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Report

High dose toremifene in advanced breast cancer resistant to or relapsed during tamoxifen treatment

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Summary

Fifty patients with advanced breast cancer refractory to prior tamoxifen therapy were assigned to investigational treatment with high-dose toremifene administered 120 mg orally twice a day. Treatment was generally well tolerated. The majority (80%) of the patients had no side effects, and among the remaining 10 patients reported side effects were mostly mild and/or transient. Two objective tumor responses were observed: one complete response (CR), duration 6.2 months, and one partial response (PR), duration 8 months. The response rate was thus 4% (95% CI: 0.5 to 14%). In addition 3 patients experienced a mixed response, some metastatic sites responding, while at other sites disease progressed; 22 patients had disease stabilization for > 2 months. A subset analysis disclosed that a small subgroup of patients, including 7 patients in this study, who had achieved CR at some of the sites during preceding tamoxifen therapy, experienced a long progression-free time during high dose toremifene treatment. The median time to progression in this subgroup of patients was 9.4 months (95% CI: 3.8 to 9.4) as opposed to 2.1 months (95% CI: 2.0 to 2.8) for all the remaining 43 patients, which is a significant decrease in disease progression ($p < 0.03$). Such results reveal that although this kind of second-line hormonal treatment with high dose toremifene cannot be recommended for all tamoxifen failures, there might be a subset of patients, i.e. those who achieve CR in some lesion during tamoxifen therapy, who benefit from this type of treatment.

Introduction

Toremifene is a chlorinated triphenylethylene derivative, chemically related to tamoxifen. At least five different phase III trials comparing tamoxifen with toremifene in postmenopausal patients with breast cancer are currently underway or under analysis [1]. In preclinical studies some differences have been observed between tamoxifen and toremifene in efficacy as well as in toxicity in favor of toremifene [2]. Especially in high doses, toremifene has been less toxic both in animal experiments [2] and in clinical phase I [3, 4] and II studies [5–7]. Daily doses up to 240 mg have been well tolerated even during prolonged treatment [5–7]. Also some dose-response relationship has been observed in animal model tumors, high doses of toremifene being more effective than low and moderate doses [2]. Even es-

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trogen-receptor (ER)-negative tumors like murine uterine sarcoma have responded to high doses of toremifene [2]. The subsequent phase II clinical studies as primary hormonal treatment in advanced breast cancer also reveal existence of some dose-response relationship, the highest response rate (over 60%) being achieved with a 240 mg daily dose [6] while a 20 mg daily dose has yielded only a 21% response rate in similar patients [8, 9]. All these observations have focused interest on high dose toremifene as a second- or third-line treatment in advanced breast cancer for tamoxifen-refractory patients. Preliminary observations from the U.K. revealed that high-dose toremifene might be an effective second-line treatment for such patients [10]. Consequently this confirmatory study was initiated to provide more knowledge of the feasibility of high-dose toremifene as second-line treatment for patients with advanced breast cancer resistant to tamoxifen or patients relapsed during tamoxifen therapy.

Patients and methods

Patients

Fifty consecutive postmenopausal women with ER-positive tumors (≥ 10 fmol/mg prot) were recruited into this study between June 1986 and April 1990. All had advanced disease: inoperable primary or metastatic breast cancer progressing during tamoxifen treatment. Prior chemotherapy, except adjuvant treatment, was not allowed. Other prerequisites included performance status ≥ 50% (Karnofsky), life expectancy > 3 months, measurable or evaluable disease, no evidence of severe heart, liver or renal disease nor uncontrolled diabetes. The disease could either be primarily resistant to tamoxifen treatment or relapsed after a response. The study was approved by the local ethical committees and verbal informed consent was obtained from all the patients. The main patient characteristics and localization of lesions are depicted in Table 1. Twelve patients had only soft tissue lesions, i.e. cutaneous, subcutaneous, or lymph node metastases, while the majority of the patients had more advanced disease, in prognostically less favorable sites. Four patients were treated previously with adjuvant chemotherapy. Twenty-four patients had disease progression during adjuvant tamoxifen treatment and 26 patients during the treatment of advanced disease. Median disease free interval among these two groups of patients was 20.2 and 30.0 months, respectively. This difference was not statistically significant (p = 0.3, Mann-Whitney test).

Treatment

Toremifene was administered as 120 mg orally twice a day. Toremifene treatment was started immediately (next day) after cessation of tamoxifen therapy. The treatment was discontinued on signs of progressive disease, or intolerable side effects, or according to the patient's desire.

