

WJCO 5th Anniversary Special Issues (2): Breast Cancer**Toremifene in the treatment of breast cancer**

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Abstract

Although more widespread screening and routine adjuvant therapy has improved the outcome for breast cancer patients in recent years, there remains considerable scope for improving the efficacy, safety and tolerability of adjuvant therapy in the early stage disease and the treatment of advanced disease. Toremifene is a selective estrogen receptor modifier (SERM) that has been widely used for decades in hormone receptor positive breast cancer both in early and late stage disease. Its efficacy has been well established in nine prospective randomized phase III trials compared to tamoxifen involving more than 5500 patients, as well as in several large uncontrolled and non-randomized studies. Although most studies show therapeutic equivalence between the two SERMs, some show an advantage for toremifene. Several meta-analyses have also confirmed that the efficacy of toremifene is at least as good as that of tamoxifen. In terms of safety and tolerability toremifene is broadly similar to tamoxifen although there is some evidence that toremifene is less likely to cause uterine neoplasms, serious vascular events and

it has a more positive effect on serum lipids than does tamoxifen. Toremifene is therefore effective and safe in the treatment of breast cancer. It provides not only a useful therapeutic alternative to tamoxifen, but may bring specific benefits.

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Key words: Breast cancer; Toremifene; tamoxifen; Adjuvant treatment; Advanced breast cancer

Core tip: Toremifene is safe and effective in the treatment of breast cancer. Toremifene and tamoxifen are equivalently effective in the treatment of breast cancer, although some studies show an advantage for toremifene. Safety and tolerability is also broadly equivalent, although toremifene may cause fewer uterine neoplasms, serious vascular adverse events and has a more beneficial effect on plasma lipids than does tamoxifen.

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INTRODUCTION

Despite improvements in screening and treatment, breast cancer remains a significant cause of morbidity and mortality; accounting for almost one-third of all cancer diagnoses in the US and is second only to lung cancer as a cause of cancer mortality^[1]. Over a million women are diagnosed each year worldwide and almost half a million deaths due to breast cancer are recorded each year^[2]. Whilst incidence rates are considerably higher in developed than in developing countries, survival rates are low in developing countries, probably due to the lack

of screening and systematic use of adjuvant therapy^[2]. Historically low rates of breast cancer in, for example, the Eastern World have shown a rapid increase in recent years^[3,4]. Although typically a disease of later life, breast cancer among younger, pre-menopausal women appears to be more common than in the Western World^[5,6]. Breast cancer among young women, although comprising only around 7% of diagnosed cases, is associated with later presentation, high grade tumors, hormone receptor negativity and human epidermal growth factor receptor 2 (HER2) overexpression; factors that lead to a poorer overall prognosis^[7].

The place of estrogen receptor modifiers (SERMs) in the treatment of breast cancer is now well established. Survival in breast cancer patients in the developed world has increased considerably over the past several decades, due principally to more widespread screening and the systematic use of adjuvant therapy^[8,9]. Whilst adjuvant therapy with SERMs, aromatase inhibitors, cytotoxic agents, monoclonal antibodies and other agents has transformed the outlook for breast cancer patients, there remains considerable unmet need for improvements in both efficacy and tolerability.

Toremifene

The first SERM to be introduced, tamoxifen, provided a revolutionary new treatment option for patients with hormone receptor positive breast cancer. With more than 30 years of experience now available this treatment modality has shown itself to be effective and physicians have learned how to manage its side effects. The mixed agonist/antagonist properties of SERMs define both their therapeutic effects and their undesirable effects. The different structural properties of different SERMs appears to influence their oncogenicity in both laboratory^[10,11] and clinical studies^[12-19].

The structure of toremifene differs from that of tamoxifen in that a chlorine atom replaces one of the hydrogen atoms in the ethyl side chain. This difference may modify the metabolism of toremifene such that the production of DNA adducts may be prevented or reduced compared with tamoxifen^[20,21].

Almost 25 years have elapsed since the first marketing authorization of toremifene and during that time considerable clinical experience has accumulated indicating its efficacy, safety and good tolerability. Indeed, so good was the safety and tolerability that the initially registered dose (60 mg per day) has been widely increased to 240 mg per day.

Toremifene dosage

As shown in Tables 1 and 2 a variety of doses of toremifene are, or have been, in common use. Although some early dose finding studies failed to distinguish between a wide range of doses from 20 mg to 200 mg^[22], 60 mg was chosen as the most appropriate balance between anti-estrogenic effects and tolerability in Phase II studies; significant side effects being observed at the highest

doses tested (680 mg)^[23]. Dose finding and other studies suggested that 60 mg was safe and effective in breast cancer^[24-26] and more effective than 20 mg^[27,28]. However, extrapolation from animal studies suggested that even higher doses would be well tolerated; phase I studies showed that 460 mg daily for five consecutive days was the highest fully tolerated dose^[23]. A conservative approach led to 240 mg being chosen for the high dose formulation. Subsequent phase III clinical trials appear to bear out the enhanced efficacy of the higher dose formulations of toremifene^[29-31].

Randomized studies with toremifene

There have been ten randomized controlled studies comparing toremifene with tamoxifen^[29-38]. Collectively, these studies, which include a total of more than 5500 patients show rather clearly that toremifene is not less effective than tamoxifen. These studies are summarized in Table 1.

Toremifene in advanced breast cancer

An early double-blind, Japanese study in 114 women with advanced or recurrent breast cancer found toremifene 40 mg and tamoxifen 20 mg resulted in similar response rates (26.3% vs 28.1%) and duration of response (155.0 vs 154.5 d)^[39]. However, the time to onset of complete response was significantly shorter with toremifene than with tamoxifen (91 vs 169 d; $P < 0.05$).

