Delayed adjuvant tamoxifen: Ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial)

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Summary

Aim: Immediate adjuvant tamoxifen reduces disease recurrence and improves survival in patients with early breast cancer. However, is it too late to administer tamoxifen to patients who have already undergone treatment, but were unable to benefit from this adjuvant therapy? The French National Cancer Centers (FNCLCC) have investigated the efficacy of delayed tamoxifen administration in a randomized controlled trial.

Patients and methods: From September 1986 to October 1989, women with primary breast cancer, who had undergone surgery, radiotherapy, and/or received adjuvant chemotherapy but not hormone therapy more than two years earlier, were randomized to receive either 30 mg/day tamoxifen or no treatment. The 10-year disease-free and overall survival rates of the two groups of patients and of various subgroups were determined according to the Kaplan–Meyer method and compared by the log-rank test.

Results: This intention-to-treat analysis comprised 250 women in the tamoxifen group and 244 in the control group. Patient characteristics (age, T stage, number of positive nodes, receptor status, and interval since tumor treatment) were comparable in both groups. Delayed adjuvant tamoxifen significantly improved overall survival only in node-positive patients and in patients with estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) tumors. Disease-free survival, however, was significantly improved in the global population and in several patient subgroups (node-positive, ER+, PR+). Patients in whom the interval between primary treatment and delayed adjuvant tamoxifen was greater than five years also had significantly improved disease-free survival.

Conclusions: Overall and disease-free survival results indicate that delayed adjuvant tamoxifen administration (30 mg/day) is justified in women with early breast cancer, even if this treatment is initiated two or more years after primary treatment.

Key words: adjuvant treatment, breast cancer, tamoxifen

Introduction

The benefits of adjuvant tamoxifen therapy in early breast cancer were established in an overview published in 1992 [1], which indicated a 17% reduction in mortality and a 25% reduction in disease recurrence. However, there are many women, especially those who underwent primary treatment before 1985, who were unable to benefit from adjuvant tamoxifen therapy although they would qualify according to current criteria.

At least two reasons suggest that tamoxifen administration, even if delayed, might improve survival and/or disease-free interval: (i) the risk of disease recurrence is still present in the long term even in patients with a disease-free interval of more than 10 years [2]; and (ii) late recurrences tend to be hormone-dependent and might therefore be retarded by anti-hormone treatment.

To investigate the efficacy of delayed tamoxifen administration, the French 'Fédération Nationale des Centres de Lutte Contre le Cancer' set up a collaborative randomized controlled trial in September 1986. Its primary aim was to answer the question: 'In women who did not receive adjuvant tamoxifen immediately after surgery or radiotherapy, does subsequent long-term tamoxifen administration reduce recurrence and deaths, even if the treatment is initiated two or more years after surgery'? Answers were also sought for two subsidiary questions: 'Which prognostic factors define the population that might respond best to tamoxifen?' and 'When is tamoxifen treatment no longer justified?' This paper is an update of the five-year follow-up results already published in the French literature [3].

Patients and methods

From September 1986 to October 1989, during the course of routine follow-up visits, patients who had undergone treatment for early breast cancer at least two years previously and who had not received adjuvant hormone treatment were given the opportunity to participate in a collaborative randomized controlled trial comparing 30 mg tamoxifen daily for five years to no adjuvant treatment. Inclusion criteria were: histologically proven infiltrating primary adenocarcinoma regardless

Table 1. Patient characteristics.

	Tamoxifen group ($n=250$)	No treatment group ($n=244$)	P-value
Mean age (years) (range)			
At primary treatment			
At randomization	59.4 (40–83)	58.9 (39–81)	0.16
Interval primary treatment-randomization (months)	59.3 (24–233)	58.5 (24–165)	0.78
Nodal status[a]			
N− (patients)	125	138	
N+ (patients)	122	102	0.15
N+ 1–3	77	60	
N+ 4–9	33	27	
N+ 10+	8	10	0.33
Estrogen receptor			
Available results (#)	148	122	
Positive[b]	129	117	
Negative	19	5	0.01
Progesterone receptor			
Available results (#)	148	122	
Positive[b]	137	111	
Negative	11	11	0.78

[a] Knowledge of node status was missing in three patients of the tamoxifen group and four of the control group.
[b] ≥ 10 fmol/mg prot.

Table 2. Primary treatment.