Evaluation

The pretreatment evaluation included physical ex-

Table 1. Patient characteristics

Patients entered	50
Evaluable	48
Mean age (range)	68.9 years (40–83)
Mean postmenopausal period (range)	19.0 years (2.5–39.4)
Median Karnofsky index (range)	80% (50–100)
Receptors	
Median ER (range)	62.0 fmol/mg prot (11-921)
Median PR (range)	39.0 fmol/mg prot (0-1502)
Localization of lesions (total: 85 sites)	
Primary	1
Local relapse	13
Soft tissue	20
Visceral	24
Skeletal	27
Distribution of lesions in 50 patients	
Only soft tissue	12
Only visceral	8
Visceral + soft tissue	3
Only skeletal	4
Skeletal + primary or soft tissue or visceral	23

Table 2. Overall responses

Response	No. of patients (%)	Time-to-progression, in months
CR	1 (2)	5.8
PR	1 (2)	8.2
SD ≥ 5 months	9 (18)	5.5–17.0
SD < 5 months	13 (26)	2.8– 4.3
PD	24 (48)	0.9– 2.3
NE	2 (4)	1.1– 1.9

amination, laboratory tests, chest radiography, ultrasonography of the liver, and bone scan. Patients came for clinical assessment every 4 weeks during the first 16 weeks and thereafter every 8 weeks. Lesions evaluable by physical examination, routine X-rays, or ultrasonography were checked during every visit. Otherwise chest X-rays, ultrasonography of the liver, and bone scan were repeated every 6 months. The tumor response and duration of response were evaluated according to UICC criteria [11]. The evaluation of adverse effects followed the World Health Organization guidelines [12].

Statistical analysis

An estimate for the true response rate and an exact 95% confidence interval for the true response was calculated. The distribution of time-to-progression was estimated by the Kaplan-Meier method. Median times-to-progression with 95% confidence intervals (CI) are reported. Kaplan-Meier curves were compared with a log rank-test. An estimate for the true hazard ratio and a 95% CI for the true hazard ratio were calculated in order to assess the difference in time-to-progression between the two groups under consideration. A hazard ratio of 1 is indicative of identical proportions of patients with a subsequent event of interest such as disease progression at a given time point. A hazard ratio of less than 1 is indicative that a smaller proportion of patients progressed in the first group of patients compared to the second group of patients at a given time point.

Table 3. Patients with mixed responses, achieving partial or complete response at any site

Patient	Duration of treatment (wks)	Localization	Response
H-15	16	lymph node	PR
		skeletal	PD*
H-22	8	liver	CR
		skeletal	PD*
T-8	8	soft tissue and skin	PR
		lungs	PD
		liver	PD

* increase in size of lytic lesion in x-rays.

Results

Response

All 50 patients were evaluable for toxicity. Two patients discontinued the treatment in less than 2 months and were not evaluable for response. The antitumor effect of toremifene in all 50 patients is presented in Table 2. There were two objective responses; response rate 4% (95% CI: 0.5 to 14%). One patient with lung and pleural metastases achieved a complete response (CR) of 6.2 months' duration. She succumbed to chronic cardiovascular disease while in complete remission. The heart disease was diagnosed already prior to the toremifene treatment, so her death was not considered to be attributed to that drug. In another patient a partial response (PR) in multiple skin metastases was observed, duration 8.0 months. In addition to these two objective responses, 22 patients (44%) had a stable disease (SD) for longer than 2 months. Altogether 9 of these stabilized diseases remained stable longer than 5 months, the longest duration being 17 months. In addition to the 2 overall objective responses, another 3 patients experienced mixed responses, i.e. although some of the lesions regressed, the disease progressed in other sites. The metastatic sites and the corresponding responses of these mixed-responders are presented in Table 3.

Time-to-progression

The median time-to-progression (TTP) of all the

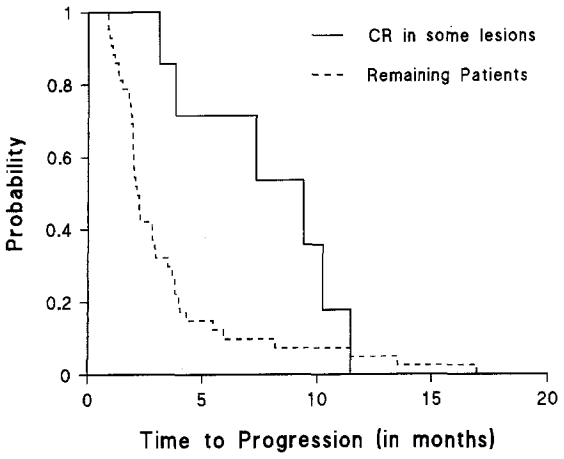

Fig. 1. Time-to-progression in 7 patients with CR in some lesions during previous tamoxifen therapy vs. all the remaining 43 patients. Difference is statistically significant (P = 0.03, Log rank-test).

treated patients was 2.8 months (95% CI: 2.0 to 3.5). Comparison of TTP to the outcome for previous tamoxifen therapy revealed some differences. The patients were first divided into 5 groups: one group suffered progressive disease while receiving adjuvant tamoxifen (24 patients), and the other 4 groups were defined according to the response of evaluable metastases during tamoxifen therapy (26 patients). As performed elsewhere [13], we selected 5 months' TTP as a cut-point of prognostic significance. Differences were as follows: only 3 of 24 patients (13%) who experienced relapse during adjuvant treatment had TTP over 5 months, in contrast to 8 of 26 (31%) patients who received tamoxifen for metastatic disease (Table 4). Interestingly, all 3 patients with CR for all sites and 5 of 7 patients (71%) with CR at any site during previous tamoxifen treatment suffered no disease progression before 5 months (Table 4). Figure 1 demonstrates the differences in probability of managing without progression among the 7 patients who had experienced CR in some of the evaluable lesions during previous tamoxifen treatment and all other patients. These 7 had a median TTP of 9.4 months (95% CI: 3.8 to 9.4) as opposed to 2.1 (95% CI: 2.0 to 2.8) for all the other 43 patients. This difference is statistically significant ($x^2 = 5.0$, $p = 0.03$, Log rank-test). No other apparent factor such as age, length of postmenopausal period, receptor content, the initial disease free interval, or localization of the lesions was associated with this prolongation of TTP.

