available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Postoperative adjuvant chemotherapy followed by adjuvant tamoxifen *versus* nil for patients with operable breast cancer: A randomised phase III trial of the European Organisation for Research and Treatment of Cancer Breast Group

Leilani Morales[a], *Peter Canney*[b], *Jaroslaw Dyczka*[c], *Emiel Rutgers*[d], *Robert Coleman*[e], *Tanja Cufer*[f], *Marzena Welnicka-Jaskiewicz*[g], *Johan Nortier*[h], *Jan Bogaerts*[i], *Patrick Therasse*[i], *Robert Paridaens*[a,*]

[a]*University Hospital Gasthuisberg, Leuven, Belgium*
[b]*Beatson Oncology Centre, Glasgow, Scotland on behalf of all the investigators of the Scottish Breast Cancer Trials Group*
[c]*Institute of Oncology, Medical Academy of Lodz, Lodz, Poland*
[d]*Antoni Van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands*
[e]*Weston Park Hospital, Sheffield, UK*
[f]*Institute of Oncology, Ljubljana, Slovenia*
[g]*Medical University of Gdansk, Gdansk, Poland*
[h]*Leiden University Medical Center, Leiden, The Netherlands*
[i]*EORTC Data Center, Brussels, Belgium*

ARTICLE INFO

Article history:
Received 12 October 2006
Accepted 17 October 2006
Available online 28 November 2006

Keywords:
Adjuvant
Chemotherapy
Early breast cancer
Endocrine therapy
Tamoxifen

ABSTRACT

Background: The contribution of adjuvant tamoxifen in breast cancer patients after receiving adjuvant chemotherapy is not fully established. We investigated the impact of tamoxifen, given sequentially after completion of adjuvant chemotherapy in patients with operable breast cancer.

Patients and methods: Between March 1991 and June 1999, 1863 women with stages I–IIIA operable breast cancer who had undergone surgery and completed six cycles of adjuvant combination chemotherapy with either CMF, CAF, CEF, FAC or FEC were randomised to receive either tamoxifen 20 mg daily for 3 years or no further treatment. Irrespective of menstrual status and hormone receptor content of the primary tumour, patients were stratified by institute, chemotherapy scheme and age (above 50 years or younger). The main end-point was to detect a 5% increase in the 5 year survival (from 80% to 85%) in favour of antioestrogen therapy. Secondary end-points were relapse free survival (RFS), local control, incidence of second primary breast cancer and correlation of results with hormone receptor content.

Results: After exclusion of all patients from three sites because of inadequate documentation, a total of 1724 patients (93%) were analysed (Tam 861 and Control 863). At a median follow-up of 6.5 years, 5-year RFS on tamoxifen was 73% *versus* 67% in controls ($p = 0.035$). No difference was seen in overall survival. The benefit of tamoxifen therapy

* *Corresponding author:* Present address: Department of General Medical Oncology, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 34 69 00; fax: +32 16 34 69 01.
E-mail address: Robert.Paridaens@uz.kuleuven.ac.be (R. Paridaens).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.10.009

was mainly seen in the subgroup of patients with histologically documented positive axillary nodes (5-year RFS on tamoxifen 71% *versus* 64% in the control group, $p = 0.044$) and in patients with tumours expressing the ER and PR positive phenotype (5-year RFS on tamoxifen 77% *versus* 70% in the control group, $p = 0.014$).

Conclusions: Tamoxifen administered for 3 years after completion of adjuvant chemotherapy in this otherwise unselected group of patients for endocrine sensitivity had a limited impact on relapse and had no detectable effect on overall survival. The beneficial effect of tamoxifen is mainly confined to the subgroup of patients with node-positive disease and to patients with tumours expressing the ER and PR positive phenotype.

1. Introduction

Adjuvant tamoxifen as monotherapy reduces recurrence and mortality in patients with hormone receptor-positive operable breast cancer. This effect is well demonstrated in the recent overview by the Early Breast Cancer Trialists' Collaborative Group showing that in oestrogen receptor-positive disease, about 5 years of tamoxifen reduces the annual breast cancer death rate by 31%.[1] However, the contribution of tamoxifen is less established in patients receiving adjuvant chemotherapy. In the past, concurrent administration of cytotoxics and tamoxifen was used on the assumption that their effects were independent. The concurrent use of chemotherapy and tamoxifen did improve the results achieved by chemotherapy alone, particularly in postmenopausal women and in those with four or more involved nodes.[2] However, experimental data suggest that tamoxifen and chemotherapy may be partially antagonistic,[3] and clinical trials confirm that concomitant administration of tamoxifen with chemotherapy yields inferior results than chemotherapy alone.[4,5] This antagonistic effect was particularly apparent in premenopausal women where concomitant administration of adjuvant chemotherapy and hormonal treatment generally did not improve outcome and sometimes led to a less favourable outcome than either therapy given alone.[6] Given the possibility of negative interactions with concomitant administration, this trial which was initiated by the European Organisation for Research and Treatment of Cancer (EORTC) Breast Group in 1991 investigated the impact of tamoxifen administered sequentially after completion of adjuvant chemotherapy in patients with operable breast cancer. At the time this study was designed, the role of hormone receptors in predicting the value of tamoxifen therapy was not yet fully established. It was thought that tamoxifen could have some beneficial effects irrespective of the presence of hormone receptors in the tumour. Therefore, tamoxifen was given to all eligible patients regardless of endocrine sensitivity.

