*Breast Cancer Research and Treatment* **25**: 57–63, 1993.


*Report*

# Toremifene and tamoxifen in advanced breast cancer – a double-blind cross-over trial

Lars E. Stenbygaard,[1] Jørn Herrstedt,[1] Jane F. Thomsen,[2] Karsten R. Svendsen,[1] Svend Aa. Engelholm[1] and Per Dombernowsky[1]

[1] *Department of Oncology, Herlev Hospital, University of Copenhagen DK-2730, Herlev, Denmark;*

[2] *Department of Internal Medicine C, Bispebjerg Hospital, University of Copenhagen, DK-2400 Copenhagen, Denmark*

*Key words:* endocrine therapy, toremifene, tamoxifen, clinical cross-resistance, advanced breast cancer, antiestrogens

**Summary**

Toremifene (TOR) is a triphenylethylene derivative related to tamoxifen (TAM). TOR has antitumor activity, not dependent on estrogen receptors, and responses with TOR have been observed in patients with progressive disease during TAM-treatment. To elucidate possible cross-resistance between these two antiestrogens, we compared their anti-tumor activity in a randomized, double-blind, cross-over study.

66 postmenopausal women with advanced estrogen receptor positive or unknown breast cancer and a median age of 63 years (range 38–82) were included. Patients were randomized to TAM 40mg/day or TOR 240mg/day. Treatment continued until progressive disease, when cross-over to the alternative treatment was done. The response rate with first line TOR was 29% (95% confidence limits 10–41%) and with TAM 42% (95% confidence limits 25–61%). Response rates and response durations, survival and toxicity were not significantly different between the two treatments. 44 patients progressing on first line TAM or TOR were evaluable for second line TOR or TAM treatment. As no responses were observed, the possibility of overlooking a response rate of 20% or more is less than 1%.

In conclusion, this study strongly indicates that TOR and TAM are clinically cross-resistant in patients with advanced breast cancer.

## Introduction

Toremifene (TOR) is a triphenylethylene derivative related to tamoxifen (TAM). TOR has a high affinity for the estrogen receptor (ER) in breast cancer tissue and is active against the MCF-7 breast cancer cell line [1]. Furthermore, TOR inhibits the growth of rat mammary carcinomas induced by dimethylbenzanthracene and causes regression of such tumors [2]. TOR appears to have less estrogenic effect than TAM at equivalent antiestrogenic doses [1]. In ER-negative murine uterine sarcomas, high doses of TOR (100 and 200mg/kg) had cytotoxic activity, an effect not observed with high doses of TAM [2]. It has been proposed that this is independent of ERs and mediated by specific antiestrogen binding sites [2] or by stimulation of transforming growth factor beta-1 [3].

In phase I studies, TOR has been well tolerated in doses up to 460mg/day [1, 4]. In phase II trials in-

*Address for offprints:* L.E. Stenbygaard, Department of Oncology, University of Copenhagen DK-2730, Herlev, Denmark

cluding previously untreated patients with ER-positive advanced breast cancer, response rates between 48 and 68% have been observed [5–8]. These results are comparable to those obtained with TAM.

Anti-tumor activity of TOR has been described in patients previously treated with TAM. Ebbs *et al.* [3] treated 16 patients with locally advanced breast cancer who had progressed on TAM treatment with TOR 200 mg daily. Partial responses were observed in 4 patients with a median duration of 10 months (range 4–11). In another small study, activity of TOR was also observed after progression on TAM-treatment [9].

The dose of TAM has been prospectively tested over a range of 2–100 mg/m$^2$ body surface area twice daily. No clear benefit of using doses higher than 20–40 mg a day was shown [10]. As a few cases of remission have been reported after escalating the daily dose of TAM from 20 to 40 mg [11], we used the 40 mg daily dose. Based on the proposed different mechanisms of action, when TOR is given in high doses compared with low doses, and on the unexpected responses obtained with high-dose TOR in patients previously treated with TAM, we designed a double-blind crossover study to further elucidate whether TOR and TAM are clinically cross-resistant.

## Methods

### *Patients*

Patient inclusion criteria were: histologically verified inoperable primary, metastatic, or recurrent breast cancer, measurable or evaluable disease according to WHO criteria [12], ER-positive (>10 fmol/mg protein) or unknown tumors, at least 6 months since termination of any adjuvant endocrine therapy, a performance status of ≤2 (WHO), and postmenopausal stage defined as: 1) more than one year since last menstruation or 2) surgical or radiation castration or 3) ≥55 years if a hysterectomy had been performed. Patients previously treated with TAM for advanced breast cancer or patients receiving corticosteroids were not eligible.

Patients were randomized to TAM (40 mg orally o.d.) or TOR (120 mg orally b.i.d.). To ensure blinding of the trial, patients receiving TOR were given identical placebo tablets of TAM (and vice versa). Treatment was continued until progressive disease (PD) when patients were crossed over to the alternative treatment.

Clinical examination, tumor measurements, and blood tests (hemoglobin, leukocytes, thrombocytes, sodium, potassium, creatinine, calcium, LDH, alkaline phosphatase, bilirubin, albumin, and ASAT) were done before inclusion and then every 4 weeks. Chest X-rays and X-ray and/or ultrasound of suspicious areas were performed before inclusion and then every 8 weeks or when clinically indicated.

