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Report

Estrogenic effects of toremifene and tamoxifen in postmenopausal breast cancer patients

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Summary

Intrinsic estrogenicities of the selective estrogen receptor modulators (SERMs) toremifene 60 mg daily or 200 mg daily and tamoxifen 20 mg daily (TOR60, TOR200 and TAM20) were compared in a randomized clinical study in postmenopausal women with advanced breast cancer. The study was open label in three parallel groups. Variables for analysis were serum follicle stimulating hormone (FSH), luteinizing hormone (LH), sex hormone binding globulin (SHBG), estradiol (E2), antithrombin III (AT III), aspartate aminotransferase (ASAT) and vaginal cytology. Clinical efficacy and safety have been reported earlier. A total of 648 patients were randomized (221 to TOR60, 212 to TOR200 and 215 to TAM20). Sera were available for the analysis from 148, 165 and 156 and for vaginal cytology from 98, 93 and 86 patients, respectively. All treatment regimens showed tissue-specific and dose-dependent estrogen agonist effect. In the primary measure of *in vivo* estrogenicity, effect on hypothalamus–pituitary-axis, all three treatment regimens decreased serum FSH ($p < 0.001$). TOR200 was more potent than the two other treatments ($p < 0.05$), but surprisingly, TAM20 was more estrogenic than TOR60 ($p < 0.001$). As could be expected in postmenopausal women, the treatments had no effect on mean serum E2 concentrations and decrease of serum LH was similar to that of FSH. Estrogenic effect on the liver was seen as dose-dependent increase of SHBG with statistically significant differences between the treatment groups ($p < 0.001$). Trends of transient ASAT elevations in TOR200 group ($p = 0.07$) and in all treatment groups AT III decrease ($p = 0.1$) were seen in the beginning of the treatment. TOR60 or TAM20 did not have an effect on mean ASAT values, and AT III decreased in TAM20 group more than in the two other groups ($p = 0.1$ compared to TOR60 and $p < 0.05$ compared to TOR200). Estrogenic effects on vaginal superficial cells were higher in TOR60 and TOR200 groups when compared to TAM20 ($p < 0.05$). Toremifene and tamoxifen had tissue-specific and partially dose-dependent estrogenic effects in hypothalamus–pituitary-axis, in the liver and in the vaginal epithelium of postmenopausal women. In some tissues tamoxifen 20 may be more estrogenic than toremifene 60 mg/day.

Introduction

Triphenylethylene antiestrogens, which have more recently been designated as selective estrogen receptor modulators (SERMs), are widely used to treat all stages of breast cancer [5, 13, 29]. Clinical trials to study breast cancer preventive effects of SERMs at high-risk patients are ongoing, although the first results are controversial [9, 30, 36]. The triphenylethylene derivative toremifene acts mainly as an antiestrogen in humans [21, 22] and, like tamoxifen, another tripehenylethylene SERM, it binds to intracellular estrogen receptor (ER).

The effect of SERMs depend on the target tissue. Typically, in breast they inhibit cell proliferation, whereas in liver, they stimulate protein synthesis, for example, sex hormone binding globulin (SHBG) [22, 23]. In the central nervous system, toremifene inhibits TRH-stimulated prolactin secretion [40]. The estrogenic or antiestrogenic activity of SERMs is also species specific. Toremifene has clear estrogenic effect in mouse and dog while in rats and humans it is

predominantly antiestrogenic. In postmenopausal women toremifene doses 20, 40 or 60 mg daily induce dose-dependent estrogenic action by decreasing LH and FSH in and increasing SHBG concentrations in serum [6]. Toremifene 10 mg daily has no clear antiestrogenic activity on vaginal cytology in postmenopausal women with concomitant estradiol (E2) [18]. However, doses of 20, 40 and 80 mg daily exert marked antiestrogenic effects, which are not different from each other or from tamoxifen 20 mg/day.

