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RANDOMIZED TRIAL OF ADJUVANT TAMOXIFEN IN NODE NEGATIVE POSTMENOPAUSAL BREAST CANCER

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The paper presents long-term results of a randomized trial of adjuvant tamoxifen (40 mg daily for 2 or 5 years) versus surgery alone including 1 347 postmenopausal patients with histologically negative axillary nodes and a tumour diameter ⩽30 mm. Data on the estrogen receptor status of the primary tumour were available in 1 136 patients (84%). At a median follow-up of 7 years (range 1.7–13.0 years) there was a significant prolongation of the recurrence-free survival among those allocated to tamoxifen ($p < 0.01$), significantly fewer deaths due to breast cancer ($p = 0.02$) and a trend towards improved overall survival ($p = 0.11$). The treatment benefit was restricted to patients with ER-positive tumours. There was no significant reduction of breast cancer recurrences in the tamoxifen group among patients whose tumours were classified as ER-negative. The results support and extend previous studies in showing a long-term benefit of tamoxifen in postmenopausal breast cancer patients with node-negative, estrogen receptor positive disease.

Key words: Breast cancer, adjuvant tamoxifen, node-negative, estrogen receptors.

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Tamoxifen has become widely used as an adjunct to primary surgery in early breast cancer. The benefit has been considered to be most clearly established in node-positive, ER-positive disease among postmenopausal women. The NSABP-B14 trial showed a treatment benefit—in terms of short-term recurrence-free survival (RFS)—also among node negative patients (1).

The present paper reports long-term results of a randomized trial of adjuvant tamoxifen in node-negative, postmenopausal women with early breast cancer. A total of 1 347 patients were included in the study during 1976–1987. There was no selection for inclusion in the trial on the basis of the hormone receptor status of the primary tumour but such data were available in 84% of all patients.

Material and Methods

Details of the trial design have been published previously (2, 3). In short, the main inclusion criteria were: 1) postmenopausal menstrual status (>6 months since last menstruation), 2) age below 71 years, 3) unilateral invasive breast cancer, 4) modified radical mastectomy or breast conserving surgery including an axillary dissection (all patients treated with breast conserving surgery also received postoperative radiation therapy to the breast with 50 Gy during 5 weeks), 5) no involved axillary lymph

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nodes and a tumour diameter—measured on the surgical specimen—of 30 mm or less, and 6) no previous history of cancer.

The patients were randomized between tamoxifen given postoperatively at a dose of 40 mg daily for 2 years or no adjuvant endocrine therapy. The selection of a daily dose of 40 mg was based on an over-view of studies in advanced breast cancer showing a higher objective response rate with 40 mg compared to lower doses (4). Tamoxifen was initiated within 4–6 weeks of surgery. From November 1976 to May 1990, a total of 1 767 patients entered the trial. The present report concerns 1 347 patients randomized before December 31, 1987. Clinical characteristics by allocated treatment are summarized in Table 1. The treatment groups were well balanced. No patient for whom a treatment was allocated was subsequently withdrawn from the analysis which was on the basis of 'intention to treat'.

It is possible that a prolonged treatment with tamoxifen might be more efficient than a shorter course. Therefore, a new trial was initiated in 1983: tamoxifen patients who were disease-free at 2 years were randomly allocated to discontinue tamoxifen or to continue for 3 more years, i.e. a total treatment period of 5 years. Of the 672 patients in the tamoxifen group, 386 entered into this trial (57%). Due to short follow-up and small numbers results relative to the 2 versus 5 year comparison will not be reported in this paper.

Table 1

Clinical characteristics by allocated treatment. Figures within parentheses denote percentages

	Tamoxifen n = 672	Control n = 675
Mean age	61.5 years	61.4 years
Menopausal status		
Premenopausal[1)]	2	0
Postmenopausal	670	675
Tumor size		
< 10 mm	194 (29)	189 (28)
11–20 mm	324 (48)	334 (49)
21–30 mm	130 (19)	119 (18)
⩾31 mm	0 (0)	4 (1)
Size unavailable	24 (4)	28 (4)
Nodal status		
pN0	666 (98)	665 (98)
pN + [1]	3 (1)	6 (1)
pN?[1]	3 (1)	4 (1)
ER-status		
Positive	118 (18)	118 (18)
Negative	442 (66)	458 (68)
Data unavailable	112 (16)	99 (15)
Primary therapy		
Mod. rad. mast.	549 (82)	546 (81)
Breast-cons. surg. +RT of the breast	123 (18)	129 (19)

[1] Ineligible patients.

The current 1 347 patients constitute a separate stratum of a larger trial (the Stockholm Adjuvant Tamoxifen Trial) which also includes high-risk, node-positive patients. Preliminary results for the high-risk patients have been published previously (5).

