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Dose-dependent hormonal effects of toremifene in postmenopausal breast cancer patients

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Abstract *Purpose*: The purpose of the study was to compare hormonal effects of three toremifene doses, 20 mg (TOR20), 40 mg (TOR40) and 60 mg (TOR60) administered daily, in postmenopausal women with advanced breast cancer. *Methods*: The study was randomized and open label in three parallel groups. Biochemical variables were identified as the serum concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and sex hormone binding globulin (SHBG). The changes were compared with objective clinical responses and to progression-free time. Adverse reactions and liver function test (aspartate aminotransferase, ASAT) were assessed for safety. *Results*: A total of 260 patients were randomly grouped (90 to TOR20, 81 to TOR40 and 89 to TOR60). Of these patients 29, 29 and 22 completed at least 3 months of treatment and the results were analyzed for biochemical variables. All treatments had intrinsic estrogen agonist activity by decreasing of serum FSH and LH and by increasing of SHBG during the first 3 months ($P < 0.01$). Dose TOR20 showed slightly longer times to exert maximum estrogenic effects than did the two higher doses. No increases in liver function tests were seen in any of the groups. Objective response rates were 24.4, 39.5 and 32.6% ($P = 0.01$) and median times-to-progression were 206, 189 and 196 days in TOR20, TOR40 and TOR60, respectively ($P = 0.913$). Fewer responses were observed in the TOR20 group than in TOR40 ($P = 0.05$). Adverse events were reported in 19, 23 and 30 patients in the treatment groups ($P = 0.20$). The most frequently reported events were hot flushes and nausea. These were mostly mild or moderate, and only 1.5% of treatments was discontinued due to toxicity. *Conclusions*: Toremifene doses of 40 and 60 mg daily were effective and safe treatments of breast cancer in postmenopausal women, and no differences in their biochemical or clinical effects were seen. Toremifene at 20 mg/day had similar but slightly less potent antiestrogenic and estrogenic effects than the two higher doses.

Key words Toremifene · Dose · Hormonal effects · Breast cancer · Postmenopausal women

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Introduction

Triphenylethylene antiestrogens or specific estrogen receptor modulators (SERM) are used for the first-line palliative treatment of metastatic breast cancer [10, 14] and especially for adjuvant treatment after breast cancer surgery [3, 7]. Clinical trials to evaluate the effect of SERMs in breast cancer prevention in high-risk patients are ongoing, although the first results are controversial [4, 25, 32]. The triphenylethylene-derivative, toremifene, acts mainly as an antiestrogen in humans [17, 18], and like other SERMs [15, 24], it binds to the intracellular estrogen receptor (ER). The effects of SERMs depend on the target tissue. Typically, in the breast they inhibit cell proliferation, whereas in liver they stimulate protein

synthesis (e.g., sex hormone binding globulin (SHBG) [18, 30]). In rodents the maximum estrogen-like uterotropic effect was achieved at doses of 1.0–10 mg/kg. The estrogenic effect of toremifene, within this range, was seen at doses 40 times higher than that of tamoxifen. When toremifene was administered with estradiol, the minimum antiestrogenic dose was ten times higher than that of tamoxifen, suggestive of a lower estrogenic potential of toremifene when compared with tamoxifen [29]. In postmenopausal women, toremifene at a dose of 220–680 mg daily for 5 days induced a decrease in serum LH and FSH and an increase in SHBG levels [16]. In postmenopausal women with concomitant transdermal estradiol, toremifene given at 10 mg/day had little or no antiestrogenic activity in vaginal cytology, but 20, 40 and 80 mg/day exerted marked antiestrogenic effects, similar to those of tamoxifen at 20 mg/day [13]. In phase II clinical studies in postmenopausal patients with advanced breast cancer, the lowest dose of toremifene, 20 mg/day [26], was not as effective as 60 mg/day [8, 21, 31], and the highest amount used, 240 mg/day, still improved response rate [11]. In a meta-analysis of early tamoxifen trials [22] tamoxifen at 40 mg/day was more effective than at 20 mg/day, but in a comparative study between the two doses [2] no difference in efficacy was seen. In phase III studies, toremifene at 60 mg/day has been equally as effective as tamoxifen in 20 or 40 mg/day doses [5, 9, 27] and the higher dose of toremifene, 200–240 mg/day, again showed a slightly higher response rate [6]. In a Japanese comparative study [23] 40mg/day of toremifene was as effective as 20 mg/day of tamoxifen. Clinical studies in adjuvant treatment of breast cancer with toremifene at both 40 and 60 mg daily doses are currently ongoing [12]. First results indicate that toremifene at 40 mg/day is as effective and safe as tamoxifen at 20 mg/day in the adjuvant treatment of postmenopausal women with node positive breast cancer. The aim of the present study was to compare hormonal and other clinical effects of toremifene at doses of 20 mg (TOR20), 40 mg (TOR40) and 60 mg (TOR60) daily in the first-line treatment of advanced, estrogen receptor (ER) positive breast cancer in postmenopausal women. The study complied with the WHO criteria and the principles of the Helsinki declaration. Ethical committees in each site approved the study and the patients gave their informed consent before randomization took place.