In clinical studies, toremifene doses from 20 to 300 mg/day have been studied for the treatment of advanced breast cancer in postmenopausal women. Twenty milligram daily produces fewer responses than 60 mg daily with similar times to progression [6, 14, 26, 32, 41]. Higher dose (240 mg/day) may increase the response rate slightly more [16]. In early trials [27] tamoxifen 40 mg/day was more effective than 20 mg, but in a comparative study [3] no difference in efficacy of the two doses was seen. In postmenopausal women with advanced breast cancer toremifene 60 mg/day has been equally effective as tamoxifen 20 or 40 mg/day [11, 15, 33, 34] and again the higher dose of toremifene 200 or 240 mg show slightly increased response rate [12].

Three years or longer of adjuvant tamoxifen treatment has been shown to be more effective in preventing breast cancer recurrences than less than 2 years [5]. However, more than 5 years of treatment is apparently not superior to 5 years [8]. Tamoxifen treatment has been associated with increased incidence of subsequent endometrial cancer [2, 4, 7, 10, 24, 31, 36]. The observed carcinogenicity is considered to be due to estrogenic stimulation on the endometrium. Some endometrial cancers cases have been reported following toremifene administration, but in early results from prospective randomized and epidemiological studies, no increase of endometrial cancer incidence has been observed [28, 31]. The aim of the present study was to investigate estrogenic effects of the standard SERM doses, toremifene 60 mg and tamoxifen 20 mg daily, and compare them to a high dose, toremifene 200 mg daily, which was only used in clinical trials.

Patients and methods

Study design

The clinical trial from which samples were obtained was a multicenter, randomized, open label study comparing TOR60 and TOR200 to TAM20. The clinical efficacy and safety results of the study have been published earlier [15]. The variables for the present analysis were serum follicle stimulating hormone (FSH), luteinizing hormone (LH), SHBG, E2, aspartate aminotransferase (ASAT), antithrombin III (AT III) and vaginal superficial cell count.

The study was conducted to comply with the WHO criteria and the principles of the Helsinki declaration. It was approved by ethical committees in each study site and signed informed consents were given by the patients before randomization.

Patient selection

Eligibility included postmenopausal women, at least 1 year since their last menstruation or serum FSH >50 mIU/ml or perimenopausal women >45 years of age and with menopausal symptoms. Previously untreated patients with advanced ER positive (ER concentration ≥ 10 fmol/mg protein), or ER unknown breast cancer were eligible for the study. ECOG scale performance status needed to be 0–2. Previous radiotherapy and tamoxifen for advanced breast cancer were allowed, provided that tamoxifen had not lasted for more than 14 days. Patients with previous adjuvant tamoxifen or chemotherapy were eligible, provided that at least 12 months had elapsed since the discontinuation of tamoxifen. Patients with severe renal (serum bilirubin >2 mg/dl) insufficiency, advanced liver disease (SGOT >100 IU/l) brain metastases, history of thromboembolic disease or concomitant active second malignancy were excluded.

Randomization and treatment regimen

Six hundred and forty-eight patients with advanced breast cancer were enrolled at 129 sites in six countries and were randomized to one of three arms (one toremifene 60 mg tablet daily, one toremifene 200 mg tablet daily or two tamoxifen 10 mg tablets daily in TOR60, in TOR200 and in TAM20, respectively). No dose modifications were allowed and the treatments were scheduled to continue to breast cancer progression, intolerable toxicity serious intercurrent illness or patient non-compliance ($<80\%$ of planned drug taken). Other cancer treatment was not allowed during the study. Accrual began 11 November 1988 and was completed 31 August 1991.