Data on estrogen receptor content were available in 1 136 patients (84%). All assays were done in one laboratory using isoelectric focusing (6, 7). The receptor value was normalized to DNA content as measured by Burton (8). There were no significant differences between the patients with and without receptor data in regard to age, tumour size, or mean follow-up (data not shown). A cut-off level of 0.05 fmol/μg DNA was used to separate ER-positive and ER-negative cases. A conversion factor of 40–50 can be used for comparison of receptor content expressed as fmol per μg DNA with values expressed as fmol per mg of tissue protein. The mentioned cut-off level for receptor negativity thus roughly corresponds to 2–3 fmol/mg protein. Follow-up visits were scheduled once every three months during 0–2 years, every 6 months during 2–5 years, and yearly thereafter. Routine visits only included a physical examination and a yearly mammography. Treatment after recurrence was decided individually for each patient by the responsible clinician.

Actuarial methods were used to estimate the cumulative incidence of events such as loco-regional recurrence or distant metastasis as well as the recurrence-free survival (RFS), the recurrence-free interval (RFI), overall survival and breast cancer survival (9). The endpoint in calculations of RFI was disease recurrence (loco-regional or distant). Deaths in patients without a reported recurrence were thus treated as withdrawals. The endpoint in calculations of RFS was disease recurrence or death without a reported recurrence. The rationale for analysis of RFI in addition to RFS was that an increasing number of intercurrent deaths during follow-up may obscure the effect of treatment on breast cancer-related events. The endpoint in calculations of breast cancer survival was death due to breast cancer.

Loco-regional recurrence was defined as a relapse on the chest wall (or in the ipsilateral breast among patients treated with breast conserving surgery) or in the ipsilateral axillary or supraclavicular nodes. All other recurrences were regarded as distant. Results concerning the incidence of loco-regional recurrences and distant metastases refer to the total incidence, i.e. not only to events that represented the first evidence of treatment failure.

New primary malignancies were not recorded as treatment failures and were thus not included as events in calculations of RFS or RFI. Results concerning the occurrence of new primary malignancies in the trial have been reported previously (10). Distributional comparison were made with the log-rank test (11, 12); p-values refer to two-tailed tests. Relative hazards were calculated according to Haybittle (13).

The results were based on follow-up data available in January, 1990. The follow-up times among patients who were alive on that date thus ranged from 1.7 to 13.0 years with a mean of 7.0 years. Less than 1% of the patients were lost to follow-up.

Results

The number of events are summarized in Table 2. There was a significant benefit of tamoxifen in terms of both loco-regional recurrences ($p < 0.01$) and distant metastases ($p = 0.05$). Among the patients treated with breast conserving surgery plus radiation therapy, there were 2 breast recurrences among the 123 patients in the tamoxifen group (2%) compared to 7 among the 129 patients in the control group (5%). The relative hazard for this comparison was 0.31 (95% confidence interval: 0.08–1.14, $p = 0.15$).

There were 83 deaths in the tamoxifen group compared to 105 in the control group. This difference corresponded to a relative hazard of 0.78 which was of borderline significance ($p = 0.11$). However, when the survival analysis was restricted to deaths due to breast cancer, the difference in favour of the tamoxifen group was greater with a relative hazard of 0.65 ($p = 0.02$). There was no significant difference between the treatment groups in terms of deaths due to intercurrent disease which accounted for about 30% of all deaths.

Fig. 1 shows the recurrence-free survival and survival according to allocated treatment. The recurrence-free survival benefit of tamoxifen was largest (11%) at 6 years (85% vs 74%). After 6 years there was a reduction of the benefit which decreased to 3% at 10 years (72% vs 69%). A formal analysis of treatment failures by period of follow-up confirmed this observation (Table 3). The number of failures after 6 years was significantly larger in the tamoxifen group than in the control group (37 vs 16, $p < 0.01$). Since deaths due to intercurrent disease may have obscured the treatment effect during long-term follow-up an analysis was also made of the risk of disease recurrence alone over time, i.e. excluding deaths in patients without a reported recurrence. However, the result was similar, i.e. after 6 years the benefit of tamoxifen decreased (Fig. 2). For survival there was a continued benefit of tamoxifen up to at least 8 years (Table 4). After 8 years the number of

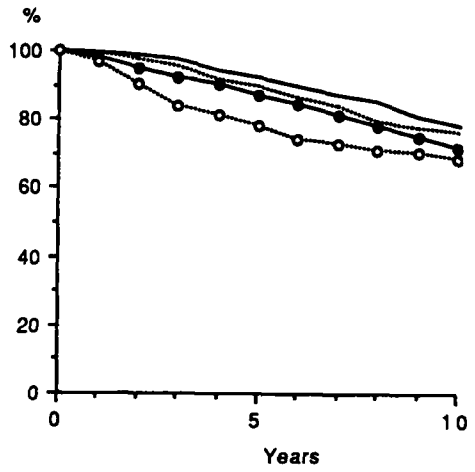

Fig. 1. Recurrence-free survival (—●— tamoxifen; ···○··· control) and survival (—— tamoxifen; · · · control).