A Nordic study compared toremifene 60 mg with tamoxifen 40 mg in 415 postmenopausal women with advanced breast cancer in a double-blind randomized manner^[32]. Response rates were similar in toremifene and tamoxifen groups (31.5% vs 37.3%). Time to treatment failure and median overall survival were also similar.

An open study conducted in Eastern Europe compared toremifene 60 and 240 mg, with tamoxifen 40 mg in 463 postmenopausal women with advanced breast cancer^[31]. Response rates of 20.4% and 20.8% were achieved with toremifene 60 mg and tamoxifen, respectively. Although the response rate with the higher dose of toremifene was slightly higher (28.7%), it did not differ significantly from the other treatments. The findings were similar for time to progression and overall survival, quality of life, as assessed by changes in the Eastern Cooperative Oncology Group (ECOG) scale, was better with toremifene 60 mg than with tamoxifen.

A four-way randomized study was undertaken in 541 women in Russia comparing two doses of toremifene (60 mg and 240 mg) with tamoxifen (20 mg) and letrozole (2.5 mg)^[30]. Objective responses were most frequent in the toremifene 240 mg group (41.5%); objective responses were lower (though not statistically significantly so) in the toremifene 60 mg and letrozole groups (33.0% and 35.4% respectively). The proportion of responses in the tamoxifen group was statistically significantly lower than in the other three treatment groups. Similarly, the median duration of remission was longest in the toremifene 240 mg group (14.5 mo), shortest in the tamoxifen group (9.2 mo) and intermediate in the toremifene 60 mg and

Table 1 Randomized controlled clinical trials

Ref.	Type	Pts	Diagnosis	Receptor status	Follow-up	Treatment	Results
Nomura <i>et al</i> ^[39] , 1993	DB	114 women	Advanced or recurrent breast cancer	NS	NS	RR TOR 40 mg 26.3% TAM 20 mg 28.1%	Time to onset of CR 91 d Duration of efficacy 155 d 169 d (<i>P</i> < 0.05) 154.5 d
Hayes <i>et al</i> ^[29] , 1995	OL	648 post- or peri-menopausal women	Metastatic breast cancer	Positive or unknown	NS	Overall RR TOR 60 mg 50% TOR 200 mg 48% TAM 20 mg 44% (ns)	CR + PR 21% 23% 19% (ns) PFS 5.6 mo 5.6 mo 5.8 mo (ns)
Gershanovich <i>et al</i> ^[31] , 1997	OL	463 post-menopausal women	Advanced breast cancer	Positive or unknown	Median 20.5 mo	RR TOR 60 mg 20.4% TOR 240 mg 28.7% TAM 40 mg 20.8%	PFS 49 61 50
Pyrhonen <i>et al</i> ^[32] , 1997	DB	415 post-menopausal women	Advanced breast cancer	Negative or unknown	Median 20.5 mo	CR+PR TOR 60 mg 31.3% TAM 40 mg 37.3%	TIF 6.3 mo TTP 7.3 mo 10.2 mo Median OS 33 mo 38.7 mo
Holli <i>et al</i> ^[33] , 2000	OL	899 post-menopausal women	Early invasive breast cancer (adjuvant treatment)	Any	Median 3.4 yr	Time to recurrence TOR 40 mg 21.6 mo TAM 20 mg 23.5 mo	Overall recurrence rate 23.1% 26.1% 20.3% 24.3% 20.7% 18.5% 20.7%
Milla-Santos <i>et al</i> ^[34] , 2001	DB	217 women	Advanced breast cancer	Positive	NS	CR (mo) TOR 60 mg 12.2 TAM 40 mg 8.1	PR (mo) 25.4 24.3 SD (mo) 26.4 11.9 15.4 9.2 (ns) 12.3 (ns)
Pagani <i>et al</i> ^[35] , 2004	OL	1035 peri- or post-menopausal women	Lymph node positive breast cancer (adjuvant treatment)	ER positive	5.5 yr	5-yr DFS TOR 60 mg 72% TAM 40 mg 69%	5-yr OS 85% 81%
Zeinalov <i>et al</i> ^[30] , 2006	OL	541 post-menopausal women	Disseminated breast cancer	Positive	NS	CR + PR TAM 20 mg 25.6% (<i>P</i> < 0.05 compared with three other treatments) TOR 60 mg 33.0% TOR 240 mg 41.5% LTZ 2.5 mg 35.4%	Median duration of remission 9.2 mo 11.3 mo 14.5 mo 13.1 mo
Lewis <i>et al</i> ^[36] , 2010	OL	1813 peri- or post-menopausal women	Stage I or II Early primary invasive breast cancer (adjuvant treatment)	Positive	Median 59 mo	5-Yr DFS TOR 60 mg 91.2% TAM 20 mg 91.2%	
Kimura <i>et al</i> ^[37] , 2012	OL	253 post-menopausal women	Early phase breast cancer (adjuvant treatment)	Positive or unknown	Median 66.5 mo	5-yr survival TOR 40 mg 97% TAM 20 mg 96.7%	Cumulative OS 97.5% 97.3% 90.6%
Yamamoto <i>et al</i> ^[38] , 2013	OL	91 post-menopausal women	Advanced, Non-steroidal aromatase inhibitor resistant in metastatic breast cancer	Positive	Median 16.9 mo	CB TOR 120 mg 41.3% Exemestane 25 mg 26.7% (ns)	ORR 10.80% 2.2% (ns) PFS 7.3 mo 3.7 mo OS 32.3 mo 12.9 mo (<i>P</i> = 0.045) (ns)

DB: Double blind; CR: Complete response; PR: Partial response; SD: Stable disease; LSD: Long stable disease; TOR: Toremifene; TAM: Tamoxifen; DFS: Disease-free survival; OS: Overall survival; (O)RR: (Objective) response rate; CB: Clinical benefit; DFS: Disease-free survival; PFS: Progression-free survival; R: Randomized; OL: Open label; UC: Uncontrolled; RA: Retrospective analysis; CC: Case control; Pr: Prospective; CS: Cohort study; AIU: Aromatase inhibitor; TTP: Time to progression.