Patient evaluation and response criteria

Within 3 weeks prior to the treatment, the patients underwent medical history, physical examination, blood

chemistry, hemoglobin, leukocyte and platelet counts, performance status and tumor evaluation. Mandatory blood samples were to be drawn during the control visits, sera were separated and stored at −20°C for analysis. The assessments and sampling were repeated at 8-week intervals with the methods used at baseline. The biochemical variables of interest were changes in nonfasting serum FSH, LH, E2 and in SHBG assessed by standard immunometric methods at laboratories collaborating with each clinical site. Liver function tests in terms of changes in serum ASAT and AT III concentrations were assessed for tolerability. All patients who had baseline and at least one subsequent serum assessment available, that is, at least 8 weeks treatment were included into the primary efficacy analysis. Each individual value obtained was compared to the laboratory reference range of the laboratory. Gynecological examination including vaginal cytology, that is, superficial cell counts was performed at baseline, at week 8 and off treatment.

Statistics

Sample size for the clinical trial [15] was estimated to show equivalence in response rates among TOR60, TOR200 and TAM20. Each pair of treatment arms was compared using an overall type-one error rate (α) of 0.05. In this study, treatment effect on the hormonal variables were assessed with analysis of covariance for repeated measurements, that is, between factor treatment and within factor time. The values at the start of the treatment were considered as baseline. The primary analysis was based on baseline assessments and all available data obtained thereafter. If the patients baseline value was missing, the patient was excluded from the analyses. Primary analysis was supported by the so-called last point analysis, in which only baseline and the last available data point of each variable were analyzed. Rank sum test was used for the analysis of vaginal cytology. Descriptive statistics were used to characterize the patient population. All data were independently verified for correctness and subjected to both manual and computerized checks for logic and consistency before being made available for statistical analysis.

Results

Patient characteristics

Between 11 November 1988 and 31 August 1991, 648 patients (221 in TOR60, 212 in TOR200 and 215 in TAM20) were randomized. A total of 327 patients (165 in TOR60, 156 in TOR200 and 148 in TAM20) received at least 8 weeks treatment and were eligible for the present analysis of hormonal variables. The main reason for nonevaluability was breast cancer progression at or before 8 weeks control excluding patient from further analysis. The patient characteristics in the present study population were not different from the whole population in the clinical study [15]. The pretreatment characteristics of the patients are evenly balanced among the treatment arms as shown in Table 1.

FSH

Serum mean FSH concentrations declined in all treatment groups during the first 10 months of treatment (Figure 1) reaching premenopausal values in about 8 weeks. The mean FSH concentrations were different among the treatment groups. The lowest concentration was seen in TOR200 group when compared to TOR60 ($p < 0.05$) or TAM20 groups ($p < 0.001$). Lower mean concentrations were seen in TAM20 than in TOR60 group ($p < 0.001$). Analysis of last available data point compared to baseline confirmed the observed fall of serum FSH. In this analysis, the difference between TOR60 and TAM20 was not significant ($p = 0.15$).

LH

The mean serum LH concentrations declined in all treatment groups during the first 2 months of treatment (Figure 2). Although the mean baseline concentrations were not clearly within the postmenopausal range, the decline in the treatment groups were similar to those seen in FSH. The mean concentrations of LH were different among the treatment groups ($p < 0.01$). Again, the lowest concentrations were seen in TOR200 group and the differences when compared to TAM20 ($p < 0.001$) and TOR60 ($p = 0.07$) were similar to those seen in FSH. As in FSH, lower mean LH concentrations were seen in TAM20 group than in TOR60 group ($p < 0.07$). Last point analysis confirmed the LH decline during the treatments, but again, the difference between TOR60 and TAM20 was not significant ($p = 0.5$).

E2

Mean serum E2 concentrations increased ($\geq$30 pcg/ml) in TAM20 and TOR200 groups after 10

Table 1. The baseline characteristics of postmenopausal patients with advanced breast cancer in toremifene 60 mg/day (TOR60), toremifene 200 mg/day (TOR240) and tamoxifen 20 mg/day (TAM20) treatment groups