2. Patients and methods

2.1. Study design

Between March 1991 and June 1999, 1863 women with stages I–IIIA operable breast cancer were included in this study. The women had undergone mastectomy or breast conserving surgery ± radiotherapy and completed six cycles of adjuvant combination chemotherapy with either CMF (cyclophosphamide, methotrexate, 5-fluorouracil), or 4–6 cycles of an anthracycline based regimen including CAF (cyclophosphamide, adriamycin, 5-fluorouracil), CEF (cyclophosphamide, epirubicin, 5-fluorouracil), FAC (5-fluorouracil, adriamycin, cyclophosphamide) or FEC (5-fluorouracil, epirubicin, cyclophosphamide). A minimum of four cycles of anthracycline based chemotherapy was allowed on the basis that four cycles of AC is at least as effective as six cycles of CMF.[7] Patients were accrued irrespective of their menstrual status and of the hormone receptor content of their primary tumour.

Investigations before randomisation included chest X-ray, contralateral mammogram, and if clinically indicated, screening for distant bone metastasis with isotope scanning and ultrasound or CT scanning of the liver. Patients were excluded from the study if they had signs of relapse or residual disease at study entry, and those with any other malignant disease including contralateral breast cancer, other than adequately treated *in situ*/microinvasive cervix carcinoma or basal cell carcinoma of the skin.

Patients consenting to participate were stratified by institute, chemotherapy scheme and age (above 50 years or younger). Randomisation took place at the start of the last cycle of chemotherapy to either tamoxifen 20 mg daily for 3 years or no further treatment. Tamoxifen was started within two weeks of the end of the last cycle of chemotherapy. At the time this trial was initiated in 1991, the optimal dose and duration of adjuvant tamoxifen was not known. The above dosage and duration of treatment was chosen as the most suitable at that time. Informed consent was required according to the criteria established within the individual countries at the time of patient accrual and the protocol was approved by institutional review boards.

Patients were reviewed at least every 4 months during the first 3 years and at least every 6 months thereafter. Clinical, haematologic, and biochemical assessments were required on each visit, chest X-ray and contralateral mammography were performed yearly, while other tests such as bone isotope scanning and ultrasound or CT scan of the liver were required only when clinically indicated.

2.2. End-points and statistical considerations

This study was designed to detect a 5% increase in the 5 year survival from 80% to 85% in favour of antioestrogen therapy

with a statistical power of 80% at a two-sided alpha level of 0.05. This design required 159 deaths in each treatment arm. Overall survival was defined as the length of time from the date of randomisation to death from any cause or the date the patient was last known to be alive. Secondary end-points were relapse free survival, local control, incidence of second primary breast cancer and correlation of results with receptor content. Relapse-free survival was defined as the length of time from the date of randomisation to any relapse (including ipsilateral breast recurrence) or death, whichever occurred first.

All analyses were performed on an intention-to-treat basis. Probabilities of overall survival and relapse free survival were calculated using the Kaplan–Meier method and treatment effect comparisons were carried out using the log-rank test. Adjusted hazard ratios (HRs) with their associated 95% confidence intervals (95% confidence intervals (CIs)) were estimated using the Cox proportional hazards model. Subgroup analyses according to receptor content were also performed. If measured, the receptor concentration of the primary tumour was considered positive if there was at least 10 fmol of receptor protein per mg cytosol protein in the tumour or if there was any immunohistochemical evidence of receptor protein. If hormone receptors were not measured or unavailable, it was considered as ER-unknown or PR-unknown. The ER/PR content was categorised as ER-positive/PR-positive *versus* ER-positive/PR-negative *versus* ER-negative/PR-positive *versus* ER-negative/PR-negative, excluding patients with one or both receptor measurements missing. Analyses for ER receptor protein per mg cytosol protein were split into categories of <10, 10–20, 20–40, 40–80, and more than 80 fmols/mg. Analyses of efficacy by other prognostic factors, as well as subsets defined by such factors were based on patients from whom data were available. All probability values were obtained from two-sided tests. The results are reported at a median follow-up of 6.5 years.

3. Results

A total of 1863 patients were randomised by 51 institutions from 14 countries. Seven institutions randomised 777 (42%) of the patients. The intent-to-treat principle was modified as follows: three institutions that accrued a total of 139 patients were excluded from all analyses because of poor compliance with documentation. All remaining 1724 patients (93%) are included in this report, 861 in the tamoxifen group and 863 in the control group. Upon medical review, there were 47 patients (2.7%) who were deemed ineligible because of wrong stage ($n = 40$), presence of contralateral breast cancer ($n = 2$), relapse at entry ($n = 1$), presence of other malignancies ($n = 3$) and for other reasons ($n = 1$) but all were included in this intention-to-treat analysis. The median duration of tamoxifen administration was 36 months (range, 0–83 months). One hundred thirty eight patients (16%) in the tamoxifen arm received the treatment for a duration of 5 years upon advice of their attending physicians on the basis of emerging studies showing that this was the optimal duration while this trial was ongoing. Among the patients randomised in the tamoxifen arm, nineteen patients (2.2%) did not start tamoxifen and 27 (3.1%) refused treatment. Overall, 8 patients (0.5%) inadvertently received the opposite treatment to the randomised allocation, including 6 patients in the control arm who received tamoxifen. However, all patients were evaluated according to their randomised assignment.