Table 2 Non-randomized clinical trials (case reports or series with fewer than 10 patients excluded)

Ref.	Pts	Study type	Diagnosis	Treatment	CR + PR	SD > 6 mo	Results	Results	Results	Results
Asaishi <i>et al</i> ^[68] , 1993	51 women	Not stated	Advanced breast cancer refractory to TAM	TOR 120 mg	11.8%	15.7%	Median duration of response 127 d	Median duration of SD > 6 mo 238.5 d		
Gams <i>et al</i> ^[69] , 2002	102 women peri- or postmenopausal women	Pr	Advanced breast cancer refractory to TAM	TOR 200 mg	5% (TTF 10.9 mo)		SD 23% (TTF 7.8 mo)			
Pyrhönen <i>et al</i> ^[70] , 1994	50 Women	Pr	Advanced breast cancer refractory to TAM	TOR 240 mg	4%		Mixed response 6%	SD 18% < 5 mo 26% > 5 mo		
Hietanne <i>et al</i> ^[71] , 1997	73 postmenopausal women	Pr	Advanced breast cancer	TOR 240 mg	OR (CR + PR) 59%	NC 29%	PD 12%			
Yamamoto <i>et al</i> ^[72] , 2005	10 Women	RA	Metastatic breast cancer	TOR 120 mg	OR 30%	CB 70%	Media TTP 9 mo	Median OS 21.5 mo		
Ohtake <i>et al</i> ^[73] , 2009	12 postmenopausal women who had failed AI therapy	RA	Advanced/recurrent breast cancer	TOR 120 mg	CR 16.70%	CB 58.30%	Mean TTP 33.8 wk			
Okita <i>et al</i> ^[74] , 2009	15 women	Pr	Metastatic breast cancer	TOR 120 mg Paclitaxel 80 mg/m ² on 5 d	CR 0%	PR 6.7%	No change 66.7%,	Stable > 6 mo 26.7%	PD 26.7%	Mean TTF 2.7 mo
Koyama <i>et al</i> ^[75] , 2011	19 postmenopausal women	RA	Advanced or metastatic breast cancer	TOR 120 mg	OR 36.8% (1 CR, 6 PR 6)	CB 47.4%				
Gu <i>et al</i> ^[40] , 2012	810 premenopausal women	RA	Early invasive breast cancer (adjuvant treatment)	TOR 60 mg TAM 20 mg	5-yr OS 100% 98.4 (ns)%	DFS 97.2% 90.4% (P = 0.022)				
Sawaki <i>et al</i> ^[76] , 2012	13 postmenopausal women	Pr	Adjuvant aromatase inhibitor resistant metastatic breast cancer	TOR 120 mg	CR 7.7%	SD 53.8%	PD 38.5%	CB 46.2%	PFS 5.9 mo	
Tokura <i>et al</i> ^[77] , 2012	18 women	Pr	Advanced/recurrent breast cancer	TOR 120 mg	CB 58% (5 PR, 5 long SD)	PD 22%	Media PFS 5.5 mo			
Koike <i>et al</i> ^[78] , 2013	21	Pr	Recurrent or metastatic breast cancer	TOR 120 mg	CR (12 wk) 0%	PR/SD (12 wk) 21.1%/47.4%				
Ogata <i>et al</i> ^[79] , 2013	23 women	Pr	Recurrent breast cancer who were receiving or had received adjuvant aromatase inhibitor therapy	TOR 120 mg	PR 13%	SD 62%	CB 78.30%	Median TTP 8.1 mo		
Qin <i>et al</i> ^[41] , 2013	1847 premenopausal women	RA	Operable breast cancer (adjuvant treatment)	TOR 60 mg TAM 20 mg	DFS 10.3 yr 10.3 yr	5-Yr DFS 87% 85%	5-Yr OS 94.3% 93.5%			

DB: Double blind; CR: Complete response; PR: Partial response; SD: Stable disease; LSD: Long stable disease; TOR: Toremifene; TAM: Tamoxifen; DFS: Disease-free survival; OS: Overall survival; (O)RR: (Objective) response rate; CB: Clinical benefit; DFS: Disease-free survival; PFS: Progression-free survival; R: Randomized; OL: Open label; UC: Uncontrolled; RA: Retrospective analysis; CC: Case control; Pr: Prospective; CS: Cohort study; AIU: Aromatase inhibitor; TTP: Time to progression.

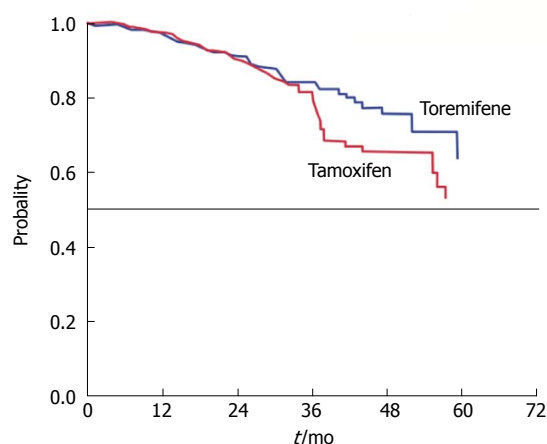


Figure 1 Time from randomization to recurrence in estrogen-receptor positive invasive breast cancer patients receiving adjuvant toremifene or tamoxifen^[33].

letrozole groups (11.3 and 13.1 mo, respectively), the difference between tamoxifen and the other treatments was statistically significant.