Characteristic	Treatment		
	Tamoxifen 20 mg ($n = 148$)	Toremifene 60 mg ($n = 165$)	Toremifene 200 mg ($n = 156$)
Age (years)			
Mean ± std dev.	61.4 ± 10.960	63.5 ± 10.277	62.6 ± 10.360
Range	35–82	43–88	41–85
Weight			
Mean ± std dev.	71.1 ± 16.823	68.9 ± 17.021	69.4 ± 15.462
Range	43–124.3	33.6–124.3	35–123
Height			
Mean ± std dev.	161.7 ± 7.469	161.0 ± 6.591	160.4 ± 6.659
Range	145–188	149.8–190.5	137–185.4
Menopausal status:	($n = 147$)	($n = 164$)	($n = 156$)
Postmenopausal with absence of menses 1 year	124 (84.4%)	142 (86.5%)	135 (86.5%)
Perimenopausal with irregular menses/hot flash	8 (5.4%)	6 (3.7%)	6 (3.9%)
Surgically menopausal after prior ooph.	15 (10.2%)	16 (9.8%)	15 (9.6%)

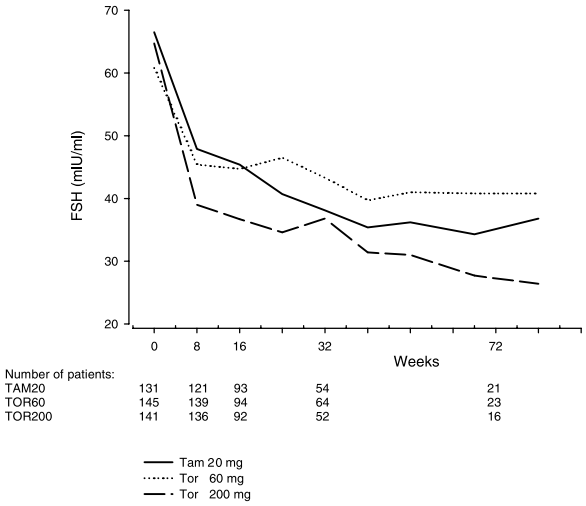

Figure 1. Mean FSH concentrations (IU/l) in the serum of postmenopausal breast cancer patients receiving tamoxifen 20 mg (TAM20, solid line), toremifene 60 mg (TOR60, dotted line) or toremifene 200 mg (TOR200, dashed line) daily for at least 8 weeks.

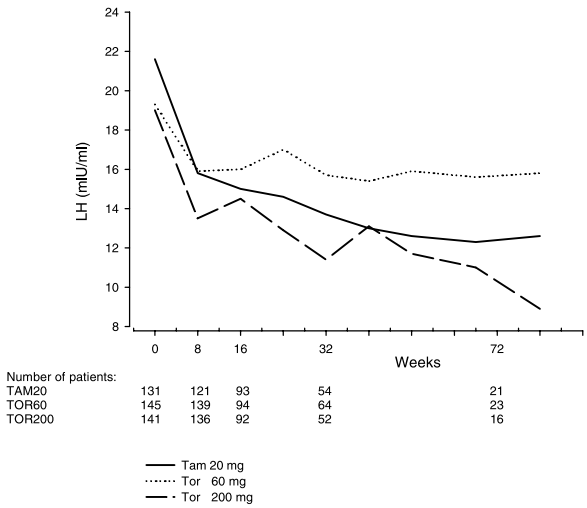

Figure 2. Mean LH concentrations (IU/l) in the serum of postmenopausal breast cancer patients receiving tamoxifen 20 mg (TAM20, solid line), toremifene 60 mg (TOR60, dotted line) or toremifene 200 mg (TOR200, dashed line) daily for at least 8 weeks.

months of treatment ($p < 0.05$, for time and treatment interaction), although overall mean concentrations were not statistically different ($p = 0.09$) among the treatment groups (Figure 3). Likewise no significant increases were observed in last point analysis.

