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The Christie Hospital Tamoxifen (Nolvadex) Adjuvant Trial for Operable Breast Carcinoma — 7-yr Results*

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Abstract—*The Christie Hospital Tamoxifen Trial was a randomised trial to assess the efficacy of tamoxifen (Nolvadex) as an adjunct to surgical treatment for operable breast carcinoma. From 1 November 1976 to 1 June 1982 1005 patients were registered, of whom 961 are evaluable. Following surgery, premenopausal women were randomly allocated to either tamoxifen (TAM) 20 mg/day for 1 yr or to have an irradiation menopause. Postmenopausal women had TAM 20 mg/day for 1 yr or no further treatment (controls). The analysis at 7 yr shows that there is no statistically significant difference in the overall survival for premenopausal women between those given TAM and those given ovarian irradiation. Similarly for the postmenopausal women there was no significant difference in overall survival between the TAM and control groups. However, if the series of 961 patients is analysed as a whole and allowance is made for node status then the TAM-treated patients show a significant survival benefit (P = 0.05). There was also a statistically significant delay in first relapse for the TAM-treated patients (P = 0.04); with a particularly marked reduction in distant metastases in postmenopausal patients (P = 0.06). TAM was extremely well tolerated, with very few side-effects.*

INTRODUCTION

THE ROLE of tamoxifen (TAM) in the treatment of advanced breast carcinoma is now well established [1]; the role of TAM as an adjuvant to surgery for operable breast carcinoma will become clearer as the results of prospective randomised clinical trials mature. Early results [2-4] have been promising but the follow-up time has been relatively short.

The 5-yr results of the Christie Hospital Tamoxifen Trial have been published previously [5]. The present paper is an update of this trial at 7 yr from its inception.

MATERIALS AND METHODS

These have been described in detail previously [5]. Briefly, patients aged 35-70 yr with operable stage I-III (T1-T3a, N1-N2b, M0) breast carcinoma were eligible. Surgeons had a choice of three different operations which were practiced in the North-west of England at the time: (1) a simple mastectomy only; (2) a simple mastectomy with node sampling; and (3) a radical mastectomy. Following surgery, premenopausal women were allocated to have either an irradiation menopause or tamoxifen (TAM) 20 mg daily. Postmenopausal women were randomised to TAM 20 mg daily for 1 yr or no adjuvant treatment (controls). Patients with positive nodes on sampling of the axilla and those with stage III disease received postoperative radiotherapy. The technical details of the postoperative radiotherapy and the artificial menopause have been described previously [5]. Every patient had a full blood count, biochemical profile and modified skeletal survey.

Endocrine receptor status was not determined as the assay would only have been available on a limited number of patients.

All the patients have been seen at follow up by

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radiotherapists from the Christie Hospital. No patients have been lost to follow up as yet.

Survival curves were calculated by the life table method. Differences between curves were examined using the log rank test.

RESULTS

A total of 1005 patients were entered in the trial between 1 November 1976 and 1 June 1982, of whom 44 were excluded due to protocol violations. These were mainly due to patients being entered with T4 disease or with previously treated disease or in the wrong age category. Of the 961 evaluable patients, 373 were premenopausal and randomised to either TAM or an irradiation menopause and 588 were postmenopausal and randomised to TAM or follow-up only (controls). The treatment allocation of the patients is shown in Table 1.

Four patients allocated to TAM did not receive the drug and two patients did not have an irradiation menopause. These six patients have been analysed within the groups to which they were originally allocated.

Ninety-four per cent of the patients allocated to TAM completed a full year on a dosage of 20 mg daily, 2% completed a year on a reduced dose of 10 mg daily and 4% stopped the drug due to side-effects.

Primary irradiation of the ovaries to induce an artificial menopause was unsuccessful in only six patients, and they all became menopausal after further irradiation.

Of the premenstrual patients 70% had clinical stage I carcinomas, 21% stage II and 9% stage III. In postmenopausal patients 65% had stage I carcinomas, 21% stage II and 14% stage III.

Table 2 shows the allocation of the 961 patients to the three types of surgery performed.