The baseline characteristics of the 1724 patients, tumours and primary treatment received are summarised in Table 1. The median age was 47 years and the majority were premenopausal (65%). Local therapies were the following: Fifty-nine percent ($n = 1022$) had a mastectomy, 33% ($n = 572$) had breast-conserving surgery. Information on primary surgery was unknown or missing in 8% of the patients (130). A total of 55% (947) received radiotherapy. Half of the patients had T2 tumours (size >2 cm and $\leqslant$5 cm) and 71% (1229) had positive axillary lymph nodes. Twenty-eight percent (491) of the patients had primary tumours classified as ER and PR-positive; 8% (132) were classified as ER-positive and PR-negative, 6% (100) were classified as ER-negative and PR-positive, 20% (341) were negative for both receptors. Since hormone receptor content was not an inclusion criterion in our study, receptors (ER and/or PR) were unknown or missing in 38% (660) of the patients. Seventy-seven percent ($n = 1320$) received adjuvant CMF chemotherapy, 6% ($n = 110$) CA(E)F or FA(E)C, and 10% ($n = 166$) other anthracycline containing regimens. As expected, main demographic characteristics and prognostic factors were well balanced between the two treatment groups.

3.1. *Outcomes*

3.1.1. *Survival*

At a median follow-up of 6.5 years, 396 deaths (23%) and 602 RFS events (35%) (relapse and/or death) have been observed. There was no difference in survival between patients who were randomised to receive tamoxifen for 3 years and those who were randomised to no further treatment (HR 0.97; 95% CI, 0.79–1.18; $p = 0.7377$ by log-rank test) (Fig. 1). The cause of death and the incidence of recurrence with respect to treatment group are summarised in Table 2. There have been 195 deaths in the tamoxifen arm (23%) and 201 (23%) in the control group. Breast cancer was the cause of death in 362 patients, 185 patients (92%) in the control arm and 177 (91%) in the tamoxifen arm.

3.1.2. *Relapse free survival*

The five-year estimates of relapse free survival were 73% (95% CI, 70–76%) in the tamoxifen group and 67% (95% CI, 63–70%) in the control group. There was a statistically significant 16% reduction in the risk for this end-point. Relapse free survival was significantly greater in the tamoxifen group than in the control group (HR 0.84; 95% CI, 0.72–0.99; $p = 0.0349$) (Fig. 2).

3.1.3. *Prognostic factors*

In exploratory, hypothesis-generating analyses, the prognostic value of several factors was assessed for both overall survival and relapse free survival. The prognostic value of some factors for overall survival is shown in Table 3. Better prognosis for survival was seen in patients with ER and PR positive tumours with a 5-year estimate of 88% (95% CI 85–91%, $p < 0.0001$) and was directly proportional to the level of ER

Table 1 – Baseline characteristics of the patients, tumours and primary treatments

Characteristics	Tamoxifen (N = 861)	Control (N = 863)	Overall (N = 1724)
Age at randomisation – years			
Median	47	47	47
Range	22–73	24–76	22–76
Menopausal status – No. (%)			
Premenopausal	555 (64.5)	573 (66.4)	1128 (65.4)
Perimenopausal	70 (8.1)	69 (8.0)	139 (8.1)
Postmenopausal	122 (14.2)	136 (15.8)	258 (15.0)
Artificially induced	8 (0.9)	10 (1.2)	18 (1.0)
Unknown or missing	106 (12.3)	75 (8.7)	181 (10.5)
Clinical tumour size – No. (%)			
T0	3 (0.3)	3 (0.3)	6 (0.3)
T1	282 (32.8)	286 (33.1)	568 (32.9)
T2	418 (48.5)	447 (51.8)	865 (50.2)
T3	69 (8.0)	74 (8.6)	143 (8.3)
T4	1 (0.1)	0 (0.0)	1 (0.1)
Unknown or missing	88 (10.2)	53 (6.2)	141 (8.2)
Pathological nodal status – No. (%)			
Negative (including Nx)	163 (18.9)	203 (23.5)	366 (21.3)
Positive	618 (71.7)	611 (70.8)	1229 (71.3)
Unknown or missing	80 (9.3)	49 (5.7)	129 (7.5)
ER and PR status – No. (%)			
ER-and PR-positive	233 (27.1)	258 (29.9)	491 (28.5)
ER-positive and PR-negative	71 (8.2)	61 (7.1)	132 (7.7)
ER-negative and PR-positive	52 (6)	48 (5.6)	100 (5.8)
Both negative	178 (20.7)	163 (18.9)	341 (19.8)
ER and/or PR unknown or missing	327 (37.8)	333 (38.5)	660 (38.3)
Surgery – No. (%)			
Mastectomy	492 (57.1)	530 (61.4)	1022 (59.3)
Breast-conserving surgery	287 (33.3)	285 (33.0)	572 (33.2)
Unknown or missing	82 (9.5)	48 (5.6)	130 (7.5)
Radiotherapy – No. (%)			
Yes	468 (54.4)	479 (55.5)	947 (54.9)
No	312 (36.2)	336 (38.9)	648 (37.6)
Unknown or missing	81 (9.4)	48 (5.6)	129 (7.5)
Adjuvant chemotherapy – No. (%)			
CMF	641 (74.4)	679 (78.7)	1320 (76.6)
CA(E)F or FA(E)C	53 (6.2)	57 (6.6)	110 (6.4)
Other	87 (10.1)	79 (9.2)	166 (9.6)
Missing	80 (9.3)	48 (5.6)	128 (7.4)
Cycles of adjuvant chemotherapy – No. (%)			
⩾6 cycles	344 (39.9)	347 (40.2)	691 (40.2)
4–5 cycles	437 (50.7)	468 (54.2)	905 (52.5)
Missing	80 (9.3)	48 (5.6)	128 (7.4)

concentrations. The five-year estimates were 87% (95% CI, 80–93%) for groups with ER concentrations >80 fmols/mg compared to 72% (95% CI, 65–78%) in those with ER negative tumours ($p = 0.0017$). Likewise, better prognosis was seen for those with smaller tumours and negative lymph nodes (5-year estimates were 87%, 95% CI, 84–93% and 86%, 95% CI, 84–89%, respectively, $p < 0.0001$ for both). Age (⩽50 years *versus* >50 years) and menopausal status (premenopausal *versus* perimenopausal *versus* postmenopausal) were not significant predictors for overall survival.