Patients and methods

Study design

This was a multicenter, randomized, open label study which compared TOR20, TOR40 and TOR60 in three parallel groups. The biochemical variables were identified as the changes in the non-fasting patient's serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) and in sex hormone binding globulin (SHBG) assayed by immunometric methods. Objective responses and times to breast cancer progression were assessed for clinical efficacy. Adverse effects such as hot flushes, nausea, vaginal discharge, bleeding and liver function tests in terms of changes in serum aspartate aminotransferase (ASAT) concentrations were assessed for tolerability.

Patient selection

Patients who had undergone the menopause at least 2 years ago, and who had histologically-verified, previously untreated advanced breast cancer were eligible for the study. They had to have at least one measurable metastasis or osteolytic bone lesion. The breast cancer had to be ER positive with an ER concentration of 10 fmol/mg protein assessed by charcoal dextran methods, or be positive when tested by immunohistochemical methods. Karnofsky performance status had to be ≥50% and the patients should not have had any previous invasive malignancies. Those suffering from severe renal or hepatic insufficiency (creatinine or bilirubin >2 mg/dl) were excluded. Patients were eligible if they had had previous adjuvant therapy, provided that at least 12 months had elapsed between the discontinuation of the treatment and breast cancer recurrence.

Randomization and treatment regimen

The patients were randomized centrally and stratified by the 26 centers in South Africa, France, UK and Italy. The study treatments were one TOR20 tablet, two TOR40 tablets or one TOR60 tablet daily. No dose-modifications were allowed. Treatment was scheduled for 3 months, after which patients with the disease stabilized were allowed to be taken off the study. Otherwise the treatment was continued until breast cancer progression. Other cancer treatment excluding local radiotherapy and/or steroids was not allowed during the study.

Patient evaluation

Before being treated the patients were evaluated for physical and performance status and for medical history. Samples were taken for blood chemistry analysis and hemoglobin, leukocyte and platelet counts. Breast cancer lesions were measured bidimensionally or evaluated by chest X-ray, bone scan and liver ultrasonography. The patients were studied at 4-weekly intervals for the first 3 months. In the cases where treatment was continued beyond 3 months the patients were seen at 4 months and every 3 months thereafter. Each individual laboratory value obtained was compared with the laboratory reference-range of the hospital. The response classifications were defined according to the WHO criteria [20], as complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). To be in the NC category in this analysis, the required response was stabilization of the disease on two consecutive visits. Adverse events were recorded at each visit. The severity grading of adverse events was based on the WHO guidelines [33].