Another open study, carried out in the United States, compared toremifene 60 mg and 200 mg with tamoxifen 20 mg in 648 post- or peri-menopausal women with metastatic breast cancer^[30]. As in the previous studies, there were no significant differences between the treatments with regard to response rates (21%, 23% and 19% with toremifene 60 mg, toremifene 200 mg and tamoxifen, respectively), time to progression, response duration or overall survival. There was again a suggestion that the 60 mg dose of toremifene resulted in the greatest improvement in quality of life, although the differences were not statistically significant. Compared with tamoxifen, more patients given toremifene 60 mg reported an improvement in enjoyment of life, pain and mood.

A Spanish double-blind, randomized study in 217 postmenopausal women with advanced breast cancer reported a somewhat higher response rate with toremifene 60 mg than with tamoxifen 40 mg (64% vs 52%), although the difference did not achieve statistical significance^[34]. Time to progression and overall survival rates were similar in the two groups.

The most recent randomized study reported in 2013 and compared toremifene 120 mg with the aromatase inhibitor exemestane in 91 post-menopausal women with non-steroidal aromatase inhibitor-resistant breast cancer^[37]. After a median 16.9 mo follow-up there were advantages for toremifene over exemestane in clinical benefit [41.3% vs 26.7% respectively (ns)], objective response rate [10.8% vs 2.2% respectively (ns)], progression-free survival (7.3 mo vs 3.7 mo respectively; $P = 0.045$) and overall survival [32.3 vs 21.9 mo respectively (ns)].

Toremifene in early stage breast cancer

The International Breast Cancer Study group combined the results from two studies with almost identical protocols in which a total of 1035 peri- or post-menopausal

women with breast cancer received either toremifene 60 mg or tamoxifen 40 mg^[31]. In common with other similar studies the efficacy of toremifene and tamoxifen were approximately equal; 5-year disease-free survival was 72% and 69% respectively and 5-year overall survival was 85% and 81%. Likewise, in an even larger randomized study in [North American Fareston vs Tamoxifen Adjuvant (NAFTA) trial] 1813 peri- or post- menopausal women with invasive breast cancer toremifene 60 mg and tamoxifen 20 performed similarly (5-year disease-free survival 92.2% in both groups)

After a median follow-up of 3.4 years a Finnish study found a number of efficacy parameters showing advantages for toremifene compared with tamoxifen, although none achieved statistical significance. Overall, time to recurrence, recurrence rate, recurrence at distant sites and the number of patients dying during follow-up were similar in toremifene- and tamoxifen- treated patients. Although the Kaplan-Meier analysis of the time to recurrence or the time to progression or disease free survival in this study (Figure 1) appears to show a separation between toremifene and tamoxifen from 3 years onwards, the difference is not statistically significant (hazard ratio toremifene:tamoxifen 0.88 (95%CI: 0.70-1.09)). The respective 5-year survival rates were 70.3% vs 65.6% (also not statistically significantly different)^[33].

Whilst most randomized controlled studies of toremifene have been performed in patients with advanced or metastatic disease, another small study has been undertaken in an adjuvant setting in women with early stage breast cancer; 91 post-menopausal women with early stage, lymph node negative breast cancer were randomized to adjuvant treatment with toremifene 120 mg or tamoxifen 20 mg^[36]. Five-year survival (97% and 96.7% respectively), cumulative disease-free survival (97.5% and 97.3% respectively) and cumulative disease-free survival (88.5% and 90.6% respectively) were very similar between the two groups after 66.5 mo follow-up.

Non-randomized trials

Whilst there are at least 14 published non-randomized studies of toremifene in advanced breast cancer many include rather few patients or have imperfect methodologies. However, there are two recent retrospective studies that merit further description

The study of Gu *et al*^[40] reviewed the records of 810 women with early invasive breast cancer and identified 240 eligible patients who had received tamoxifen and 212 who had received toremifene. Following median follow-up times of 50.8 mo, although 5-year overall survival rates were similar (100% for toremifene and 98.4% for tamoxifen), recurrence-free survival was significantly longer in the toremifene group than in the tamoxifen (97.2% and 90.4% respectively, $P = 0.022$).

Another retrospective study, this time including 1847 pre-menopausal women who had undergone surgery followed by chemotherapy toremifene or tamoxifen similarly found no significant differences between the

