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DROLOXIFENE—A NEW ANTI-ESTROGEN

A phase II study in advanced breast cancer

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Twenty-six patients with advanced breast cancer were treated with a new anti-estrogen, Droloxifene (3-hydroxy-tamoxifen). They had all used tamoxifen either in the adjuvant or the advanced situation. The dose schedule was 100 mg orally daily. Partial remissions were observed in 4 (15%) of the patients, and in another 5 patients stable disease (>24 weeks of duration) was observed. Three of the responders were resistant to tamoxifen. Fourteen of the 26 patients had no side-effect. In 2 patients therapy had to be stopped due to fatigue. Droloxifene seems to be an interesting new anti-estrogen which should be further exploited.

Endocrine therapy is the most important systemic therapy in breast cancer in both adjuvant (1, 2) and advanced situations (2). Due to its documented effects and favorable side-effect profile, the anti-estrogen tamoxifen is the prevailing first-line choice among the endocrine treatment alternatives (2, 3). To further improve endocrine therapy, it will above all be necessary to select drugs and schedules resulting in higher efficacy (higher response rates and prolonged duration of effects) and/or a more favorable side-effect profile (4).

New anti-estrogens as Toremifene (chlor-tamoxifen) and Droloxifene (3-hydroxy-tamoxifen) have recently been introduced in clinical trials, after promising results from preclinical testing (5, 6). Droloxifene has a shorter half-life in animals (7) and humans (8, 9), and has been claimed to be less estrogenic than tamoxifen in animals and in in vitro experiments (10). Some dose dependent estrogenicity has also been shown in humans (9).

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Based on these promising preclinical data, the Norwegian Breast Cancer Group (NBCG) decided to start a phase II trial with Droloxifene in advanced breast cancer, as second- or third-line endocrine treatment.

Material and Methods

Twenty-five postmenopausal women and one man with metastatic breast cancer were included in this study. Patient characteristics are given in Table 1. Patient inclusion criteria were: 1) recurrent, evaluable disease; 2) postmenopausal (or male); 3) Steroid receptor in primary tumor and/or metastasis positive (>10 pmol/g) or unknown; 4) previous tamoxifen treatment in adjuvant or metastatic situation (stopped >3 months before Droloxifene treatment); 5) all other anti-cancer treatment stopped at least 3 weeks before start of Droloxifene; 6) performance status >4 (11); and 7) life expectancy of more than 3 months.

The aim of the study was, within this rather heterogeneous group of patients, to evaluate preliminarily the efficacy (response rate and duration) and safety of the drug. The number of patients to be included was 25–30, with a stop after the first 14, if no responses had been seen. The dose was Droloxifene 100 mg orally once daily. Tumor response was evaluated according to the UICC standards (11). The study was approved by the regional ethical commitee.

Table 1

Patient pretreatment characteristics

		No. of cases
Total No. of patients		26
Age at diagnosis, median (range)	57 (32–79) years	
DFI, median (range) (n = 26)	44 (0–165) months	
Previous therapy		
Endocrine therapy		
Tamoxifen		
	Adjuvant	6
	Metastatic disease	21
	Both	1
Ooophorectomy		
	Adjuvant	2
	Metastatic disease	3
Progestins		
MPA	Metastatic disease	8
MA	Metastatic disease	12
Both (in sequence)	Metastatic disease	2
AG		
	Metastatic disease	4
Other		
	Metastatic disease	1
Chemotherapy		
	Doxorubicin, weekly	5
	FuMi	3
	Other	1
Time from first rec. until start of Droloxifene, median (range)	24 (1–87) months	
Main metastatic location		
	Soft tissue	11
	Bone	7
	Viscera	8
	Liver	3
	Lung	4
	Both	1
No. of metastatic locations		
	1 location	17
	2 locations	7
	>2 locations	2

DFI = disease-free interval; MPA = medroxyprogesterone acetate (500 mg × 2 orally); MA = megestrol acetate (160 mg × 1); AG = aminoglutethimide (250 mg × 4 with hydrocortisone); Weekly doxorubicin, 20 mg weekly (fixed dose); FuMi = 5-fluorouracil (1 000 mg/m^2, day 1 and 2) and mitomycin C (6 mg/m^2, day 2) q 3 weeks.

Results

As seen from Table 1, the patients had been treated with at least one endocrine modality before start of Droloxifene. In 21 patients more than one endocrine and/or chemoterapeutic modality (results not shown) had been used.

An objective remission was observed in 4 patients (Table 2). No complete remission was seen. Three of the four objective responders had progressed on tamoxifen, two after initial response in the advanced situation, and one while on adjuvant tamoxifen. The last of the responders had stopped adjuvant tamoxifen more than 1 year before start of Droloxifene. In another 5 patients a stabilization was observed, SD = 24 weeks, i.e. in 9/26 a meaningful response was observed. Mean time to progression in all patients (n = 26) included was 22 weeks. The drug was generally well tolerated (Table 3). Fourteen of the 26 patients had no registered side-effect. Troublesome fatigue was observed in 2 patients. The treatment was stopped for both, and the fatigue decreased. In one of the patients (a PR) the drug was reintroduced and the symptom worsened again. All other possible side-effects were only tentatively associated with the treatment. The treatment was not stopped in the patient with the deep venous thrombosis, as the condition was not considered to be related to the Droloxifene treatment.

Table 2

Response rate and duration

	Treatment result		Median duration (weeks) of response (range)
	No.	%	
CR	0	0	
PR	4	15.4	27 (7–52)
NC	5	19.2	57 (35–67)
PD	13	50	
Not evaluable	4	15.4	(<4 weeks)
TTF (n = 26)			22 (mean)

Table 3

Registered side-effects

	n
Patients without side-effects	14
Nausea	3
Fatigue[1]	2
Vertigo	2
Constipation	1
Deep venous thrombosis	1
Hot flushes	1
Weight gain	1
Reactive depression	1
Initial pelvic pain	1

[1] Fatigue, caused withdrawel of medication in both patients (one of these PR, 7 weeks).

Discussion

Important characteristics of tamoxifen are its long half-life and its estrogenic/antiestrogenic effects. This last characteristic is, at least partially, dependent on the amount of endogenous estrogens offered to the target cells. The drug could be beneficial in postmenopausal women with regard to its estrogenic effects on lipid (12, 13) and bone mineral (14, 15) metabolism. However, adverse effects on the endometrium have been reported (16). Furthermore, the long half-life of tamoxifen at least partly precludes trials with new schedules to explore alternating endocrine treatment (17), and continuous versus intermittent treatment (18). Droloxifene has a short half-life in humans (8, 9), is reported to be less estrogenic (10), and also in animals seems to have less carcinogenic potential in the liver (19).

The results from the present study indicate that the drug can be safely used in humans, and that about one-third of this heterogenous group of patients experienced a meaningful effect. It is interesting that 3 of the 4 responders were resistant to tamoxifen when starting with Droloxifene.

The fatigue seen in 2 patients seems to be related to the treatment. In both patients the medication had to be stopped. This side-effect has not been reported so far in 15 patients included in our new Droloxifene trial, and has not been reported as a problem in other trials (20–22).

This is the first report from a phase II trial of Droloxifene, using 100 mg once daily. In another phase II study (19) a response rate of 17% (4/23) was observed with Droloxifene 80 mg once daily, and 29% (4/14) using 120 mg daily. Two large phase II dose-finding studies are under way (21, 22), comparing 20, 40 or 100 mg once daily. It seems reasonable to explore further the potential role of Droloxifene in the treatment of breast cancer.

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