Statistics

Sample size was estimated to find a 20% difference in response rates among TOR20, TOR40 and TOR60 arms with an overall type I error rate (α) of 0.05 and a type II error rate (β) of 0.20. Primary analysis of the data was done according to the "intent to treat" principle. The time and treatment effect on the hormonal variables was evaluated by analysis of covariance. Response rates among the treatment groups were compared, by the Chi-square test and by Fisher's exact test. Descriptive statistics were used to describe the patient-population. The Kaplan-Meier method was used to estimate, and the Log-rank test was applied to compare the treatment arms with regard to time-to-progression (TTP). 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 October 1987 and April 1990, 260 patients (90 in the TOR20 group, 81 in TOR40 and 89 in TOR60) were accrued. The pretreatment characteristics of the patients were evenly balanced among the treatment arms as shown in Table 1. Altogether 219 (84.2%) patients (77 in the TOR20 group, 67 in TOR40 and 75 in TOR60) were considered evaluable and eligible according to the protocol criteria, with no difference among the treatment groups. The most frequent reasons for patient inevaluability were early withdrawals due to death, lost to follow-up and protocol violation (31 patients), or not evaluable for response assessment (10 patients). Eighty people (29 in TOR20, 29 in TOR40 and 22 in TOR60) completed at least 3 months of treatment and were assessed for hormonal changes.

Biochemical effects

Serum FSH and LH decreased significantly ($P < 0.01$) reaching premenopausal levels after 7 months of treatment (Figs. 1, 2). In the TOR20 group the change took place slightly slower and there was a nonsignificant trend of higher values in the TOR20 group during the first 4 months of therapy. The SHBG in serum increased significantly ($P < 0.01$) in all treatment groups during the first 3 months. (Fig. 3). The most rapid change was seen in the highest dosed group in which the maximum concentration was reached after 2 months, whereas in the TOR20 group, maximum concentration was reached after 4 months.

Response rates

The response rates are shown in Table 2. There was a statistically significant difference among the three treatment groups ($P = 0.01$), with TOR20 patients showing response rates lower than those in the two other groups. The difference between TOR20 and TOR60 was 8.2%

Table 1 Characteristics of postmenopausal women with advanced breast cancer, who were randomized to receive toremifene 20 mg/day (TOR 20), 40 mg/day (TOR 40) or 60 mg/day (TOR 60)

		TOR 20	TOR 40	TOR 60
Patients (*n*)		90	81	89
Age (mean ± SD, years)		65 ± 10	66 ± 10	65 ± 10
Years since menopause	< 4	11	6	8
	5–9	15	14	17
	> 10	58	58	62
	Unknown	6	3	2
Performance status (ECOG)	0	33	26	27
	1	36	29	41
	2	19	19	18
	3	1	4	1
	Unknown	1	3	2
Disease status	Recurrence	53	47	49
	First diagnosis	37	34	40
Disease-free time (years)	< 1	3	2	4
	1–5	31	31	25
	> 5	19	14	20
	Unknown	37	34	40
Histology	Inv. ductal	74	64	67
	Inv. lobular	5	4	6
	Other	11	13	16
Tumor ER	Positive	88	79	87
	Unknown	2	1	2
	Negative	–	1	–
Measurability	Measurable	78	72	80
	Bone	10	6	7
	Non-measurable	1	2	1
Dominant site	Primary	19	15	17
	Soft tissue	20	22	12
	Visceral	6	7	7
	Skeletal	6	6	6
	Multiple	13	8	11
	Mult. skeletal	25	22	35
	Other	1	1	1