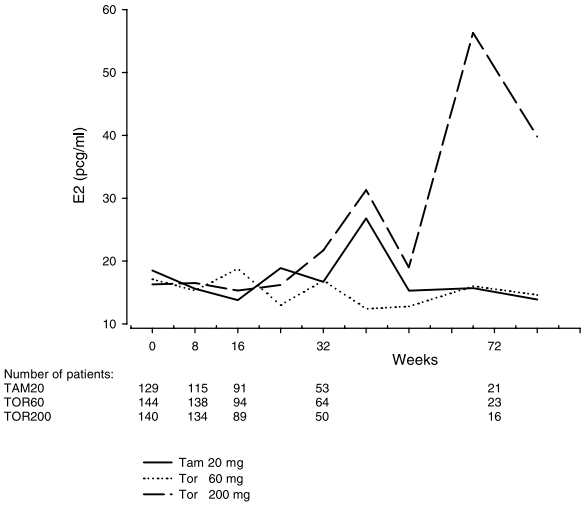

Figure 3. Mean E2 concentrations (pcg/ml) in the serum of postmenopausal breast cancer patients receiving tamoxifen 20 mg (TAM20, solid line), toremifene 60 mg (TOR60, dotted line) or toremifene 200 mg (TOR200, dashed line) daily for at least 8 weeks.

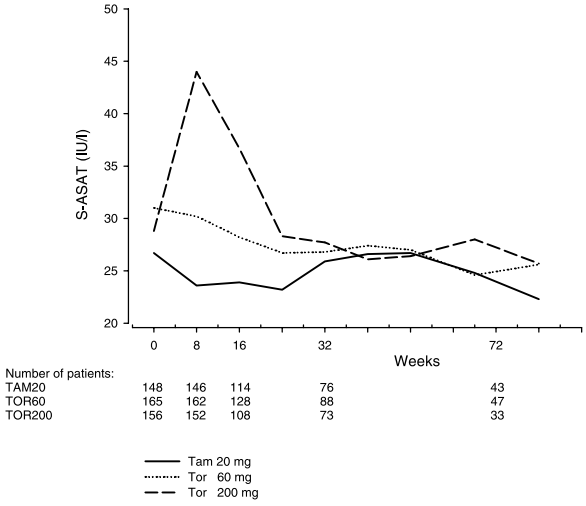

Figure 5. Mean ASAT concentrations (IU/l) in the serum of postmenopausal breast cancer patients receiving tamoxifen 20 mg (TAM20, solid line), toremifene 60 mg (TOR60, dotted line) or toremifene 200 mg (TOR200, dashed line) daily for at least 8 weeks.

SHBG

Dose-dependent increase of SHBG concentration was seen in all treatment groups during the first 8 weeks of treatment (Figure 4). The mean concentrations were different among the treatment groups ($p < 0.001$), so that the concentration in theTOR200 group was higher when compared to TAM20 ($p < 0.001$) or TOR60 ($p < 0.01$). In the contrary to FSH and LH, SHBG concentrations increased more in the TOR60 than in the TAM20 group. Last point analysis confirmed this finding.

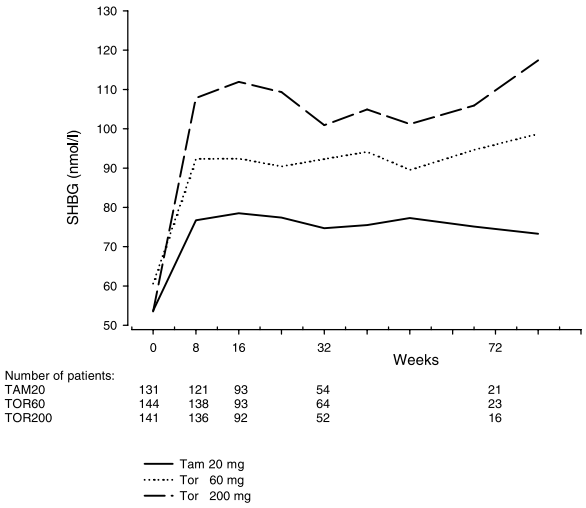

Figure 4. Mean SHBG concentrations in the serum of postmenopausal breast cancer patients receiving tamoxifen 20 mg (TAM20, solid line), toremifene 60 mg (TOR60, dotted line) or toremifene 200 mg (TOR200, dashed line) daily for at least 8 weeks.