Similar to overall survival, borderline better prognosis for relapse free survival was seen in patients with ER and/or PR positive tumours with a 5-year estimate of 73% (95% CI 69–77%, $p = 0.0923$); however the level of concentrations was not significantly correlated with RFS (Table 4). Also, a better prognosis was seen for those with smaller tumours and negative lymph nodes (5-year estimates were 77% , 95% CI, 74–81% and 76%, 95% CI, 73–79%, respectively, $p < 0.0001$ for both). Again, age (⩽50 years *versus* >50 years) and menopausal status (premenopausal *versus* perimenopausal *versus* postmenopausal) were not significant predictors for RFS.

3.1.4. *Subgroup efficacy analyses*

Exploratory analyses were also performed in a number of subsets to more fully characterise treatment effects. The beneficial effect of tamoxifen appeared to be greatest in the

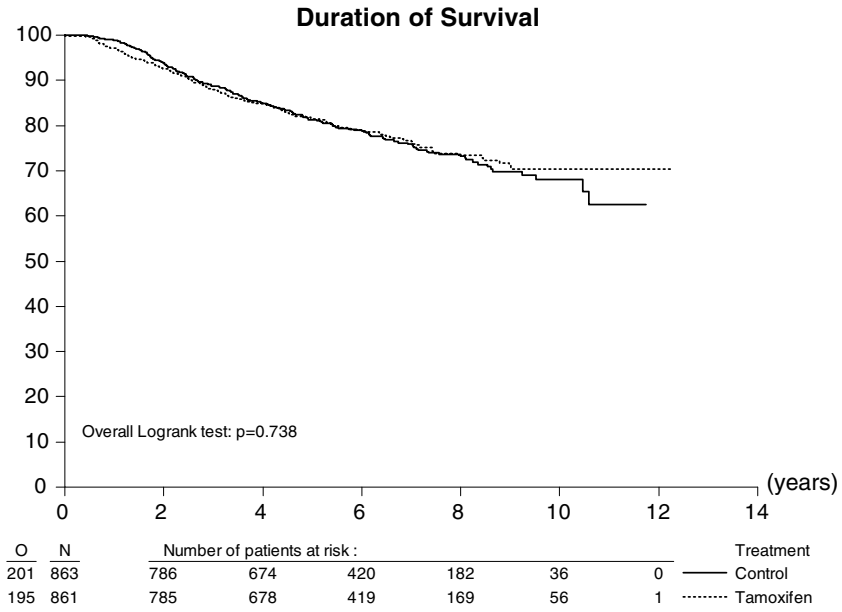

Fig. 1 – Kaplan–Meier estimates of overall survival.

subgroup of patients with histologically documented positive axillary nodes (pN1) with a relapse free survival of 71% on tamoxifen compared to 64% in the control group (HR 0.83; 95% CI, 0.69–0.99, $p = 0.044$). Also in patients with tumours expressing the ER and PR positive phenotype, relapse free survival was significantly greater on tamoxifen, with 5-year RFS of 77% compared to 70% in the control group (HR 0.68; 95% CI, 0.50–0.93, $p = 0.014$) (Fig. 3). This treatment effect was not seen in terms of overall survival (Fig. 4). Menopausal status and tumour size did not appear to influence the effect of treatment.

3.1.5. *Toxicity*

Thirty eight patients (4.4%) in the tamoxifen arm discontinued treatment because of toxicity. The most common reasons for discontinuation were hot flashes ($n = 8$), vaginal bleeding ($n = 7$), weight gain ($n = 4$) and nausea ($n = 4$). The other toxicities that required treatment discontinuation are listed in Table 5.

Table 2 – Incidence of efficacy end-point events

	Tamoxifen (N = 861)	Controls (N = 863)
Death from any cause – No. (%)	195 (23)	201 (23)
Breast cancer	177 (91)	185 (92)
Other cancer	5 (3)	4 (2)
Cardiovascular	4 (2)	2 (1)
Other	9 (5)	10 (5)
Alive – No. (%)	666 (77)	662 (77)
Without relapse	578 (67)	544 (63)
With relapse	88 (10)	118 (14)
DFS events[a] – no.	283	319
Loco-regional relapse	46	62
Distant relapse	179	205
Second primary/contralateral	39	40
Death without recurrence	12	10
Not specified	21	17

a First event for DFS analysis. Some patients had more than one event at the same time.

4. Discussion

The limitations of this study are mainly due to the timing upon which this study was designed. At that time, in 1991, some of the basic principles of endocrine therapy for breast cancer patients were not yet fully elucidated. These principles which are now accepted by the medical community are the separation of endocrine sensitive and endocrine non-sensitive disease by the presence or absence of hormone receptors, respectively, and the 5-year duration of tamoxifen therapy. Consequently, this study has a mixed population of endocrine sensitive and endocrine non-sensitive patients and a relatively short duration of tamoxifen therapy.