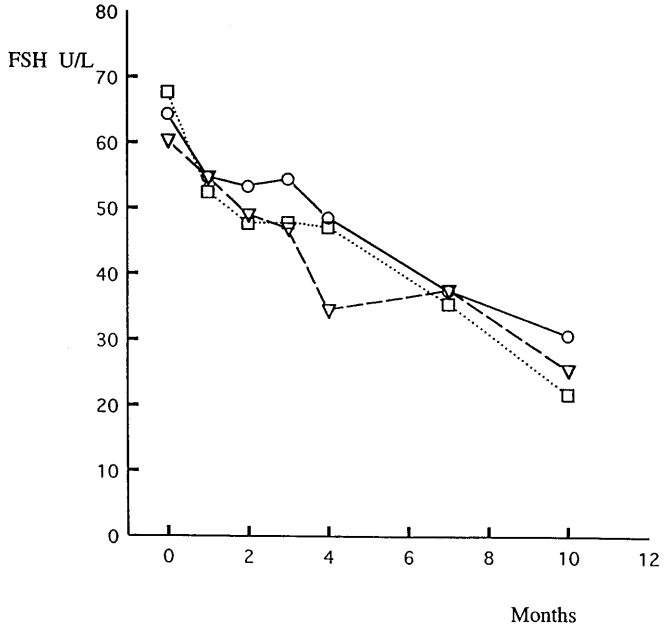

Fig. 1 Mean follicle stimulating hormone (FSH) concentrations (IU/l) in the serum of postmenopausal breast cancer patients receiving toremifene 20 mg (*TOR20, circles*), 40 mg (*TOR40, squares*) or 60 mg (*TOR60, triangles*) daily for at least 3 months

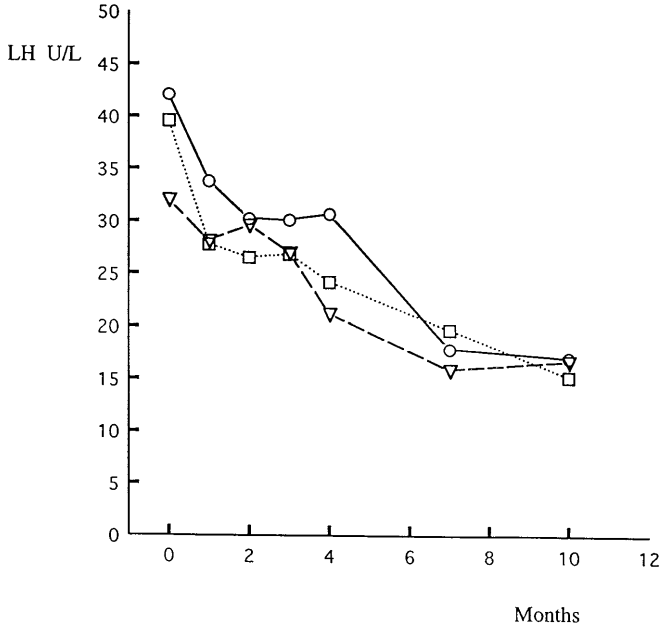

Fig. 2 Mean luteinizing hormone (LH) concentrations (IU/l) in the serum of postmenopausal breast cancer patients receiving toremifene 20 mg (*TOR20, circles*), 40 mg (*TOR40, squares*) or 60 mg (*TOR60, triangles*) daily for at least 3 months

($P = 0.25$), that between TOR40 and TOR60 was 6.9% ($P = 0.42$) and between TOR20 and TOR40 it was 15.1% ($P = 0.05$). The results suggest that TOR20 was less effective than the two other doses although only the difference with TOR40 became statistically significant.

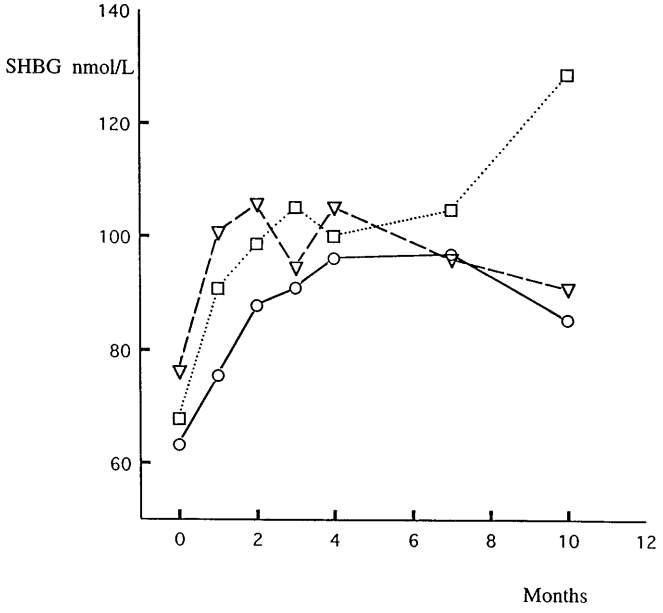

Fig. 3 Mean sex hormone binding globulin (SHBG) concentrations (nmol/l) in the serum of postmenopausal breast cancer patients receiving toremifene 20 mg (*TOR20, circles*), 40 mg (*TOR40, squares*) or 60 mg (*TOR60, triangles*) daily for at least 3 months