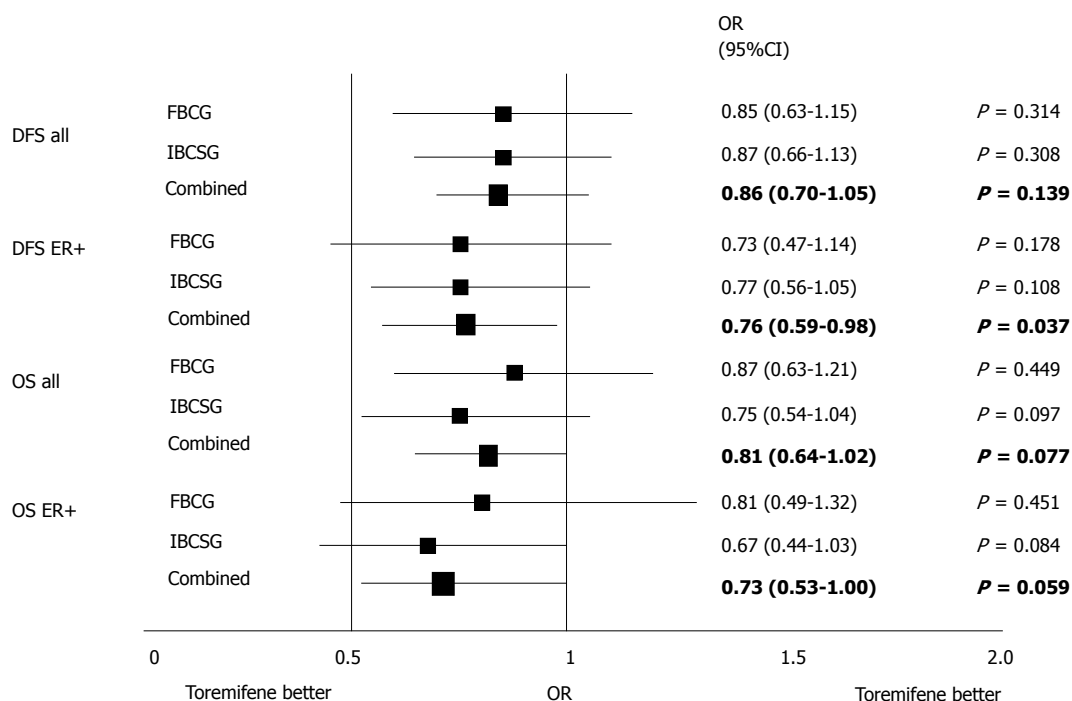


Figure 2 Disease-free survival and overall survival in patients receiving adjuvant toremifene and tamoxifen: meta-analysis of the Finnish Breast Cancer Group^[30] and International Breast Cancer Study Group^[34] (data on file). DFS: Disease-free survival; OS: Overall survival; IBCSG: International Breast Cancer Study Group; FBCG: Finnish Breast Cancer Group.

treatments^[41]. All survival figures were identical between toremifene and tamoxifen; disease-free survival (10.3 years in both groups). Five-year disease-free survival (87% *vs* 85%, respectively) and 5-year overall survival (94.3% *vs* 93.5%, respectively)

META-ANALYSES

Whilst individual clinical trials can provide invaluable data on the efficacy of a medication in restricted populations, meta-analysis can provide information about more generalized patient populations and increase statistical power. The randomized clinical trials described above have been the subject of several meta-analyses. The earliest combined two randomized studies comparing toremifene (200 or 240 mg) and tamoxifen (20 or 40 mg) and included a total of 733 patients with advanced breast cancer^[42]. Response rates were higher in toremifene patients than in tamoxifen patients (25.2% *vs* 19.8%), but not statistically significantly ($P = 0.87$). Disease progression and survival also showed no statistically significant differences between toremifene and tamoxifen.

A subsequent meta-analysis in 1999 included results from the five randomized studies completed to that date^[43]. This meta-analysis represented 1421 postmenopausal patients with previously untreated, locally advanced or metastatic breast cancer that were treated with either toremifene 40-60 mg ($n = 725$) or tamoxifen 20-40 mg ($n = 696$). As in the previous meta-analysis toremifene and tamoxifen proved to be broadly equivalent in terms of response rate (24.0% *vs* 25.3%, respectively),

time to treatment failure (4.9 *vs* 5.3 mo) and survival (31.0 *vs* 33.1 mo).

Another meta-analysis has been performed on the disease-free and overall survival findings from two pivotal randomized studies comparing toremifene and tamoxifen in an early breast cancer^[31,33] (data on file, Orion). As shown in Figure 2, there are indications that toremifene may be superior to tamoxifen, most notably in estrogen-receptor-positive patients. In this subgroup of patients the combined data showed a significant ($P = 0.037$) benefit for toremifene with regard to disease-free survival, although the difference with regard to overall survival did not achieve statistical significance ($P = 0.059$).

A more recent meta-analysis using somewhat more restrictive criteria for inclusion analyzed three eligible randomized comparisons with tamoxifen^[44]. However, the overall results were similar in that no significant differences in efficacy between toremifene and tamoxifen were identified with risk ratios close to unity for overall survival and disease-free survival.

A recent meta-analysis identified 23 randomized clinical trials comparing toremifene with tamoxifen involving a total of 7242 patients with breast cancer^[45]. This large study found that although for most efficacy parameters there were no significant differences between toremifene and tamoxifen, toremifene was significantly more effective in terms of 5-year survival [odds ratio (OR) 1.25; 95%CI: 1.04-1.50] among patients with early stage breast cancer.

A Cochrane review on toremifene *vs* tamoxifen for advanced breast cancer compared randomized controlled comparisons providing data on objective response rate,

Table 3 Incidence of adverse events among 1847 women with invasive breast cancer treated with tamoxifen or toremifene^[41]

Adverse event	Adverse event incidence (%)		P value
	Tamoxifen (n = 1451)	Toremifene (n = 396)	
Flushing	480 (33.1)	39 (35.1)	0.450
Sweating	295 (20.3)	82 (20.7)	0.869
Nausea or vomiting	213 (14.7)	57 (14.4)	0.881
Fatigue	74 (5.1)	18 (4.5)	0.653
Insomnia	62 (4.3)	14 (3.5)	0.513
Dizziness	14 (1.0)	6 (1.5)	0.408
Dry eyes	60 (4.1)	17 (4.3)	1
Blurred vision	40 (2.8)	9 (2.3)	0.595
Cataracts	7 (0.5)	2 (0.5)	1
Weight gain	68 (4.7)	17 (4.3)	0.740
Vaginal discharge	241 (16.6)	69 (17.4)	0.701
Irregular menses	145 (10)	25 (6.3)	0.025
Endometrial cancer	1 (0.1)	0 (0)	0.601
Ovarian cyst	20 (1.4)	4 (1.0)	0.631
Thromboembolic events	22 (1.5)	5 (1.3)	0.709
Hypertriglyceridemia	76 (5.2)	19 (4.8)	0.725
Hyper-LDL cholesterolemia	65 (4.5)	16 (4.0)	0.783
Fatty liver	64 (4.4)	13 (3.3)	0.320
Elevated ast	59 (4.1)	15 (3.8)	0.802
Elevated alp	33 (2.3)	7 (1.8)	0.571
Hepatic cyst	29 (2.0)	6 (1.5)	0.550
Bilirubin	27 (1.9)	8 (2.0)	1