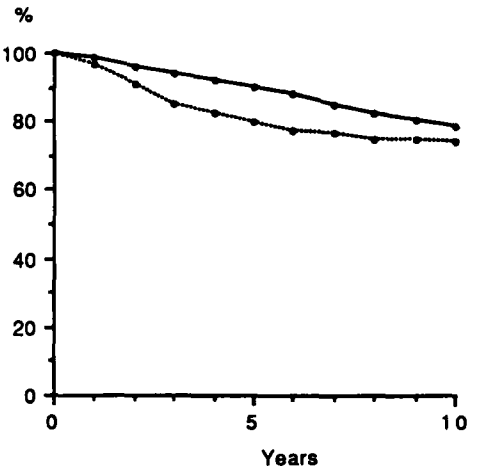

Fig. 2. Survival relative to breast cancer recurrence (RFI). —●— tamoxifen, ···●··· control.

Table 2

Analysis of events by allocated treatment

Type of event	Tamoxifen n = 672	Control n = 675	Relative hazard (95% C.I.)	Log-rank p-value
Loco-regional recurrence	43 (6)	69 (10)	0.61 (0.42–0.88)	<0.01
Distant metastasis	66 (10)	90 (13)	0.72 (0.52–0.98)	0.05
Treatment failure[1]	123 (18)	167 (25)	0.70 (0.56–0.88)	<0.01
Disease recurrence[2]	92 (14)	141 (21)	0.62 (0.48–0.81)	<0.01
Death	83 (12)	105 (16)	0.78 (0.59–1.04)	0.11
Death due to breast cancer	52 (8)	79 (12)	0.65 (0.46–0.92)	0.02
Intercurrent death	31 (5)	26 (4)	1.19 (0.71–2.00)	0.60

[1] Endpoint in calculation of RFS.
[2] Endpoint in calculations of RFI.

Table 3

Treatment failures by allocated treatment and period of follow-up

Period of follow-up	Tamoxifen		Control		Relative hazard (95% C.I.)
	No. entering interval	No. of failures (%)	No. entering interval	No. of failures (%)	
0–2 yrs	672	33 (5)	675	63 (9)	0.53 (0.35–0.79)
2–4 yrs	618	29 (5)	597	57 (10)	0.48 (0.32–0.74)
4–6 yrs	472	24 (5)	432	31 (7)	0.71 (0.42–1.21)
6–8 yrs	317	21 (7)	288	10 (3)	1.88 (0.93–3.80)
8–10 yrs	184	12 (7)	171	4 (2)	2.61 (0.98–6.95)
10 + yrs	98	4 (4)	102	2 (2)	2.31 (0.46–11.53)
Total	672	123 (18)	675	167 (25)	0.70 (0.56–0.88)

Table 4

Deaths by allocated treatment and period of follow-up

Period of follow-up	Tamoxifen		Control		Relative hazard (95% C.I.)
	No. entering interval	No. of failures (%)	No. entering interval	No. of failures (%)	
0–2 yrs	672	9 (1)	675	18 (3)	0.51 (0.24–1.09)
2–4 yrs	641	24 (4)	641	32 (5)	0.74 (0.44–1.24)
4–6 yrs	494	22 (5)	485	24 (5)	0.91 (0.51–1.62)
6–8 yrs	340	14 (4)	334	22 (7)	0.63 (0.33–1.21)
8–10 yrs	204	13 (6)	194	6 (3)	2.04 (0.83–5.01)
10 + yrs	109	1 (1)	111	3 (3)	0.43 (0.06–3.10)
Total	672	83 (12)	675	105 (16)	0.78 (0.59–1.04)

deaths was too small to permit a meaningful statistical analysis. At 5 years the survival in the tamoxifen and control groups was 92% and 90% respectively. At 10 years the corresponding figures were 79% and 77% (Fig. 1).

Table 5 shows an analysis of events by ER status. In the ER-negative subgroup there were no significant differences between the treatment groups for any type of event. The benefit with tamoxifen appeared to be restricted to the ER-positive subgroup. Fig. 3 shows the recurrence-free survival by ER-status. At 10 years the RFS benefit of