The primary aim of this study was to determine whether 3 years of adjuvant tamoxifen following postoperative chemotherapy adds to the established disease free and overall survival advantage from adjuvant chemotherapy. This study shows that after a median follow-up of 6.5 years, 3 years administration of adjuvant tamoxifen, given sequentially after completion of adjuvant chemotherapy in patients with operable breast cancer who were not selected for the presence of hormonal receptors, has a limited impact on relapse, increasing the proportion of patients alive without relapse at 5 years from 67% in controls to 73% in those who received tamoxifen. This corresponds to a relative risk reduction of 16%. No effect on survival was demonstrated.

In the first report of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) on a meta-analysis of data from 28 trials comparing tamoxifen *versus* no treatment, or chemotherapy with or without tamoxifen,[8] it was shown that chemotherapy in women aged under 50 gave an overall

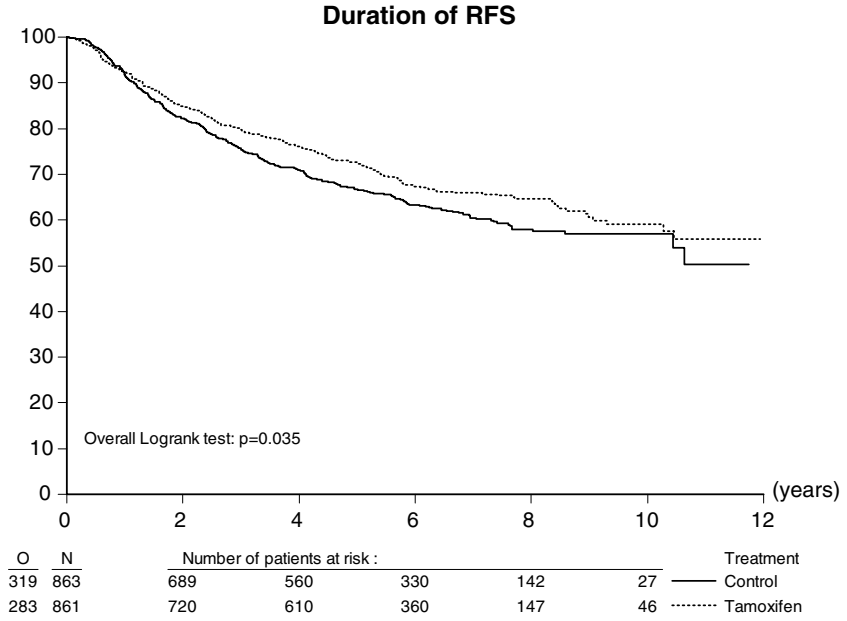

Fig. 2 – Kaplan–Meier estimates of relapse free survival.

Table 3 – Prognostic factors for overall survival

Factor	N	Prognostic value		Treatment comparison corrected for factor, and within subsets	
		p	HR + CI	p	HR + CI
Treatment arm	1724			0.738	0.97 (0.79–1.18)
Menopause	1525	0.156		(0.826)	1.02 (0.83–1.26)
Pre	1128		1	0.695	1.05 (0.82–1.34)
Peri	139		1.10 (0.77–1.57)	0.819	0.92 (0.47–1.81)
Post	258		1.31 (0.99–1.72)	0.922	0.98 (0.60–1.59)
Clinical T size	1576	<0.0001		(0.958)	1.01 (0.82–1.23)
T1	568		1	0.599	0.90 (0.60–1.35)
T2	865		1.77 (1.39–2.24)	0.552	1.08 (0.84–1.40)
T3	143		2.12 (1.49–3.02)	0.659	0.88 (0.49–1.57)
Pathological N	1592	0.001		(0.964)	1.00 (0.81–1.22)
pN0	365		1	0.382	1.27 (0.74–2.19)
pN1	1188		1.65 (1.23–2.22)	0.703	0.96 (0.77–1.20)
pN2	39		2.33 (1.29–4.21)	0.903	0.94 (0.32–2.71)
ER/PR	1064	<0.0001		(.388)	0.89 (0.69–1.15)
+/+	491		1	0.332	0.81 (0.52–1.25)
+/−	132		1.91 (1.29–2.83)	0.541	1.23 (0.64–2.37)
−/+	100		1.92 (1.25–2.95)	0.645	1.19 (0.57–2.50)
−/−	341		2.15 (1.59–2.89)	0.270	0.80 (0.53–1.19)

reduction of the odds of mortality of 22 ± 6%, compared to only 4% in women over 50. Reduction of the odds of recurrence from chemotherapy was significant in both age groups: 36 ± 5% and 19 ± 4%, respectively. From this report, it was still uncertain whether chemotherapy had a significantly different effect on mortality in the presence or absence of tamoxifen. A comparison of the age-standardised recurrence rate reduction from chemotherapy alone *versus* nil (30 ± 4%) and chemotherapy plus tamoxifen *versus* tamoxifen (26 ± 10%) showed similar sizes of effect. Although not statistically significant, this was also observed for mortality and was considered to be compatible with any real effects of tamoxifen and chemotherapy being probably independent of each other. In this context, the present study was designed to explore whether the benefits of adjuvant chemotherapy and tamoxifen given sequentially might be additive.