Table 1. *Allocation by menopausal status*

Premenopausal (n = 373)	tamoxifen 199 irrad. menop. 174
Postmenopausal (n = 588)	tamoxifen 282 control 306

Table 2. *Allocation by surgery of* 961 *patients*

	No. of patients
Simple mastectomy	304 (31%)
Simple mastectomy and node sampling	410 (43%)
Radical mastectomy	247 (26%)

Because all of the patients did not have an axillary clearance done, it is probably not completely accurate to carry out an analysis of survival, using the number of lymph nodes involved as a prognostic variable. Instead three groups have been looked at; (a) patients whose node status is unknown; (b) those with histologically negative axillae; and (c) those with histologically positive axillae.

Survival

Figure 1 shows the overall survival for premenopausal women. There is no significant difference in the survival between those given TAM and those given an irradiation menopause (P = 0.19). Figure 2 similarly shows the overall survival for postmenopausal women, and once again there is no statistical difference between those patients given TAM and the control patiets (P = 0.24).

However, as shown in Table 3, if the pre- and postmenopausal patients are combined and then reanalysed within the three groups (node-negative, node-positive and node status unknown), the survival benefit in favour of TAM is now of statistical significance despite the fact that the control group includes patients who have had adjuvant endocrine therapy in the form of an irradiation menopause. This suggests that in all the subgroups there was a consistent benefit in favour of tamoxifen in both the pre- and postmenopausal patients, the cumulative effect of which is significant for all the patients treated.

An analysis was done to assess any effect of tamoxifen on the occurrence of events. An event can be defined as the first evidence of relapse, whether it be recurrence in the flaps or lymph node areas, distant metastases (including con-

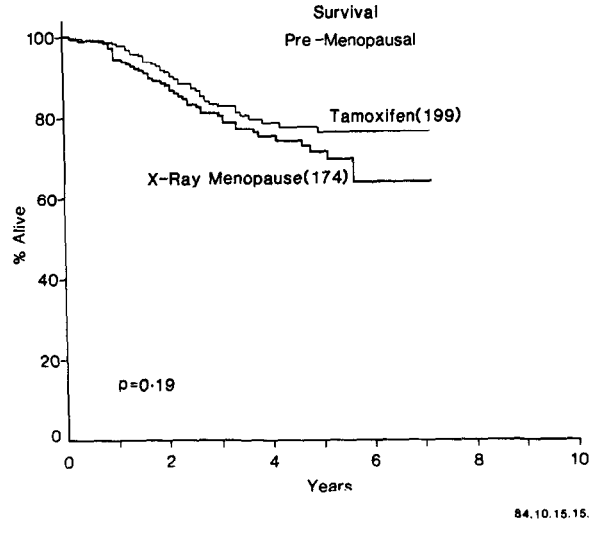

Fig. 1. *Overall survival of* 373 *premenopausal patients.*

tralateral disease) or death before a relapse is recorded. Local regional recurrence was only counted if it preceded distant metastases.

As shown in Table 4, an analysis of the events that have taken place for the total of 961 patients shows that patients treated with TAM had statistically fewer events (chi-square 3.94, 1 d.f., $P = 0.04$) than patients in the irradiation menopause/control groups.

TAM has had a considerable effect in reducing the number of distant metastases in postmenopausal women, with 81/282 women developing distant metastases in the TAM group compared with 107/306 in the control group ($P = 0.06$). It is not possible to state if a similar effect has occurred in the premenopausal women as there is no untreated control group.

Of the patients who developed loco-regional

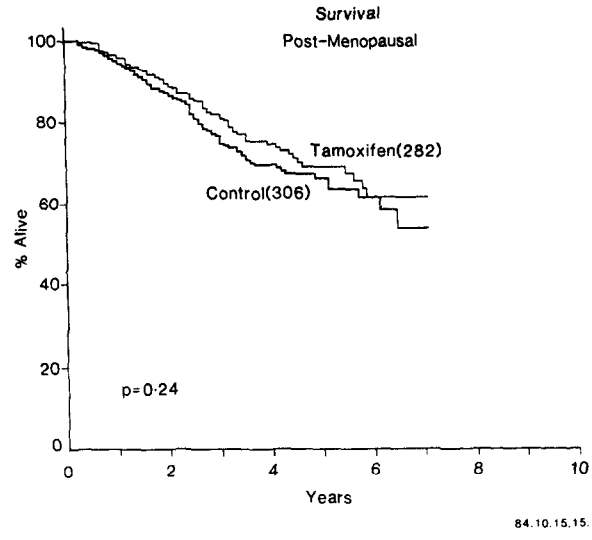

Fig. 2. Overall survival of 588 postmenopausal patients.