ASAT

During treatment, no increases of mean ASAT values were observed in TAM20 or TOR60 groups. In the TOR200 group mean ASAT concentrations increased during weeks 8–24 ($p < 0.01$, for time and treatment interaction), but the mean concentrations were not different among the treatment groups ($p = 0.07$, Figure 5). Last point analysis indicated significant overall difference among the groups ($p < 0.05$). This was due to the increase in the TOR200 group, which was more than in TOR60 ($p < 0.05$) or TAM20 ($p < 0.01$). TOR60 and TAM20 groups did not differ from each other ($p = 0.49$). ASAT increases >100 IU/l were observed in 11, 22 and 4 patients in the TOR60, in the TOR200 and in the TAM20 groups, respectively [33]. The difference between TAM20 and TOR200 was statistically significant ($p < 0.05$). However, in no case the treatments were discontinued due to the elevated liver function tests.

AT III

AT III was assessed most often at baseline and at week 8. Serum samples of 116, 115 and 98 patients in TOR60, TOR200 and TAM20 were available for the analysis. AT III decreased 8.8% in TOR60, 8.4% in TOR200 and 13.8% in TAM20 groups. In the last

point analysis, more reduction was seen in the TAM20 group than in TOR60 ($p = 0.09$) or in TOR200 ($p < 0.05$), but the decrease over the treatment groups was not statistically significant ($p = 0.10$).

Vaginal cytology

A total of 277 patients 86 in TAM20, 98 in TOR60 and 93 in TOR200 had baseline and 8 weeks superficial cell counts available for assessment. The mean counts at baseline were 3.3, 4.0 and 4.5, and in all treatment groups the counts increased by week 8 up to 10.0, 15.7, and 15.8, respectively. The counts were higher in TOR60 and TOR200 groups when compared to TAM20 ($p < 0.05$).

Clinical safety

Overall all treatments were well tolerated. A total of 21 patients discontinued the treatment due to clinical toxicity (3 in TAM20, 6 in TOR60 and 12 in TOR200). The most frequent single reasons for withdrawal were hypercalcemia and CNS symptoms in four patients in both groups. Two patients were removed from the TOR200 group due to multiple liver function abnormalities, which were resolved after discontinuation of the drug.

Table 2. Relative decreases (−/− −/− − −), increases (+/+ +/+ + +) or no change (NC) in FSH, LH, E2, SHBG, ASAT, AT III concentrations and vaginal superficial cell counts in postmenopausal breast cancer patients receiving tamoxifen 20 mg (TAM20), toremifene 60 mg (TOR60) or toremifene 200 mg (TOR200) daily for at least 8 weeks

	Treatment		
	Tamoxifen 20 mg ($n = 148$)	Toremifene 60 mg ($n = 165$)	Toremifene 200 mg ($n = 156$)
FSH	− −	−	− − −
LH	− −	−	− − −
SHBG	+	+ +	+ + +
E2	+	NC	+
ASAT	NC	NC	+
AT III	−	NC	NC
Vaginal superficial cell count	+	+ +	+ +

Discussion

SERMs are used for the treatment of breast cancer mainly to prevent breast cancer growth by their antiestrogenic activity. However, some of the estrogenic actions of the SERMs are also beneficial, such as prevention of osteoporosis or lowering LDL cholesterol. Endometrium stimulating effects, increased incidence of thromboembolic complications or even stimulation of breast cancer cell growth [20, 43] are unwanted effects.