In a recently published study by the French Adjuvant Study Group on oestrogen receptor-positive postmenopausal breast cancer patients,[9] it was shown that the addition of adjuvant chemotherapy (FEC 50) to tamoxifen significantly improved disease free survival compared to tamoxifen alone. In this study, chemotherapy and tamoxifen were adminis-

Table 4 – Prognostic factors for relapse free survival

Factor	N	Prognostic value		Treatment comparison corrected for factor, and within subsets	
		p	HR + CI	p	HR + CI
Treatment arm	1724			**.035**	**0.84 (0.72–0.99)**
Menopause	1525	.235		(.137)	0.88 (0.74–1.04)
Pre	1128		1	.167	0.87 (0.71–1.06)
Peri	139		1.02 (0.76–1.38)	.910	1.03 (0.59–1.81)
Post	258		1.22 (0.97–1.52)	.416	0.85 (0.56–1.27)
Clinical T size	1576	**<.0001**		(.091)	0.87 (0.73–1.02)
T1	568		**1**	.819	0.96 (0.70–1.32)
T2	865		**1.61 (1.33–1.95)**	.123	0.84 (0.68–1.05)
T3	143		**2.26 (1.71–2.98)**	.293	0.78 (0.49–1.24)
Pathological N	1592	**<.0001**		(.058)	0.85 (0.72–1.01)
pN0	365		**1**	.794	0.94 (0.59–1.49)
pN1	1188		**1.94 (1.52–2.48)**	.044	0.83 (0.69–1.00)
pN2	39		**2.52 (1.52–4.18)**	.844	1.10 (0.44–2.70)
ER/PR	1064	.092		(.037)	0.81 (0.66–0.99)
+/+	491		1	.014	0.68 (0.50–0.93)
+/−	132		1.32 (0.96–1.80)	.685	0.89 (0.51–1.55)
−/+	100		1.33 (0.94–1.87)	.264	1.42 (0.76–2.66)
−/−	341		1.28 (1.01–1.62)	.228	0.80 (0.57–1.15)

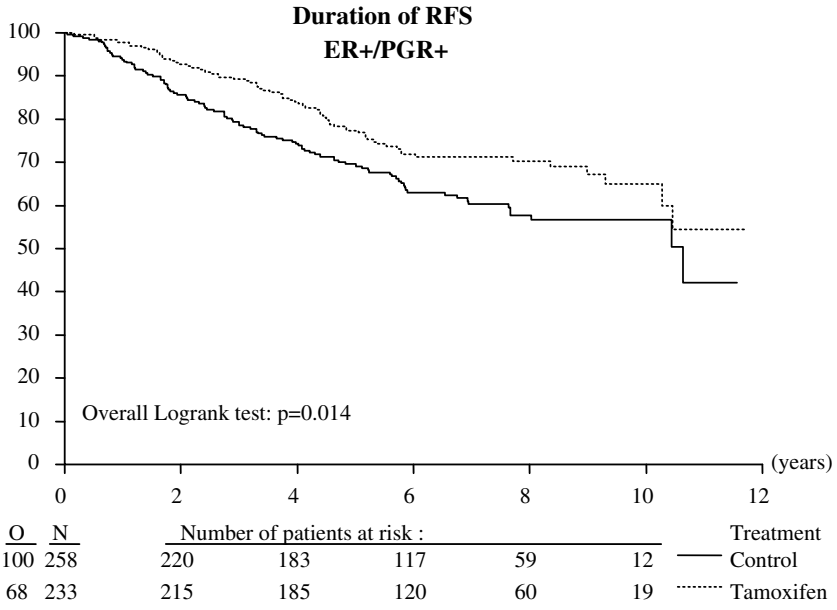

Fig. 3 – Kaplan–Meier estimates of relapse free survival according to ER+/PR+ phenotype.

tered concurrently. Other studies on the optimal timing of hormonal therapy, whether given sequentially or concomitantly with chemotherapy, have generally shown an advantage of the sequential administration. Recent data presented by the Southwest Oncology Group strongly suggest that a sequential administration of tamoxifen after chemotherapy improves disease free and overall survival.[5] In another study in postmenopausal node-positive breast cancer patients, a trend was also seen in favour of sequential administration of tamoxifen after epirubicin and cyclophosphamide.[10]

Whereas the majority of patients randomised in our trial received adjuvant chemotherapy with CMF, current data demonstrate a significant advantage of anthracycline containing regimens over CMF regardless of age.[1] Chemotherapy regimens continue to evolve with the increasing use of taxanes and the anti-HER-2 monoclonal antibody, trastuzumab.[11,12] Nevertheless, our study shows that, even following the use of fairly conservative chemotherapy by today's standards, tamoxifen given sequentially after adjuvant chemotherapy has a modest impact on relapse free survival.

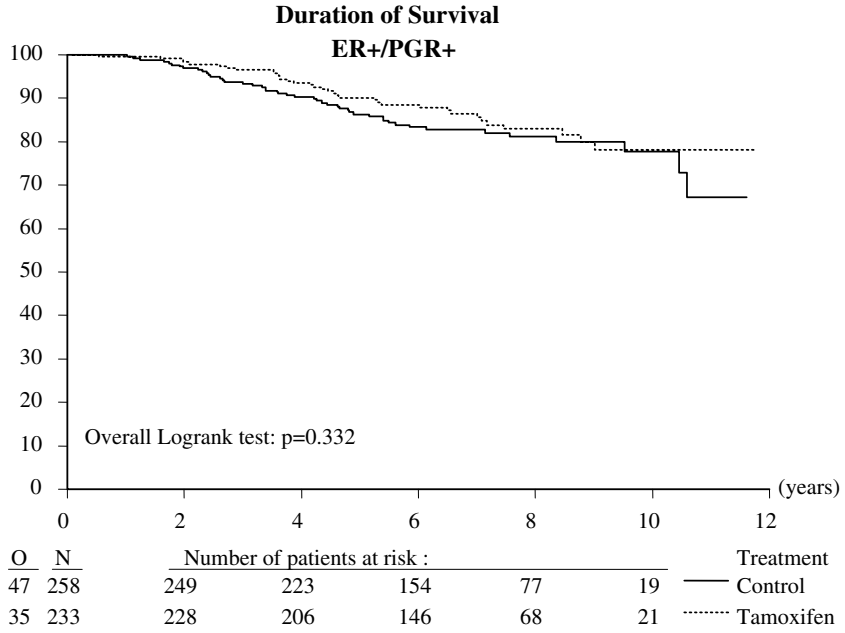

Fig. 4 – Kaplan–Meier estimates of overall survival according to ER+/PR+ phenotype.