Table 4 Frequency of subjective adverse events among 499 patients with invasive breast cancer randomised to adjuvant toremifene or tamoxifen therapy^[33]

	Toremifene		Tamoxifen	
	Number of patients	%	Number of patients	%
Sweating	247	53.8	225	51.1
Hot flashes	237	51.6	209	47.5
Vaginal discharge	193	42.0	156	35.5
Vaginal dryness	120	26.1	117	26.6
Itching	118	25.7	119	27.0
Depression	112	24.4	119	27.0
Rash	90	19.6	75	17.0
Nausea	78	17.0	85	19.3
Vaginal bleeding	40	8.7	37	8.4
Diarrhea	37	8.1	51	11.6
Weight increase	23	5.0	19	4.3

time to progression and overall survival^[46].

The review identified 2061 patients from seven studies (1226 patients received toremifene and 835 patients received tamoxifen). The pooled risk ratio for the objective risk ratio was 1.02 suggesting that there was no statistically significant difference between toremifene and tamoxifen [objective risk ratios (ORR) were 25.8% vs 26.9%, respectively]. Similarly the hazard ratio for time to progression was 1.08, again, implying no statistically significant difference between toremifene and tamoxifen (time to progression 6.1 mo and 5.8 mo respectively). Overall survival also showed equivalence between the two medications [hazard ratio (HR) 1.02; overall survival 27.8 mo and 27.6 mo, respectively]. The authors conclude that toremifene and tamoxifen are equally effective in the first-line treatment of patients with advanced breast cancer.

The results of the randomized clinical trials are remarkably consistent and supported by both meta-analyses and retrospective studies; toremifene is at least as effective as tamoxifen in the treatment of breast cancer. Rather few studies find significant differences between the two SERMS, those that do differentiate between the two treatments find significant differences in favor of toremifene^[31,37,38]. None find significant advantages for tamoxifen.

Safety and tolerability

Toremifene and tamoxifen have similar adverse event profiles and are well tolerated, both in women with advanced breast cancer and in those receiving adjuvant therapy. Hot flushes, sweating, nausea and vaginal dis-

charge are among the most common adverse effects and serious adverse events are rare.

A large retrospective analysis of 1847 breast cancer patients treated with toremifene or tamoxifen showed the expected pattern of adverse events with sweating and nausea/vomiting as the most common undesirable effects (Table 3). Although the great majority of adverse effects occurred at similar rates in toremifene- and tamoxifen-treated patients, irregular menses were significantly more common in the tamoxifen group (10% vs 6.3%, $P = 0.025$)^[40].

In the largest randomized study comparing tamoxifen and toremifene there were few differences in thromboembolic, gynecological and ocular adverse events between the two treatment groups. Fever and chills were significantly more common among tamoxifen-treated patients^[35].

A safety analysis in the Finnish Breast Cancer Study Group data also illustrates the similar tolerability and safety profiles of toremifene; sweating and hot flashes being observed in more than half of the patients, followed by vaginal dryness and discharge with itching and depression observed in more than 20% of patients^[32]. (Table 4) In no case were significant differences between toremifene and tamoxifen observed. There was similarly little difference in the incidence or pattern of serious adverse events between toremifene and tamoxifen (Table 5).

The above described studies were conducted with the low dose toremifene (60 mg), however high dose toremifene 200 or 240 mg is not associated with a significantly increased incidence, or different profile, of adverse events compared with the 60 mg dose^[30,31]. For example, in a randomized study that involved 648 women with metastatic breast cancer, with the exception of a slightly greater incidence of nausea in the high dose group, the incidence of the most common side effects was similar with toremifene 60 mg and 200 mg^[30]. Similarly, there were no significant differences between the incidence of side effects with toremifene 60 mg and 240 mg in a randomized study of 463 women with advanced breast can-

Table 5 Frequency of serious adverse events among 499 patients with invasive breast cancer randomised to adjuvant toremifene or tamoxifen therapy^[33]

	Toremifene		Tamoxifen	
	Number of patients	%	Number of patients	%
Serious adverse events	72	15.7	74	16.8
Cardiac events	9	2.0	6	1.4
Myocardial infarctions	7	1.5	5	1.1
Angina pectoris	2	0.4	1	0.2
Thromboembolic events	16	3.5	26	5.9
Pulmonary embolisms	3	0.7	3	0.7
Deep vein thrombosis	8	1.7	11	2.5
Cerebrovascular events	5	1.1	12	2.7
Endometrial events	17	3.7	19	4.3
Polyps	8	1.7	7	1.6
Hemorrhage	2	0.4	3	0.7
Disorders	7	1.5	9	2.0
Subsequent cancers	12	2.6	8	1.8
Breast	3	0.7	1	0.2
Uterine			2	0.5
Gastrointestinal	3	0.7	1	0.2
Other	6	1.3	4	0.2
Cataracts	3	0.7	8	1.8
Increased liver enzyme levels	2	0.4	2	0.5
Bone fractures	13	2.8	5	1.1
Osteoporotic	2	0.4	3	0.7

cer^[31]. In a pooled-analysis of two studies involving 733 women with advanced breast cancer^[41], high-dose toremifene 200 or 240 mg was tolerated as well as tamoxifen 20 or 40 mg.