In this study, we have found that the estrogenicity of TOR60, TOR200 and TAM20 in postmenopausal women were similar but not identical. The SERMs were estrogenic in both the pituitary and liver, documented by decreased serum FSH and LH and increased SHBG, respectively (Table 2). As well as in the vaginal epithelium as shown by the increase of superficial cell counts. Premenopausal levels of FSH and LH were reached within 8 weeks and maximal estrogenic effect in the liver at 16 weeks. In the TAM20 and TOR200 groups the FSH and LH concentrations decreased further after reaching the expected steady state level of the study drugs at 4 weeks [1]. Estrogens increase SHBG concentrations [42] and, as expected, serum SHBG correlated positively with the dose and serum concentration of the SERMS. However, the estrogenic effects of the two SERMs were not directly dose-dependent in the pituitary. Again, most estrogenic activity was shown by toremifene 200 mg, but tamoxifen 20 mg was more estrogenic than toremifene 60 mg. This is consistent with the preclinical finding by di Salle et al. [39], who found toremifene less estrogenic than tamoxifen within equipotent antiestrogenic doses in the rat. In postmenopausal breast cancer patients toremifene 40–60 mg had similar bone sparing [25, 38] and serum LDL decreasing/HDL increasing effect [19, 37], that is, estrogenic effects.

Toremifene 200 mg induced more clinically nonsignificant abnormalities in the liver function tests, which is consistent with the higher SHBG synthesis induction capacity of the regimen. No difference between toremifene 60 mg and tamoxifen 20 mg was seen in this respect. Treatment regimens slightly decreased serum AT III concentrations. TAM20 tended to decrease AT III more than the two other regimens but the fall over the treatment groups was not statistically significant. Tamoxifen has observed to increase incidence of thromboembolic complications seen during long term treatment [9]. In a recently reported study, fewer thromboembolic complications were observed in postmenopausal breast cancer

patients treated with long term toremifene 40 mg daily treatment when compared to tamoxifen 20 mg daily [17]. This observation may be due to lower estrogenic potential and lower thrombosis risk.

Earlier studies with toremifene in doses ranging from 20 to 80 mg daily has been shown to be antiestrogenic [18] in vaginal cytology in healthy postmenopausal volunteers when given after transdermal E2. No dose response was seen and the effect was no different than with tamoxifen from 10 to 20 mg daily. In this study, when given without exogenous estrogen, all treatments were estrogenic in the vaginal epithelium. No difference between the two toremifene regimens were seen and both showed more estrogen agonist activity than tamoxifen. In clinical studies no difference in vaginal bleeding or discharge has been seen between toremifene 60–240 and tamoxifen 20–40 [11, 12, 15, 34].

The treatments were well tolerated and discontinuation due to toxicity was rare. The toxicity was most often related to the antiestrogenic effects of the drugs such as menopausal like symptoms with no differences among the groups. More patients with transiently elevated liver transaminases were seen on high dose toremifene [15] indicating that this may be a dose effect that was supported by preclinical findings [23]. However, at the lower dose of toremifene, no such dose-dependent liver stimulation was seen [6, 15, 17].

The present results agree with the earlier studies confirming that toremifene, among other hormonal agents, is an effective drug for the treatment of advanced breast cancer in postmenopausal women. According to phase I studies toremifene 20 mg/day is the lowest dose with antiestrogenic effect [18]. No difference in efficacy has been seen between tamoxifen 20 and 40 mg daily doses [3], suggesting that therapeutic window for triphenylethylene derivatives is wide and that increasing the dose does not necessarily improve the effect. TOR60 has been shown to be as effective as tamoxifen 20–40 mg/day [34] and the recent findings [17] demonstrate that 40 mg/day is as effective as tamoxifen in the adjuvant setting.

Available clinical data suggest that the maximal breast cancer growth inhibiting effect of triphenylethylenes is reached early during dose escalation and that higher total doses, possibly with added estrogenic effect, increase toxicity. This study demonstrated that although biochemical differences were induced among the three treatment groups, no clinical differences were observed in the therapeutic trial [15]. In these patients with metastatic breast cancer, response rates and times to progression were similar for TOR60, TOR200 and TAM20. Toremifene 40–60 mg daily is safe and effective treatment for postmenopausal women with ER positive or ER unknown breast cancer. The lower estrogenic potential and clinically equivalent efficacy with tamoxifen make toremifene an interesting alternative for long term treatment of breast cancer.

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