As expected, the benefit of tamoxifen therapy is most evident in the subgroup of patients with endocrine sensitive tumours expressing the ER and PR positive phenotype. Since the presence of hormone receptors was not an inclusion criterion in our study, there was no standardisation of receptor assay. This could be performed either biochemically or through immunohistochemical techniques. In addition, one or both receptors were unknown or missing in 38% (660) of the patients. This is clearly one of the limitations of our study. Nevertheless, in the subgroup of patients with measured hormone receptors, the benefit was higher in the patients with higher levels of oestrogen receptors of at least 20 fmols/mg.

Table 5 – Toxicities leading to tamoxifen discontinuation

Toxicity	No. of patients[a]
Hot flashes	8
Abnormal vaginal bleeding	7
Ovarian cyst	1
Thrombophlebitis	2
Weight gain	4
Nausea	4
Vomiting	2
Pyrosis	1
Other gastrointestinal complaints	1
Headache	1
Dizziness	1
Blurred vision	1
Shortness of breath	1
Subjective intolerance	3
Oedema	2
Alopecia	1
Skin toxicity	1
Myalgia	1
Depression	1
Unspecified	12

a Some patients had more than one toxicity at the same time.

Although tamoxifen had a modest impact on relapse free survival, this did not translate into prolonged survival. Apart from the lack of patient selection based on steroid receptor content, a possible reason for this modest benefit could be the sub-optimal duration of tamoxifen therapy, which in most patients was only 3 years in our study. Emerging studies at the time this trial was ongoing reported better outcomes for patients who received 5 years of tamoxifen treatment *versus* those who received 2 years treatment.[13–15] As a result, a small proportion of patients included in our study received 5 years tamoxifen therapy. While a duration of 3 years adjuvant anti-hormonal therapy is likely sub-optimal in our study, it is also possible that 5 years of tamoxifen therapy is not the optimal postoperative management in postmenopausal patients. Indeed, the recent breast cancer trials of adjuvant hormonal therapy have consistently shown improved disease free survival and overall survival with an aromatase inhibitor compared to tamoxifen, irrespective of whether the aromatase inhibitor was administered immediately for 5 years after 2–3 years of adjuvant tamoxifen, or as extended therapy after 5 years of tamoxifen.[16–21] It is not clear yet whether all patients should start with an aromatase inhibitor upfront as the rate of recurrence is highest in the first 2–3 years of therapy or whether some patients do as well with a sequence of tamoxifen followed by an aromatase inhibitor. Mature results from studies having compared 5 years of an aromatase inhibitor with sequential administration of tamoxifen and aromatase inhibitors (in both directions) such as the BIG 1–98[20] will probably give an answer to this question.

In conclusion, tamoxifen given for 3 years after adjuvant chemotherapy mainly consisting of the CMF schedule resulted in a moderate increase in disease free survival and no detectable increase in overall survival in the whole study

population. As expected, the benefit was most evident in the subgroup of patients with positive hormone receptors and in those with positive lymph nodes.

Conflict of interest statement

None declared.

Participating centres and representative investigator

Academisch Medisch Centrum, Amsterdam, The Netherlands (van Tienhoven); Academisch Ziekenhuis Maastricht, The Netherlands (Hupperets); Academisch Ziekenhuis Utrecht, The Netherlands (de Graeff); Algemeen Ziekenhuis Middelheim, Antwerp, Belgium (Becquart); Ayr Hospital, Ayr, Scotland (Ritchie); Crosshouse Hospital, Kilmarnock, Scotland (Ritchie); Diakonessenhuis, Utrecht, The Netherlands (Ten Bokkel); Erasmus MC, Rotterdam, The Netherlands (van der Gaast); Erasmus University Medical Centre, Rotterdam, The Netherlands (Seynaeve); Glasgow Royal Infirmary, Scotland (Soukop); Guy's Hospital, London, UK (Rubens); Hopital Cantonal, Geneva, Switzerland (Bonnefoi); Innsbruck Universitaetsklinik, Innsbruck, Austria (Margreiter); Institute Jules Bordet, Brussels, Belgium (Piccart); Institute of Oncology, Ljubljana, Slovenia (Cufer); Institute of Oncology, Medical Academy of Lodz, Lodz, Poland (Dyczka); Institute of Oncology and Radiology of Serbia, Belgrade, Yugoslavia (Vukotic); Instituto Português de Oncologia, Lisbon, Portugal (Kristeller-Tome); Instituto Português de Oncologia, Porto, Portugal (Da Silva); Inverclyde Royal Hospital, Greenock, Scotland (Jones); Jeroen Bosch Ziekenhuis, ME 's-Hertogenbosch, The Netherlands (Burghouts); King Faisal Hospital, Jeddah, Saudi Arabia (Ezzat); Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland (Rogozinska); Meander Medisch Centrum Lichtenberg, Amersfoort, The Netherlands (Rodenburg); Medical University of Gdansk, Gdansk, Poland (Welnicka-Jaskiewicz); Monklands District General Hospital, Lanarkshire, Scotland (Wallace); Nederlands Kanker Instituut – Antoni van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands (Rutgers); Ninewells Hospital, Dundee, Scotland (Dewar); Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands (De Valk); Ottawa Regional Cancer Centre, Ontario, Canada (Tomiak); Policlinico Careggi Firenze, Italy (Cataliotti); PCK Maritime Hospital Gdynia, Poland (Karnicka-Mlodkowska); Raigmore Hospital, Inverness, Scotland (Whillis); Rosebank Oncology Centre, Johannesburg, South Africa (Rapoport); Royal Alexandra Hospital, Glasgow, Scotland (Canney); Royal Sussex County Hospital, Brighton, England (Canney); Sint Lucas Andreas Ziekenhuis, Amsterdam, The Netherlands (Monasch); Sophia Ziekenhuis, Rotterdam, The Netherlands (De Vries); Spaarne Ziekenhuis, Hoofddorp, The Netherlands (van de Stadt); Stobhill General Hospital, Glasgow, Scotland (Canney); Streekziekenhuizen, Groningen, The Netherlands (Bloemer); University Hospital Antwerp, Antwerp, Belgium (Vermorken); University Hospital Gasthuisberg, Leuven, Belgium (Paridaens); Victoria Infirmary, Glasgow, Scotland (Smith); Western General Hospital, Edinburgh, Scotland (Cameron); Western Infirmary, Glasgow, Scotland (George); Weston Park Hospital, Sheffield, UK (Coleman).