### *Response criteria*

WHO response criteria were applied [12]. Complete response (CR) was defined as disappearance of all evidence of disease for at least 4 weeks. In patients with bone metastases, complete disappearance of all lesions on X-ray was required. The duration of CR was defined as lasting from the day CR was first recorded until the day of PD.

Partial response (PR) was determined by 2 observations not less than 4 weeks apart and required a decrease of 50% or more in total measured tumor size; additionally, no new lesions or increase of ≥25% of any lesion should be observed. In case of bone metastases, decrease in size of lytic lesions or recalcification were considered PR. The duration of PR was defined as lasting from the first day of treatment until PD. No change (NC) was only applied after at least 4 weeks (in case of bone metastases after at least 8 weeks) from start of treatment. PD was defined as appearance of any new lesion or an increase of ≥25% in any existing lesion.

### *Estrogen receptor analysis*

Estrogen receptors were measured biochemically or on paraffin-embedded, formalin-fixed specimens as previously described [13, 14]. In the bio-

chemical analysis, tumors were considered ER-positive when at least 10 fmol/mg cytosol protein were present.

*Ethics*

The study was carried out in accordance with the Helsinki II Declaration and was approved by the Scientific Ethics Committee of Copenhagen County and by The Danish Medical Health Authorities.

*Statistics*

All tests were two-tailed with a significance level of 5%. For comparison between groups, the Mann-Whitney U-test was applied. For overall toxicity, the Chi-square test was used. Survival distributions were estimated by the method of Kaplan and Meier and compared by the log rank test [15].

**Results**

From September 1987 to March 1989, 66 patients were included. One patient was excluded due to adverse reactions and was evaluable for toxicity only, one did not have histologically verified breast cancer, one received irradiation of the only evaluable parameter, and one had previously received TAM for advanced breast cancer, leaving 62 patients evaluable for response to first line treatment.

Patient characteristics are shown in Table 1. Nine patients starting treatment with TOR and 1 starting with TAM had liver metastases ($p = 0.01$). None of the other patient characteristics including performance status showed any statistically significant difference (Mann-Whitney U-test, Chi-square test). As of June 1992, the median observation period was 19 months (range 1–56+).

*Responses*

The response rate with first line TOR was 29%

*Table 1.* Patient characteristics

| | TOR (n = 31) | TAM (n = 31) |
|---|---|---|
| Age (years) median (range) | 64 (42–82) | 61 (38–75) |
| ER positive/unknown | 20/11 | 22/9 |
| Prior treatment | | |
| None | 15 | 14 |
| Adjuvant TAM | 8 | 4 |
| Adjuvant CMF | 2 | 4 |
| Adjuvant CMF+ TAM | 3 | 3 |
| Chemotherapy for advanced disease | 3 | 6 |
| Site of metastases | | |
| Soft tissue | 14 | 18 |
| Lung | 8 | 7 |
| Liver | 9 | 1 |
| Bone | 15 | 13 |
| Number of metastatic sites | | |
| 1 | 15 | 21 |
| 2 | 11 | 7 |
| ≥3 | 5 | 3 |
| Disease free interval (months) | | |
| Median (range) | 28 (0–264) | 33 (0–154) |

C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, TAM = tamoxifen, TOR = toremifene.

*Table 2.* Response rate (%) in 62 patients receiving TAM or TOR for advanced breast cancer

| | CR | PR | NC | PD |
|---|---|---|---|---|
| TOR (n = 31) | 3 | 26 | 23 | 48 |
| TAM (n = 31) | 16 | 26 | 26 | 32 |
| Total (n = 62) | 10 | 26 | 24 | 40 |

TAM = tamoxifen, TOR = toremifene.

(95% confidence limits 10–41%) and with TAM 42% (95% confidence limits 25–61%). The median duration of CR was 18 months (range 4–56+) and for PR 11 months (range 3–26). The combined response rates are shown in Table 2. Five patients are still on-study. Two patients treated with TAM as first line treatment continue in CR after 46+ and 56+ months, respectively. Three patients with PD after first line treatment continue in NC after cross-over to second line treatment, with the following durations of NC: TAM: 24+, 28+ and TOR: 28+ months.

Of the 62 evaluable patients, 7 died within 8 weeks after start of treatment and 4 patients died after more than 8 weeks of first line treatment due to progressive disease. Five patients refused to complete the cross-over. Two patients are still being treated in the first period, leaving 44 patients who have completed the cross-over and are evaluable for response to second line treatment. Of these patients, 21 initially received TOR and crossed over to TAM and 23 initially received TAM and crossed to TOR. Patient characteristics are given in Table 3. Prognostic factors did not differ significantly between the two groups. Seventeen patients receiving TOR after the cross-over (74%) and 11 receiving TAM (52%) were ER-positive ($p = 0.24$, Chi-square test) and three patients in each group had liver metastases. Seven of the 44 patients died due to PD within 8 weeks after the cross-over. No responses were observed (Table 4) in the 37 patients who completed at least 8 weeks treatment after the cross-over. Twelve patients (27%) had NC with a median duration of 6 months (range 2–28(+)); 7 of these patients received TOR, 5 received TAM.