Table 2 Best objective response in postmenopausal breast cancer patients who were treated with toremifene 20 mg/day (TOR 20), 40 mg/day (TOR 40) or 60 mg/day (TOR 60). Response classes are evaluated according to WHO as *CR* complete response, *PR* partial response, *NC* no change (disease stabilized), *PD* progressive disease, *NE* not evaluable, *RR* response rate

Response	TOR 20	TOR 40	TOR 60
CR	11	10	6
PR	11	22	23
NC	38	16	21
PD	18	17	17
NE	12	16	22
Total	90	81	89
RR	24.4%	39.5%	32.6%

$P = 0.014$ Chi-square test

Time-to-progression

At the time of data cut-off, 164 (62.7%) of the patients had experienced breast cancer progression. Of these, 13 (14.4%) in the TOR20 group, 7 (8.6%) in TOR40 and 10 (11.2%) in TOR60 were continuing on the study without evidence of progression. Median TTP times were 206, 189 and 196 days in TOR20, TOR40 and in TOR60, respectively, and no difference was seen among the treatment groups ($P = 0.91$, Fig. 4).

Safety

Treatment-emergent adverse events are shown in Table 3. Antiestrogen-type events such as hot flushes, nausea and leukorrhea were seen in all the groups.

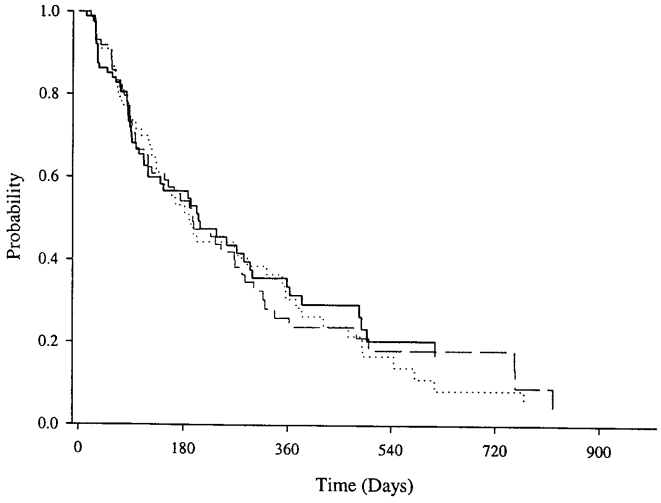

Fig. 4 Time-to-progression in postmenopausal women with advanced breast cancer, who were treated with toremifene 20 mg (*TOR20,* —), 40 mg (*TOR40,* ····) or 60 mg (*TOR60,* - - -) daily

Table 3 Postmenopausal patients with adverse events (prevalence ≥1%) during treatment of advanced breast cancer with toremifene at 20 mg/day (TOR 20), 40 mg/day (TOR 40) or 60 mg/day (TOR 60)

	TOR 20 (n = 90)	TOR 40 (n = 81)	TOR 60 (n = 89)
Hot flushes	10 (11%)	7 (9%)	14 (16%)
Nausea/vomiting	4 (4)	5 (6)	6 (7)
Leukorrhea	1 (1)	5	4 (4)
Thrombosis	1	3 (4)	1 (1)
Rash	1	–	4
Dizziness	1	2 (2)	2
Headache	1	2	2
Gastroenteritis	3 (3)	1 (1)	–
Anorexia	–	2	1 (1)
Fatigue	–	1	2
Hypertension	–	2	1
Cardiac failure	1	1	1
Edema	1	–	2
No. events	24	31	40
No. patients with events	19 (21%)	23 (28%)	30 (34%)

