifene were: 1) overall response (CR and PR); 2) time to response (time from start of treatment to verified response); 3) duration of response (time from verified response to progression (Table 2)); and 4) time to progression (time from start of treatment to progression). In addition, several hormonal parameters were evaluated before and during treatment; these results have already been reported separately (7). All study documentation was mutually re-evaluated by all the investigators.

Ethics

The study was approved by the regional ethical committee, and informed consent was obtained from all patients prior to start of treatment.

RESULTS

The study comprised a total of 44 postmenopausal women with metastatic breast cancer. Three of these patients were excluded from treatment response evaluation because of protocol violations (one receptor-negative patient and 2 patients with non-evaluable disease), and 2 patients were excluded for other reasons (one patient refused further treatment shortly after inclusion and one early death unrelated to cancer or treatment). These 5 patients were included only for evaluation of toxicity, leaving 39 patients evaluable for treatment response.

Table 2

Response and time to progression

Best response[1]	No.	%	Time to response (months) Median (range)	Duration of response (months) Median (range)	Time to progression (months)[2] Median (range)
CR	3	8	2 (1–4)	58 (28–60+)	29 (29–)[3]
PR	17	43	2 (0.5–21)	7 (1–58+)	9 (3–41)
NC	12	31	–	7 (2–35)[4]	10 (3–37)
PD	7	18	–	–	1 (0.5–2)
All	39	100	2 (0.5–21)	10 (1–60+)	8 (0.5–41)

[1] CR = complete response; PR = partial response; NC = no change; PD = progressive disease.
[2] Four patients have not yet shown progressive disease.
[3] Only one patient has yet shown progressive disease.
[4] Stable disease (NC) here defined as response.

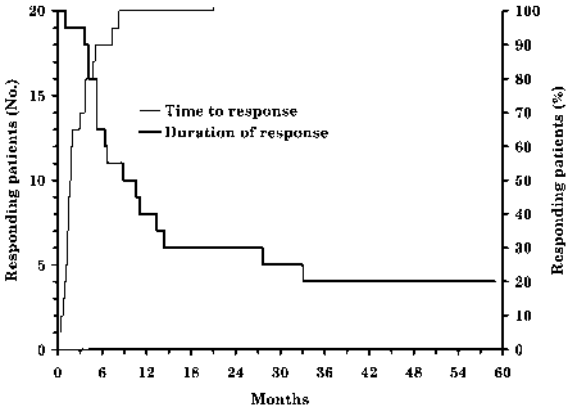

Fig. 1. Time to and duration of response (n = 20).

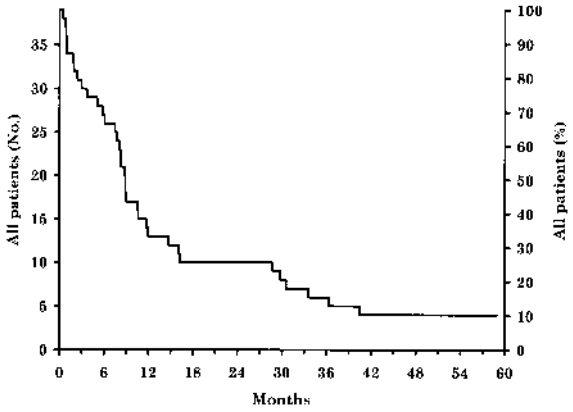

Fig. 2. Time to progressive disease (n = 39).

Fourteen patients received droloxifene as initial treatment, among them 13 for locally advanced disease (inoperable T4 tumors) and one patient for metastatic disease diagnosed immediately after mastectomy. All patients given droloxifene for locally advanced disease started treatment within 2 weeks of diagnosis and four of them had partial responses.

Twenty-five patients received droloxifene as first-line treatment at time of relapse, the median disease-free interval was 6.6 years (Table 1). Of these patients, three had previously been exposed to tamoxifen as adjuvant treatment. Fifteen out of these 25 patients responded to therapy (3 CR, 12 PR). There was no significant difference in overall response rate or median time to progression among patients receiving droloxifene either for primary disease or because of relapse.

Altogether, 3 patients showed a complete response and 17 a partial response, thus making an overall response rate of 51% (45% 'intention-to-treat'). All three patients with a complete response had local cutaneous metastases only. Four patients have not yet shown progressive disease (2 CR, 2 PR) after 54, 58, 59 and 60 months of treatment respectively. Time to response and duration of response for all responders (CR and PR) are shown in Fig. 1, time to progression for all patients in Fig. 2.