Figure 1 shows survival curves for patients initial-

*Table 3.* Patient characteristics among 44 patients after cross-over from TOR to TAM (or vice versa)

| | Treatment after cross-over | |
|---|---|---|
| | TOR (n = 23) | TAM (n = 21) |
| Age (years) median (range) | 59 (38–75) | 66 (43–82) |
| ER positive/unknown | 17/6 | 11/10 |
| Prior treatment | | |
| Adjuvant TAM | 4 | 3 |
| Adjuvant CMF | 4 | 1 |
| Adjuvant CMF+ TAM | 2 | 1 |
| Chemotherapy for advanced disease | 5 | 1 |
| TAM or TOR as the only previous treatment for advanced disease | 9 | 14 |
| Site of metastases | | |
| Soft tissue | 17 | 11 |
| Lung | 11 | 9 |
| Liver | 3 | 3 |
| Bone | 11 | 13 |
| Number of metastatic sites | | |
| 1 | 11 | 9 |
| 2 | 7 | 7 |
| ≥3 | 5 | 5 |
| Disease free interval (months) | | |
| Median (range) | 34 (0–154) | 28 (0–180) |

C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, TAM = tamoxifen, TOR = toremifene.

ly treated with TAM and TOR, respectively. There was no significant difference between the two treatment groups (p = 0.16).

*Toxicity*

Adverse reactions were few and generally mild. One patient receiving TOR was excluded due to nausea, vomiting, and headache. Overall, 8 patients treated with TOR and 5 with TAM as first line treatment reported one or more adverse reactions consisting of mild to moderate flushing, headache, or nausea. The toxicity was most pronounced during the first months of treatment. None of the patients reported adverse reactions when receiving TAM or TOR as second line treatment.

## Discussion

This study was designed to investigate possible non-cross resistance between TAM and TOR in patients with advanced breast cancer. The combined response rate with first line TOR or TAM was 36% (95% confidence limits 21–46%) and is comparable to other studies with antiestrogens [5, 16]. However, due to the limited number of patients included, the study was not designed to compare TOR and TAM as first line endocrine treatment for metastatic disease.

When this study was planned, no blinded comparative phase III trials with these two antiestrogens had been initiated, and the previously reported response rates were therefore based on open trials [17]. In our blinded cross-over trial, no responses were observed among 21 patients crossing from TOR to TAM, or among 23 crossing from TAM to TOR. This means that the possibility is less than 1% for overlooking a response rate of >20% with TAM or TOR as second line endocrine treatment for metastatic disease [18]. The fact that no responses were observed after cross-over from either of the two first line antiestrogens strongly indicates clinical cross-resistance between TOR and TAM.

*Table 4.* Response rate (%) in 44 patients receiving TOR or TAM as second line endocrine treatment for advanced breast cancer

| | CR | PR | NC | PD |
|---|---|---|---|---|
| TOR (n = 23) | 0 | 0 | 30 | 70 |
| TAM (n = 21) | 0 | 0 | 24 | 76 |
| Total (n = 44) | 0 | 0 | 27 | 73 |

TAM = tamoxifen, TOR = toremifene.

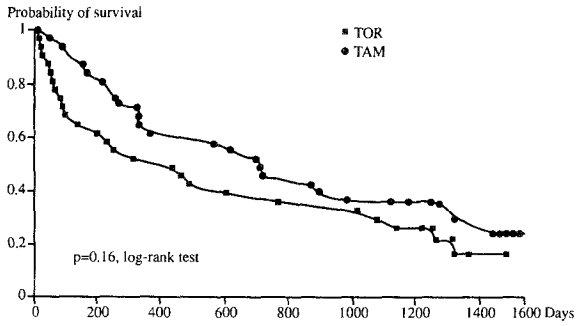


*Fig. 1.* Survival curves (Kaplan-Meier plot) for 31 patients treated with TAM and 31 patients treated with TOR as first line endocrine therapy for advanced breast cancer (p = 0.16).

Among the 22 patients who responded to TOR or TAM as first line endocrine treatment for advanced disease, 15 crossed over to the alternative treatment after PD. In this selected group, no responses were observed with second line treatment, as 8 patients had NC and 7 PD. Our study was initiated based on the proposed different mechanism of action of TOR [2] and the promising results from the study by Ebbs *et al.* [3]. Other studies have also demonstrated a low response rate with TOR, ranging from 0–7%, in patients who 1) did not respond to tamoxifen treatment, or 2) had progressive disease after initial response on TAM, or 3) had progressive disease during adjuvant TAM [15, 19–22]. On the other hand, response to TAM has been reported after re-treatment with TAM following an observation period without treatment [23]. This phenomenon could explain the few responses reported with TOR after PD following TAM treatment.

The (non-significant) difference in the survival curves after first line treatment with TOR and TAM is probably due to the fact that 9 of 10 patients with liver metastases, whom of which 5 died within a few weeks and 16 of 26 with 2 or more metastatic sites

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.