Adverse events were seen in 21% of patients in the TOR20 group, compared with 28 and 34% in the two other groups ($P = 0.20$). There was a trend of less adverse events in the TOR20 group when compared with the TOR60 group ($P = 0.07$). Twelve of the events were considered to be severe. Of these, six were seen in the TOR20 group, two in TOR40 and four in TOR60. Of the latter, two and two, respectively, were considered to be treatment-related. Therapy was discontinued prematurely due to adverse events once in TOR20 and TOR60 and twice in TOR40. Ten patients died during the course of the study; six of these received TOR60, three TOR40 and one TOR20. Most of the deaths were due to cardiovascular or respiratory complications of metastatic breast cancer. During the first 3 months, serum SGOT decreased in each treatment group ($P < 0.01$) with no differences among the groups. SGOT values above the reference ranges were seen in up to 11% of patients in the TOR60 group during the first 4 months of therapy. The respective figure in the TOR20 group was 5%, and no elevation in the levels in the group TOR40 patients was seen. None of the raised values was considered to be a clinical adverse event, and the differences among the treatment groups were not statistically significant.

Discussion

The present investigation is the first clinical study to compare the effects of three dose-levels of toremifene in the treatment of advanced ER-positive breast cancer in postmenopausal women. The aim of this study was to assess hormonal and other clinical effects of the doses.

All three dose-levels had estrogenic effects in the central nervous system (CNS) and liver, shown by the decrease of FSH and LH, and the increase of SHBG in serum, respectively. The observed changes tended to be slower in the TOR20 group, although the premenopausal ranges of FSH and LH were reached under all dose regimens within 7 months, and the maximum estrogenic effect in the liver was attained by 4 months. The continuing effect was somewhat surprising, because the concentrations decreased further after reaching the expected steady state level of the drug. All doses from 20 to 60 mg daily had antiestrogenic activity, shown by a reduction in tumor volume in one third of the patients. The lowest dose, 20 mg daily, was less effective in this respect than the two other doses. However, when the period from the start of therapy, to breast cancer progression was considered, the treatments were identical. Patients with no response after 3 months were allowed to be taken off the study, and subsequently, further patients in the TOR20 group discontinued the study, without objective breast cancer progression being seen. This may have had some effect on the TTP analysis, favoring this group. Earlier studies [5, 9] have shown that toremifene doses of up to 200 or 240 mg daily may improve response rate but do not prolong TTP when compared with standard toremifene or tamoxifen doses. Steady-state concentrations of triphenylethylenes in serum are reached after 4 to 6 weeks [1], and the possibility remains that effective concentrations of the drug are available earlier, with higher doses, allowing a more rapid onset of an antitumor effect. In the present study we could not see any clinical or biochemical differences between the 40 and 60 mg daily doses. The treatments were well tolerated and discontinuation due to toxicity was rare. The observed toxicity was mostly related to the drug's hormonal effects, such as menopausal-like symptoms. Again, more events were seen with the highest dose than with the lowest dose. More patients with transiently elevated liver function tests have been seen earlier on high-dose toremifene [6], indicating that this may be a dose effect. Also, preclinical findings [19] suggested that dose-dependent liver stimulation may take place. However, in this study, where an overall

lower dose-range of toremifene was used than in the two other mentioned studies, no such dose-dependent effect was seen.

The present results agree with those of the earlier phase II and III studies, and confirm that toremifene is an effective drug for the treatment of ER-positive advanced breast cancer in postmenopausal women. According to phase I studies, toremifene at 20 mg/day is the lowest dose with an antiestrogenic effect [13]. In this investigation, the antiestrogenic effect of the dose was confirmed. However, the time to achieve maximum hormonal effects tended to be longer with the 20 mg dose, although the only statistically significant difference was seen in response rate. All dose regimens were well tolerated. Adverse events, possibly related to hormonal actions of toremifene, were seen in all three treatment groups but again, there was a trend suggesting slightly fewer events in the TOR20 group. No differences whatsoever could be seen between toremifene 40 mg and 60 mg daily doses. Earlier, no difference in efficacy had been seen between tamoxifen at 20 mg and 40 mg daily doses [2], suggesting that therapeutic-window of triphenylethylene derivatives is wide, and that an increase in the dose does not necessarily improve the effect. Toremifene at 60 mg/day has been shown to be as effective as tamoxifen at 20–40 mg/day [28], and recent findings [12] demonstrate that 40 mg/day is at least as effective as tamoxifen in breast cancer treatment.