Toxicity

The treatment was generally well tolerated. Forty patients experienced no side effects, and among the other patients side effects were mainly mild or moderate (grade I or II) and sweating mostly only transient (Table 5). In 2 cases the treatment was discontinued within 2 months without evidence of disease progression; one of these patients had thrombosis in the left thigh, which obviously had been there prior to this treatment due to major surgery on that leg (prophylactic bone fixation a.m. Küntscher). The other patient, 74, experienced a cerebrovascular insult one month after the start of treatment. Relation of this event to the treatment cannot be excluded.

Table 4. Prediction of prolonged time-to-progression (TTP) by response to preceding tamoxifen therapy

Tamoxifen treatment and its outcome	No. of patients	No. (%) of patients with TTP over 5 months during treatment with toremifene
Adjuvant treatment	24	3 (13)
Response of evaluable disease		
PD	7	2 (29)
SD	12	2 (17)
PR	4	1 (25)
CR	3	3 (100)
CR in any of the lesions*	7	5 (71)

* Including three patients with overall response SD and one with overall response PR.

Discussion

In postmenopausal patients with metastatic breast cancer, second-line treatment with another hormonal drug is usually feasible when the first-line therapy fails. Some clinical [10] and preclinical studies [2], particularly, reveal that high dose toremifene may be active in tumors in which tamoxifen is ineffective. Preclinical studies have demonstrated that high concentrations of toremifene may have a direct receptor-independent oncolytic effect, i.e. be cytostatic or cytotoxic against tumors without estrogen receptors [2]. Recently, new estrogen-receptor-independent mechanisms of antiestrogens have been identified. These molecules are found to be effective inducers of transforming growth factor beta (TGF-beta) in fibroblastic cells [13], and TGF-beta excreted from stromal fibroblasts has the ability to inhibit growth or division of breast cancer cells [14]. The magnitude of this TGF-beta-mediated mechanism as well as the estrogen-receptor-mediated growth-inhibition of breast cancer cells are evidently to a certain extent related to the concentration of an antiestrogenic drug [14]. As confirmed in preclinical [2] as well as phase I and II clinical studies [3–7, 10], toremifene seems to be less toxic than tamoxifen in high doses although therapeutic benefit of high doses has not been established. Thus this type of high dose second-line treatment was considered in principle interesting.

In two previously published studies, experience with high dose toremifene as a second-line treatment after tamoxifen failure varied widely. A preliminary report from the U.K. [10] describes a remarkable objective response rate (25%), while in a Swedish study no response was reported among 35 patients [7]. In a recently published study from USA 5% (95 CI: 3% to 7%) response rate was detected [15]. Our observation accords very well with that study: two objective responses among 48 evaluable patients, i.e. a response rate of 4%. The great difference between the aforementioned studies may be explained mainly by differences in patient characteristics. In the U.K. study the majority of the patients had fairly localized disease and had primarily responded or exhibited prolonged stabilization under tamoxifen treatment, while in the Nordic and USA studies the patients were less selected tamoxifen failures. A large proportion of the patients in the latter studies had received tamoxifen as an adjuvant treatment or had never responded to primary tamoxifen treatment. In addition a large proportion of the patients in these studies had very extensive disease including visceral and bone involvement. Therefore the great difference in response rates with similar treatment may be expected.

Table 5. Side effects

	No. of patients (%)
Evaluable patients	50
No side effects	40 (80)
Sweating*	6 (12)
Nausea and depression*	2 (4)
Dizziness*	2 (4)
Thrombosis	1 (2)
Fatigue	1 (2)
Leucorrhea*	1 (2)

* All these side effects were mild or moderate and sweating was mostly only transient.

An objective response rate of 4 percent as in this study might be considered clinically non-significant, particularly if the treatment had considerable toxicity. The analysis, however, disclosed that 80% of the patients had no side effects, and the remaining 10 patients experienced mostly only mild or transient side effects. In this kind of palliative treatment, besides objective tumor regression, prolonged stabilization of the disease may be meaningful as well, as suggested by Howell and coworkers [16]. They analyzed prognoses of patients with advanced breast cancer under endocrine therapy and observed that patients with stabilized disease over 5 months had prognoses indistinguishable from that of those achieving partial response. When analyzing TTP in the present study, we observed that, in addition to the two patients with objective responses, another 9 patients were progression-free over 5 months and 2 of them even over 12 months. It is apparent that most of these patients also benefited from toremifene treatment.

In this kind of phase II study, the number of patients is a limiting factor for subset analysis. This study, however, confirms the observations that the outcome of previous endocrine therapy might be a

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