Table 5

Analysis of events by allocated treatment and ER-status

ER-status, Type of event	Tamoxifen n (%)	Control n (%)	Relative hazard (95% C.I.)	Log-rank p-value
ER-negative				
No. of patients	118	118		
Treatment failure (RFS)	30 (25)	34 (29)	0.89 (0.55–1.46)	0.74
Disease recurrence (RFI)	27 (23)	28 (24)	0.98 (0.58–1.66)	0.94
Death	19 (16)	25 (21)	0.74 (0.41–1.33)	0.39
Death due to breast cancer	16 (14)	19 (16)	0.81 (0.42–1.57)	0.65
Intercurrent death	3 (3)	6 (5)	0.51 (0.14–1.88)	0.50
ER-positive				
No. of patients	442	458		
Treatment failure (RFS)	74 (17)	116 (25)	0.61 (0.46–0.82)	<0.01
Disease recurrence (RFI)	53 (12)	101 (22)	0.51 (0.37–0.70)	<0.01
Death	50 (11)	69 (15)	0.74 (0.52–1.06)	0.12
Death due to breast cancer	29 (7)	73 (13)	0.56 (0.36–0.85)	0.01
Intercurrent death	21 (5)	15 (3)	1.43 (0.74–2.74)	0.37

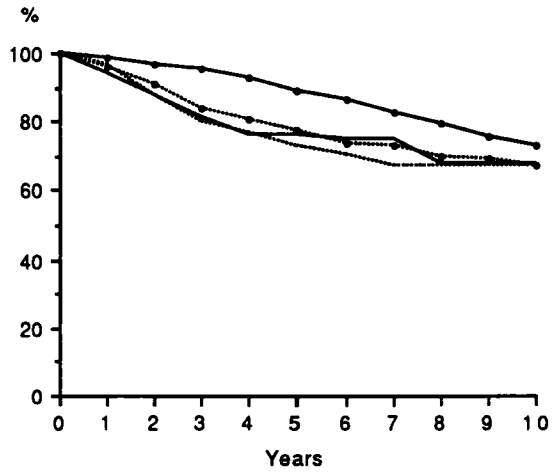

Fig. 3. Recurrence-free survival by estrogen-receptor status.
ER-positive: —●— tamoxifen; ···●··· control.
ER-negative: —— tamoxifen, · · · control.

tamoxifen in the ER-positive subgroup was 6% (73% vs 67%). For the ER-negative subgroup there was no significant difference in RFS at 10 years between the two treatment groups (68% vs 67%).

Discussion

The present study was designed to evaluate the long-term benefit of adjuvant tamoxifen among postmenopausal patients with node-negative breast cancer. For the analysis of the interaction between treatment and ER status it was an advantage that receptor assay was done in a large proportion of the cases included in the trial (84%). The results showed a significant long-term benefit of tamoxifen in terms of both loco-regional recurrences and distant metastases, a decreased incidence of deaths due to breast cancer, and a survival benefit of borderline significance ($p = 0.11$). The effect of tamoxifen was restricted to the ER-positive subset and there was no reduction of breast cancer recurrences among patients classified as ER-negative (Table 2).

Our results confirm and extend the information provided by the NSABP B-14 trial which showed a benefit at least up to 4 years in terms of an improved RFS among postmenopausal, ER-positive patients (1). In the present study the benefit of tamoxifen among the ER-positives in terms of RFS difference at 10 years was 6%. Other trials including both node-positive and node-negative patients have indicated that the effect of tamoxifen—in terms of relative risk reduction—probably is unrelated to nodal status (14, 15), a result supported by the results of the overview of all available adjuvant tamoxifen trials (16). However, this observation implies that the effect of treatment in terms of the absolute survival difference at a given point in time will be smaller among low-risk compared to high-risk patients.

The number of treatment failures after 6 years was larger in the tamoxifen group than in the control group ($p < 0.01$). This result may be interpreted to support the view of tamoxifen as a cytostatic rather than cytocidal agent, i.e. that tumour regrowth may occur when the treatment is discontinued (17). This hypothesis implies that a more prolonged course of tamoxifen may be better than treatment for only two years. However, the optimal duration of adjuvant tamoxifen needs to be addressed in prospective randomized trials. In the present study tamoxifen patients were randomized at 2 years to stop treatment or to continue for a total treatment period of 5 years. These patients are part of a Swedish multicenter trial with a target sample size of 5 000 patients. The trial includes both node-negative and node-positive postmenopausal patients and it is anticipated that patient accrual will continue until 1994.

In the NSABP B-14 trial there was a significant reduction in the tamoxifen group of recurrences in the ipsilateral breast among patients treated with lumpectomy followed by radiation therapy of the breast. In the present material there was a similar trend although it was not significant. The preliminary results of a recent Swedish randomized study of selected pT1N0 tumours suggested that the local recurrence rate after a strictly standardized surgical breast cancer conserving procedure with meticulous confirmation of excision margins could be decreased to an acceptable level (8%) even without the use of postoperative radiation therapy (18). Such an approach may become increasingly relevant in the future with a more widespread use of clinical and screening mammography and may be facilitated by the observation that adjuvant tamoxifen also decreases breast recurrences, i.e. an effect similar to that of postoperative radiation therapy.

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