Toremifene at 40 mg and 60 mg daily doses is a safe and effective treatment for postmenopausal women with ER-positive breast cancer. Similar antiestrogenic and estrogenic effects are seen even with the lower 20 mg daily dose, but the efficacy of this possibly borderline dose needs to be confirmed.

References

1. Anttila M, Valavaara R, Kivinen S, Mäenpää J (1990) Pharmacokinetics of toremifene. J Steroid Biochem 36: 249–252
2. Bratherton DG, Brown CH, Buchanan R, Hall V, Kingsley Pillers EM, Wheeler TK, Williams CJ (1984) A comparison of two doses of tamoxifen (Nolvadex*) in postmenopausal women with advanced breast cancer: 10 mg bd. versus 20 mg bd. Br J Cancer 50: 199–205
3. Early Breast Cancer Trialists' Collaborative Group (1998) Tamoxifen for breast cancer. An overview of the randomized trials. Lancet 351: 1451–1467
4. Fisher B, Costantino JP, Wickerham DL, Redmond Carol K, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N and the other National Surgical Adjuvant Breast and Bowel Project Investigators (1998) Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90: 1371–1388
5. Gershanovich M, Garin A, Baltina D, Kurvet A, Kangas L, Ellmén J (1997) A phase III comparison of two toremifene doses to tamoxifen in postmenopausal women with advanced breast cancer. Breast Cancer Res Treat 45: 251–262
6. Gershanovich M, Hayes D, Ellmén J, Vuorinen J (1997) High dose toremifene vs. tamoxifen in postmenopausal advanced breast cancer. Oncology 11 [Suppl 4]: 29–36
7. Goldhirsch A, Wood WC, Senn H-J, Glick JH, Gelber RD (1995) Meeting highlights: international consensus panel on the treatment of primary breast cancer. J Natl Cancer Inst 87: 1441–1445
8. Gundersen S (1990) Toremifene, a new antiestrogenic compound in the treatment of metastatic mammary cancer. A phase II study. J Steroid Biochem 36: 233–234
9. Hayes DF, Van Zyl JA, Hacking A, Goedhals L, Bezwoda WR, Mailliard JA, Jones SE, Vogel CL, Berris RF, Shemano I, Schoenfelder J (1995) Randomized comparison of tamoxifen and two separate doses of toremifene in postmenopausal patients with metastatic breast cancer. J Clin Oncol 13: 2556–2566
10. Henderson IC (1991) Endocrine therapy of metastatic breast cancer. In: Harris JR, Hellman S, Henderson IC et al. (eds) Breast diseases. Lippincott, Philadelphia, Pa. pp 559–603
11. Hietanen T, Hakala T, Baltina D, Johansson R, Numminen S, Helle L, Valavaara R, Thölix E (1997) Open phase II study of high-dose toremifene as first-line therapy for advanced breast cancer. Oncology 11: 37–40
12. Holli K, Joensuu H, Valavaara R, Blanco G, Kataja V, Pukkala E, for the Finnish Breast Cancer Group (1998) Toremifene vs Tamoxifen Adjuvant Trial. Abstract, 21st Annual San Antonio Breast Cancer Symposium, 283
13. Homesley HD, Shemano I, Gams R, Harry DS, Hickox PG, Rebar RW, Bump RC, Mullin TJ, Colston Wentz A, O Toole RV, Lovelace JV, Lyden C (1993) Antiestrogenic potency of toremifene and tamoxifen in postmenopausal women. Am J Clin Oncol 16: 117–122
14. Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN (1995) Use of tamoxifen for breast cancer: twenty-eight years later. J Clin Oncol 13: 513–529
15. Jordan VC, Dix CJ, Naylor KE, Prestwitch G, Rowsby L (1978) Nonsteroidal antiestrogens: their biological effects and potential mechanism of action. J Toxicol Environ Health 4: 363–390
16. Kallio S, Kangas L, Blanco G, Johansson R, Karjalainen A, Perilä M, Piippo I, Sundquist H, Södervall M, Toivola R (1986) A new triphenylethylene compound, Fc-1157a I Hormonal effects. Cancer Chemother Pharmacol 17: 103–108
17. Kangas L, Kallio S, Blanco G, Grönroos M, Kallio S, Karjalainen A, Perilä M, Södervall M, Toivola R (1986) A new triphenylethylene compound, FC-1157a. II Antitumor effects. Cancer Chemother Pharmacol 17: 109–114
18. Kangas L (1992) Agonistic and antagonistic effects of antiestrogens in different target organs. Acta Oncol 31: 143–146
19. Kendall ME, Rose DP (1992) The effects of diethylstilbestrol, tamoxifen, and toremifene on estrogen-inducible hepatic proteins and estrogen receptor proteins in female rats. Toxicol Appl Pharmacol 114: 127–131
20. Miller AB, Hoogstarten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214
21. Modig H, Borgström S, Nilsson I, Westman G (1990) Phase II clinical study of toremifene in patients with metastatic breast cancer. Preliminary communication. J Steroid Biochem 36: 235–236
22. Mouridsen H, Palshof T, Patterson J, Battersby L (1978) Tamoxifen in advanced breast cancer. Cancer Treat Rev 5: 131–141
23. Nomura Y, Tominaga T, Abe O, Izuo M, Ogawa N (1993) Clinical evaluation of NK 622 (toremifene citrate) in advanced or recurrent breast cancer – a comparative study by a double blind method with tamoxifen. Jpn J Cancer Chemother 20: 247–258
24. Osborne CK (1991) Receptors. In: Harris J, Hellman S, Henderson I et al. (eds) Breast diseases. Lippincott, Philadelphia, Pa. pp 301–325
25. Powles T, Eeles R, Ashley S, et al. (1998) Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital: tamoxifen randomized chemoprevention trial. Lancet 352: 98–101
26. Pyrhönen S, Valavaara R, Heikkinen M, Rissanen P, Blanco G, Nordman E, Holsti RL, Hajba A (1990) Treatment of advanced