In a meta-analysis of five studies significantly more tamoxifen- than toremifene-treated patients discontinued treatment prematurely (19.6% *vs* 13.7%; *P* = 0.007), predominantly due to greater non-compliance and protocol violations in the tamoxifen group^[42]. Not every study shows identical tolerability; in the Nordic study^[32], the percentage of patients discontinuing treatment prematurely was significantly lower with toremifene than with tamoxifen (14% *vs* 20% respectively; *P* = 0.011), mainly due to fewer adverse events/patients' refusals, loss to follow-up and deaths.

The recent meta-analysis of Chi *et al*^[45] however, showed that compared with tamoxifen, toremifene was associated with more vaginal discharge in patients with early stage breast cancer and more vaginal bleeding in patients with advanced disease, although the both drugs had a similar overall effect on quality of life.

Lipids

As the long-term prognosis for breast cancer patients improve, increasing attention has been focused on continuing quality of life and morbidity from other causes. This is particularly important when SERMs are used in an adjuvant setting in early-stage breast cancer where the probability of long-term survival is high. In this context, an attractive property of SERMs is their ability to improve cardiovascular risk factors. Toremifene reduces

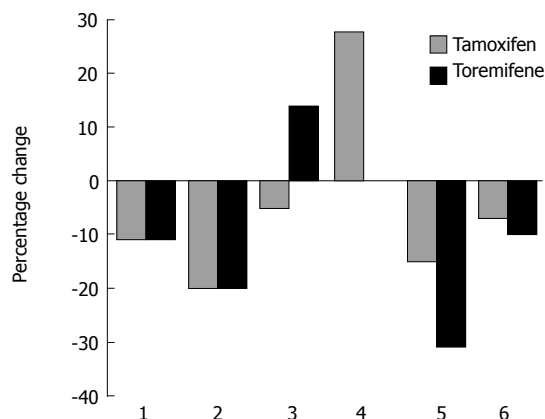


Figure 3 Percentage change in lipid parameters after one year with toremifene and tamoxifen^[47]. 1: Total cholesterol; 2: low-density lipoprotein (LDL) cholesterol; 3: high-density lipoprotein (HDL) cholesterol; 4: Triglycerides; 5: LDL:HDL; 6: Apo lipoprotein-B.

both total and low-density lipoprotein (LDL) cholesterol and increases high-density lipoprotein (HDL) cholesterol (Figure 3)^[47-50]. Particularly persuasive are the results from a crossover trial in which 197 women receiving adjuvant therapy with toremifene or tamoxifen were monitored for lipid levels^[51]. After one year of treatment the total cholesterol had decreased in both groups, but HDL-cholesterol increased only in the toremifene group (*P* < 0.001); indeed, HDL cholesterol significantly decreased in the tamoxifen-treated patients (*P* < 0.001). After one year of therapy patients who still had abnormal lipid levels were switched to the other medication. In patients switched from tamoxifen to toremifene total- and HDL-cholesterol increased and triglycerides decreased to pre-treatment levels whilst in the patients switched from toremifene to tamoxifen total cholesterol decreased and triglycerides increased. The authors conclude that the lipid profile changes associated with toremifene are better than those associated with tamoxifen^[50]. This finding was supported by the results of a recent meta-analysis of 23 clinical trials in which toremifene and tamoxifen were compared^[44]. In an early stage breast cancer patients' triglyceride levels were reduced more and HDL-cholesterol levels increased more by toremifene than by tamoxifen, although tamoxifen was more effective in reducing LDL-cholesterol. In patients with advanced disease toremifene also reduced triglyceride levels more than tamoxifen. Similar beneficial changes have also been reported from an extended randomized controlled investigation of the effects of toremifene *vs* the aromatase inhibitor anastrozole on lipid profile^[52].

The evidence seems rather clear that the effect of toremifene on patients' lipid profile is generally positive and better than that of the comparator treatments so far investigated.

Bone mineral density in breast cancer patients

Toremifene improves bone mineral density (BMD) and helps prevent osteoporosis in postmenopausal breast cancer patients. These effects are similar to those of

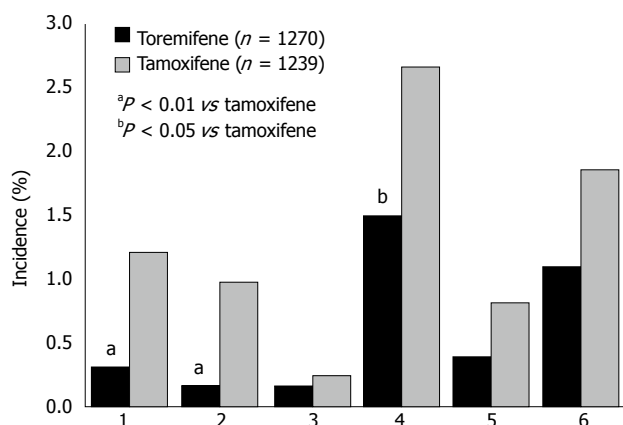


Figure 4 Incidence of serious vascular events in patients randomized to toremifene or tamoxifen adjuvant therapy in post-menopausal women^[17]. 1: Total cerebrovascular events; 2: Stroke; 3: Transient ischaemic attack; 4: Total thromboembolic events; 5: Pulmonary embolism; 6: Deep vein thrombosis.

tamoxifen. Comparative studies have shown that both toremifene and tamoxifen prevent reductions in BMD in the lumbar spine and proximal femur, and that these effects are reflected by changes in a wide range of bone biochemistry markers such as pyridinoline, deoxypyridinoline and urinary cross-linked aminoterminal telopeptide of type I collagen^[53-55]. Toremifene and tamoxifen have also been used successfully in combination with the bisphosphonate clodronate, with no significant differences between them^[56,57].