Table 3. Overall survival of 961 patients by node status

Node status	Group	No. of patients	Deaths Obs.	Exp.	O/E
Negative	tamoxifen irrad. menop.	146	15	19.73	0.76
	control	151	25	20.27	1.23
Positive	tamoxifen irrad. menop.	176	66	73.47	0.90
	control	173	77	69.53	1.11
Not known	tamoxifen irrad. menop.	159	27	29.82	0.91
	control	156	31	28.18	1.10
All	tamoxifen irrad. menop.	481	108	123.02	0.88
	control	480	133	117.98	1.13

$\chi^2 = 3.81$, 1 d.f., $P = 0.05$.

Table 4. Log rank analysis of events in 961 patients by lymph node status

Node status	Group	No. of patients	Events Obs.	Exp.	O/E
Negative	tamoxifen irrad. menop.	146	26	29.60	0.88
	control	151	35	31.40	1.11
Positive	tamoxifen irrad. menop.	176	78	87.76	0.89
	control	173	89	79.24	1.12
Not known	tamoxifen irrad. menop.	159	44	48.22	0.91
	control	156	49	44.78	1.09
All	tamoxifen irrad. menop.	481	148	165.57	0.89
	control	480	173	155.43	1.11

$\chi^2 = 3.94$, 1 d.f., $P = 0.04$.

recurrence as a first event, 72% subsequently developed distant metastases and died within 5 yr. This showed that the primary recurrence was merely a manifestation of widespread systemic disease.

Treatment on relapse

It has not proved possible to standardise treatment on relapse for the premenopausal patients as clinicians views differed on what was the best treatment after relapse for these patients.

However, with the postmenopausal women 83/122 (68%) patients who relapsed in the control group (untreated) were subsequently treated with TAM. Thirty of the 83 patients responded to TAM (36%). The remainder of the relapsed postmenopausal patients have had regional radiotherapy for local recurrence and have not yet been treated with systemic therapy.

Side-effects

An irradiation menopause led to the development of hot flushes in all the patients in whom a permanent menopause was induced.

In the actively menstruating patients given TAM 50% had no effect on their periods. In the remainder, 28% had irregular periods or developed temporary amenorrhoea, 19% went through a permanent menopause and 3% had menorrhagia.

Only 4% of the total number of patients who took TAM (477) stopped treatment due to side-effects. The main side-effect in these patients was nausea and vomiting.

DISCUSSION

In the second analysis of the Christie Hospital Tamoxifen Trial, it can be shown that at 7 yr there has been a significant reduction in the number of events in the group of women treated with TAM. This effect has been to reduce the incidence of both local recurrence and distant metastases. In turn these benefits have been translated into an improvement of the overall survival which is just statistically significant when adjusted for node status. There would appear to be no significant difference for premenopausal women between having TAM or an irradiation menopause as an adjuvant treatment, but the trend has consistently been in favour of TAM. Ideally there should have been a no treatment group for premenopausal women, but at the time it was felt that it would be unethical to deny patients an irradiation menopause as it was the standard treatment at the Christie Hospital. To have a third arm would have meant too few patients in each arm. From the evidence produced in this paper it would now appear that TAM can be considered a viable alternative to an irradiation menopause.

The initial report from the NATO trial [3] has shown a significant reduction in the number of events in pre- and postmenopausal women treated with TAM compared with those given no further therapy. A later communication [6] stated that an overall survival advantage was now present.

The Danish Breast Cancer Group [4] has reported on a trial in which 1411 high-risk postmenopausal women were randomised to receive TAM or no further therapy. An analysis at 36 months shows a statistically significant disease-free survival for women aged 50–59 yr given TAM. These results are still very early and it is still of interest to speculate what the long-term results of all these trials will be like.

However, even the preliminary results are very encouraging as adjuvant endocrine therapy can offer significant benefits to women with breast cancer. These benefits are secured with minimum toxicity compared to all the adjuvant cytotoxic studies that have been reported so far.

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