breast cancer with 20 mg toremifene, a phase II study. Preliminary communication. J Steroid Biochem 36: 227–228
27. Pyrhönen S, Valavaara R, Modig H, Pawlicki M, Pienkowski T, Gundersen S, Bauer J, Westman G, Lundgren S, Blanco G, Mella O, Nilsson I, Hietanen T, Hindy I, Vuorinen J, Hajba A (1997) Comparison of toremifene and tamoxifen in postmenopausal patients with advanced breast cancer: a randomized double blind, the "Nordic" phase III study. Br J Cancer 76: 270–277
28. Pyrhönen S, Ellmén J, Vuorinen J, Gershanovich M, Tominaga T, Kaufmann M, Hayes DF (1999) Meta-analysis of trials comparing toremifene with tamoxifen and factors predicting outcome of antiestrogen treatment therapy in postmenopausal women with breast cancer. Breast Cancer Res Treat (in press)
29. di Salle E, Zaccheo T, Ornati G (1990) Antiestrogenic and antitumor properties of the new triphenylethylene derivative toremifene in the rat. J Steroid Biochem 36: 203–206
30. Számel I, Hindy I, Vincze B, Eckhardt S, Kangas L, Hajba A (1994) Influence of toremifene on the endocrine regulation in breast cancer patients. Eur J Cancer 30A: 154–158
31. Valavaara R, Pyrhönen S, Heikkinen M, Rissanen P, Blanco G, Thölix E, Nordman E, Taskinen P, Holsti L, Hajba A (1988) Toremifene, a new antiestrogenic compound, for treatment of advanced breast cancer. Phase II study. Eur J Cancer Clin Oncol 24: 785–790
32. Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N, Boyle P on behalf of the Italian Tamoxifen Prevention Study (1998) Prevention of breast cancer with tamoxifen. Preliminary findings from the Italian randomized trial among hysterectomized women. Lancet 352: 93–97
33. WHO Adverse Reaction Dictionary. WHO Collaborating Center for International Drug Monitoring, March, 1988. Uppsala, Sweden