Some beneficial effects on BMD have been observed in premenopausal women at high risk for developing breast cancer taking toremifene 60 mg as chemoprevention, therefore making an attractive alternative to tamoxifen. A double-blind, placebo-controlled pilot study in 259 healthy premenopausal and postmenopausal women at high risk for breast cancer found a trend for a sustained increase in lumbar spine BMD after one year of toremifene therapy in premenopausal women^[58].

LONG TERM SAFETY

The long-term safety profile of toremifene was evaluated in detail in a review of all preclinical and clinical safety data from 1978 to 2004 and comparative clinical safety data between October 1995 and the end of 2004^[59]. At the time of this review, information was available from more than 350000 patient treatment years. The evidence indicated that toremifene has good long-term safety, with a lower incidence of endometrial cancer, stroke, pulmonary embolism, deep vein thrombosis and cataracts than tamoxifen.

A 3-year study specifically designed to compare the gynecological effects of toremifene 40 mg and tamoxifen 20 mg in 167 postmenopausal breast cancer patients showed that the incidence of proliferative endometrium was increased to a significantly ($P < 0.0001$) lesser extent by toremifene (from 20.0% to 32.2%) than by tamoxifen (from 20.4% to 46.8%)^[60].

Endometrial cancer

The finding that tamoxifen at high doses caused liver tumors in rats^[61] raised concern that it may be mutagenic in humans. The mechanism of this effect in laboratory animals was believed to be due to DNA adduct formation by metabolites of tamoxifen, although this has more recently been questioned^[62]. Nevertheless, endometrial cancer rates are increased in women taking tamoxifen^[13]. The chlorine substitution in the structure of toremifene alters its metabolism such that DNA adducts are much less likely to form^[13,63-66] and a case-control study based on records of 38000 Finnish breast cancer patients appears to suggest that toremifene is considerably less frequently associated with endometrial cancer than is tamoxifen [OR 2.9, 95%CI: 0.3-3.9 *vs* 0.9, 95%CI: 0.3-3.9]^[17]. However, a recent meta-analysis of studies involving a total of 7242 patients with early or advanced breast cancer found no difference in the number of endometrial cancers between patients treated with toremifene or tamoxifen, although the follow-up was relatively short in the majority of studies. There is clearly still much to be discovered concerning the oncogenicity of SERMs, but both laboratory and clinical evidence suggests an advantage for toremifene over tamoxifen in this regard.

Thromboembolic effects

A retrospective analysis of the serious vascular events reported in the manufacturer's Drug Safety Database^[67] revealed that cerebrovascular and thromboembolic events overall were significantly higher in tamoxifen than in toremifene-treated patients (Figure 4).

Other evidence suggests that toremifene may be associated with a lower risk of such thromboembolic events^[59]. A retrospective analysis of adjuvant treatment trials with toremifene 40 or 60 mg and tamoxifen 20 mg in more than 2500 postmenopausal women revealed a significantly lower incidence of ischemic stroke, total cerebrovascular events and total thromboembolic events with toremifene compared with tamoxifen.

DISCUSSION

For obvious ethical reasons the great majority of randomized clinical trials of toremifene have been undertaken with tamoxifen as the comparator, rather than placebo. The results of these studies, and the several meta-analyses that are based upon them, appear to characterize toremifene as being at least as effective as tamoxifen in the treatment of breast cancer both in the adjuvant setting and in patients with advanced and metastatic disease. Of the ten randomized controlled trials described in Table 1 all found toremifene to be at least as effective as tamoxifen. In some studies and for some parameters there was a statistically significant advantage for toremifene over tamoxifen; a shorter time to onset of complete response in Nomura *et al*^[39] 1993, a higher rate of objective response in Zejnalov *et al*^[30] 2006 and a longer progression-free survival in Yamamoto *et al*^[38] 2013. There

were no statistically significant efficacy advantages for tamoxifen in these studies. However, whilst it is tempting to claim at least a trend for better efficacy for toremifene, some statistically significant differences are likely to arise by chance when a large number of parameters are compared in several studies (68 individual parameters are represented in Table 1 far more were examined in the studies cited). So far as the efficacy of toremifene is concerned, the conclusion is that it is at least as effective as tamoxifen is reasonable seems conservative and reasonable. In addition, toremifene has been the subject of a number of meta-analyses using different criteria for inclusion of studies and all have come to the same conclusion that the efficacy of toremifene and tamoxifen are not statistically significantly different.

Modern hormonal treatment for breast cancer emphasizes continuing therapy with an anti-estrogen, or an anti-estrogen followed by a switch to an aromatase inhibitor after longer or shorter periods. Whilst toremifene appears to behave similarly to tamoxifen, there is a relative dearth of information on its use in these switch or extended adjuvant contexts.

So far as safety and tolerability are concerned, the simple substitution of a chlorine atom for a hydrogen atom appears to make a considerable difference. The altered pattern of metabolite formation with its strongly reduced DNA adduct formation is reflected in a lower incidence of endometrial cancer—a recent meta-analysis of studies involving a total of 7242 patients with early or advanced breast cancer found no difference in the number of endometrial cancers between patients treated with toremifene or tamoxifen, although the follow-up was relatively short in the majority of studies^[44]. On the other hand, the pattern of serum lipids is more favorably affected by toremifene with lower triglycerides, and an improved HDL/total cholesterol ratio. Thromboembolic events also show benefits in favor of toremifene. Overall, toremifene is well tolerated and the pattern of adverse events reported in clinical trials is rather similar between the two SERMs.

Taken together, the findings of clinical trials, meta-analyses and studies on specific aspects of the pharmacology of toremifene suggest that it is an effective and well tolerated agent for the treatment of early and advanced breast cancer. In comparison with tamoxifen, toremifene is at least as effective in all therapeutic contexts so far investigated and may have tolerability and safety advantages.

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