Acknowledgements

This publication was supported by Grant(s) Number 5U10 CA11488-21 through 5U10 CA11488-34 from the National Cancer Institute (Bethesda, MD, USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of randomised trials. *Lancet* 2005;**365**:1687–717.
2. Boccardo F, Rubagotti A, Bruzzi P, et al. Chemotherapy versus tamoxifen versus chemotherapy plus tamoxifen in node-positive, estrogen receptor-positive breast cancer patients: results of a multicentric Italian study. *J Clin Oncol* 1990;**8**:1310–20.
3. Osborne CK. Interactions of tamoxifen with cytotoxic chemotherapy for breast cancer. In: Jordan VC, editor. *Long term tamoxifen for breast cancer*. Madison (WI): University of Wisconsin Press; 1994. p. 181–98.
4. Fisher B, Redmond C, Brown A, et al. Adjuvant chemotherapy with and without tamoxifen: five-year results from the National Surgical Adjuvant Breast and Bowel Project Trial. *J Clin Oncol* 1986;**4**:459–71.
5. Albain K, Barlow W, O'Malley F, et al. For the Breast Cancer Intergroup of North America. Concurrent versus sequential chemohormonal therapy for postmenopausal receptor-positive breast cancer: mature outcomes and new biologic correlates in phase III intergroup trial 0100. *Breast Cancer Res Treat* 2004;**88**(Suppl. 1) [Abstract 37].
6. Pritchard KI. Current status of adjuvant endocrine therapy for resectable breast cancer. *Semin Oncol* 1987;**14**:23–33.
7. Fisher B, Costantino J, Redmond C, Wickerham DL, NSABP Investigators. Recent information from current NSABP trials of adjuvant therapy for breast cancer. In: Salmon SE, editor. *Adjuvant therapy of cancer VII*. Philadelphia: J.B. Lippincott Company; 1993. p. 148–61.
8. Fisher B, Redmond C, Fisher ER, Wolmark N. Sysytemic adjuvant therapy in treatment of primary operable breast cancer: National Surgical Adjuvant Breast and Bowel Project experience. *Natl Cancer Inst Monogr* 1986;**1**:35–43.
9. Namer M, Fargeot P, Roche H, et al. Improved disease-free survival with epirubicin based chemoendocrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. *Ann Oncol* 2006;**17**:65–73.
10. Pico C, Martin M, Jara C, et al. Epirubicin-cyclophosphamide adjuvant chemotherapy plus tamoxifen administered concurrently versus sequentially: randomized phase III trial in postmenopausal node-positive breast cancer patients. A GEICAM 9401 study. *Ann Oncol* 2004;**15**:79–87.
11. Dang C, Hudis C. Adjuvant taxanes in the treatment of breast cancer: no longer at the tip of the iceberg. *Clin Breast Cancer* 2006;**7**:51–8.

12. Piccart-Gebhart MJ. Adjuvant trastuzumab therapy for HER2-overexpressing breast cancer: What we know and what we still need to learn. *Eur J Cancer* 2006;**42**:1715–9.
13. Swedish Breast Cancer Cooperative Group. Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. *J Natl Cancer Inst* 1996;**88**:1543–9.
14. Current Trials Working Party of the Cancer Research Campaign Breast Cancer Trials Group. Preliminary results from the Cancer Research Campaign Trial evaluating tamoxifen duration in women aged fifty years or older with breast cancer. *J Natl Cancer Inst* 1996;**88**:1834–9.
15. Delozier T, Spielmann M, Mace-Lesec'h J, et al. Tamoxifen adjuvant treatment duration in early breast cancer: initial results of a randomized study comparing short-term treatment with long-term treatment. *J Clin Oncol* 2000;**18**:3507–12.
16. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *New Engl J Med* 2004;**350**:1081–92.
17. Boccardo E, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol* 2005;**23**:5138–47.
18. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;**366**:455–62.
19. The ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;**365**:60–2.
20. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *New Engl J Med* 2005;**353**:2747–57.
21. Goss P, Ingle J, Martino S, et al. A randomized trial of letrozole in postmenopausal women after 5 years of tamoxifen therapy for early-stage breast cancer. *New Engl J Med* 2003;**349**:1–10.