The drug was generally well tolerated, and side effects were in most cases mild (Table 3). None of the patients terminated treatment with droloxifene because of side effects. The most frequent side effect was hot flushes, which was reported by 16% of the patients. One patient was reported to have severe increased sweating, another severe vertigo. Apart from these exceptions, all reported side effects were mild.

DISCUSSION

Droloxifene is a non-steroidal antiestrogen, chemically related to tamoxifen. Even though droloxifene in phase II studies on metastatic breast cancer seems to have clinical effects comparable with those of tamoxifen, preclinical data show several interesting differences between the two drugs. Droloxifene has a serum elimination half-life ($t_{\frac{1}{2}}$) of 1 to 1.5 days, compared with almost one week for tamoxifen and even 2 weeks for its major metabolite (8). The shorter half-life of droloxifene could make it more advantageous in sequenced hormonal therapy (9), but no such clinical studies have so far been performed. Furthermore, the affinity of droloxifene with the estrogen receptor is 10 to 60 times greater than that of tamoxifen (4, 10). This property of droloxifene suggests that there could be some expectation of a shorter time to response, but there are no such indications in any clinical studies. Preclinical studies suggest droloxifene to be a more potent estrogen antagonist with less estrogen agonistic activity compared to tamoxifen. In growth inhibition studies, droloxifene inhibits different receptor-positive human breast cancer cells more effectively than tamoxifen at the same concentration (4). There are also indications of a more pronounced tumor reduction of droloxifene in rats bearing mammary tumors of either animal or human origin (4, 11). The clinical

Table 3

Adverse events/possible side effects

	No.	%	Grade
Patients without side effects	18	41	
Hot flushes	7	16	Mild
Nausea	3	7	Mild and moderate
Fatigue	3	7	Mild
Constipation	3	7	Mild
Increased blood sugar	2	5	Mild and moderate
Metrorrhagia	2	5	Mild and moderate
Increased sweating	1	2	Severe
Vertigo	1	2	Moderate/severe
Early hepatic abnormal function	1	2	Moderate
Atrophic vaginitis	1	2	Mild
Weight gain	1	2	Mild

relevance of these observations is not known. Droloxifene is likewise reported to have a lower estrogenicity compared to tamoxifen both in vitro and in animal experiments (4), a reduced estrogen activity has also been suggested in humans (7, 12). Tamoxifen treatment increases the incidence of endometrial carcinomas (13), but it is not known whether the lower estrogenic effect of droloxifene has any significance regarding a reduced risk of endometrial cancer. Large doses of tamoxifen has been shown to produce DNA adduct formation and liver tumors in rodents (13), while droloxifene seems to be devoid of any such effects (4). It is unlikely that this difference is of any clinical significance, since no increased incidence of hepatocellular carcinomas has been observed in large adjuvant studies with tamoxifen (13).

In the present study we found an over-all response rate of 51% when droloxifene 100 mg daily was given as first-line endocrine treatment to patients with advanced breast cancer. The effect of 100 mg droloxifene daily as first-line endocrine treatment yielded a 42% response rate in an earlier multiple-dose study (14). In contrast to that study, a greater number of our patients were receptor positive and had mainly soft tissue metastases, well-established indicators of an increased response rate (3). Both time to response and time to progression in the present study are in accordance with previous findings (14). However, the total number of patients in our study is smaller, making a direct comparison of the results between the two studies somewhat uncertain. Approximately one-third of unselected women with metastatic breast cancer achieve an objective response to tamoxifen therapy, while more than 50% of patients with receptor-positive tumors obtain a complete or partial remission or stabilization of the disease (3). Thus, the response rate of droloxifene in both our study and the previous dose-finding study (14) seems to be in accordance with the expected response of tamoxifen as first-line treatment in receptor-positive patients. Time to response, duration of response, and time to progression observed in the present study are similar to what is reported for tamoxifen treatment (15).

In conclusion, even though droloxifene has several potential benefits compared with tamoxifen in preclinical studies, the clinical relevance of these properties remains to be demonstrated. This study confirms a response rate of droloxifene comparable to what is seen with tamoxifen as first-line treatment in advanced breast cancer. Currently, droloxifene is being compared with tamoxifen treatment in phase III studies.

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