	Tamoxifen group	No treatment group
Surgery		
Conservative	91	106
Mastectomy	156	134
None	2	1
Unknown	1	3
Radiotherapy		
None	46	36
Post-operative	194	202
Pre-operative	4	1
Only	4	1
Unknown	2	1
Chemotherapy		
None	181	172
Adjuvant	64	64
Unknown	4	5

Table 3. Patients at risk.

	At onset	At 3 years	At 5 years	At 7 years	At 10 years
Tamoxifen	250	236	222	210	164
Control	244	216	208	193	145

of type, size (T_1, T_2, T_3, T_{4b}), and nodal involvement; treatment by either surgery (radical or not), radiotherapy (exclusively or pre- and/or post-operatively), or chemotherapy (pre- or post-operatively); and no signs of local, regional, or metastatic recurrence at trial entry according to the methods in routine use at each institution. The only exclusion criteria were previous hormone treatment and risk of inter-current events that might affect results.

Randomization was conducted from the coordinating center by telephone. Stratification was carried out by center only and not by prognostic criteria nor primary treatment type.

Analyses were performed after 5 and 10 years of follow-up. For the 5-year analysis, all data collated before December 1994 were analyzed in February 1995; the corresponding date for the 10-year analysis was November 1999. Overall and disease-free survival were determined according to the Kaplan–Meyer method; survival curves were compared by the log-rank test. The analyses were on an intention-to-treat basis. No patient was excluded from the analyses (patients lost to follow-up were censored at the date of the last consultation and date of death was collected from official lists); treatment compliance was not taken into account.

Results

Overall, 494 women were included: 250 in the tamoxifen group and 244 in the no treatment group. Their characteristics are summarized in Table 1. There was no significant difference between the groups with regard to any variable (mean age at primary treatment or at randomization; mean time interval since primary treatment; node status). Tumors were considered to be estrogen receptor- or progesterone receptor-positive when receptor level was equal to or higher than 10 fmol/mg prot. Estrogen-receptor and progesterone-receptor status was known in 55% of patients. Although progesterone and was a significant imbalance in the two groups with regard to estrogen receptors. Only five women in the tamoxifen group and seven in the control group had received primary treatment 10 or more years previously. The number of involved nodes was known for 243 patients who were allocated to the tamoxifen group and for 235 control patients (97.2% and 96.3%, respectively). There was no significant difference between the two groups with regard to the type of primary treatment (surgery, radiotherapy, and chemotherapy) (Table 2).

At the time of the five-year analysis, no patient was lost to follow-up; 56 had discontinued tamoxifen treatment either for personal reasons ($n = 9$) or because of side effects ($n = 47$). Patients were not directly questioned regarding side effects, but they were reported by 74 of 250 (29.6%) receiving tamoxifen. The most common complaints were hot flushes, leukorrhea, and weight gain. In the opinion of the consultant physicians, side effects were treatment-related in 51 women, possibly treatment-related in 16, and unrelated in 7. Side effects led – apart from the 47 definite discontinuations – to temporary treatment withdrawal in 6 women and to a decrease in tamoxifen dose in 13. At the time of the 10-year analysis, 61 women were lost to follow-up: 30 in the control group and 31 in the tamoxifen group.

The populations at risk at different times over the 10-year follow-up period are given in Table 3. The difference in overall and disease-free survival of the two groups of patients at 10 years is indicated in Table 4. There was no difference in overall survival between the two groups, while a significant difference was noted in some subgroups: node-positive population ($P = 0.02$); estrogen receptor-positive tumors subpopulation ($P = 0.001$); and

Table 4. Overall and disease-free survival at 10 years.

Patient population	Treatment	Patients (*n*)	Events (*n*)	DFS (%)	*P*-value	Deaths (*n*)	Survival (%)	*P*-value
All patients	Control	244	66	75		65	78	
	Tamoxifen	250	43	83	0.01	52	83	0.15
N+	Control	102	40	63		38	66	
	Tamoxifen	122	29	75	0.008	29	80	0.02
N−	Control	138	25	84		26	87	
	Tamoxifen	125	14	90	0.16	23	86	0.86
ER+ ⩾10 fmol/mg prot	Control	117	34	73		30	73	
	Tamoxifen	129	21	84	0.01	20	87	0.001
PR+ ⩾10 fmol/mg prot	Control	111	35	71		38	73	
	Tamoxifen	137	25	82	0.01	23	86	0.002
Interval <5 years	Control	142	40	75		40	76	
	Tamoxifen	145	29	80	0.12	31	81	0.25
Interval >5 years	Control	101	26	75		25	81	
	Tamoxifen	105	14	87	0.02	21	86	0.37

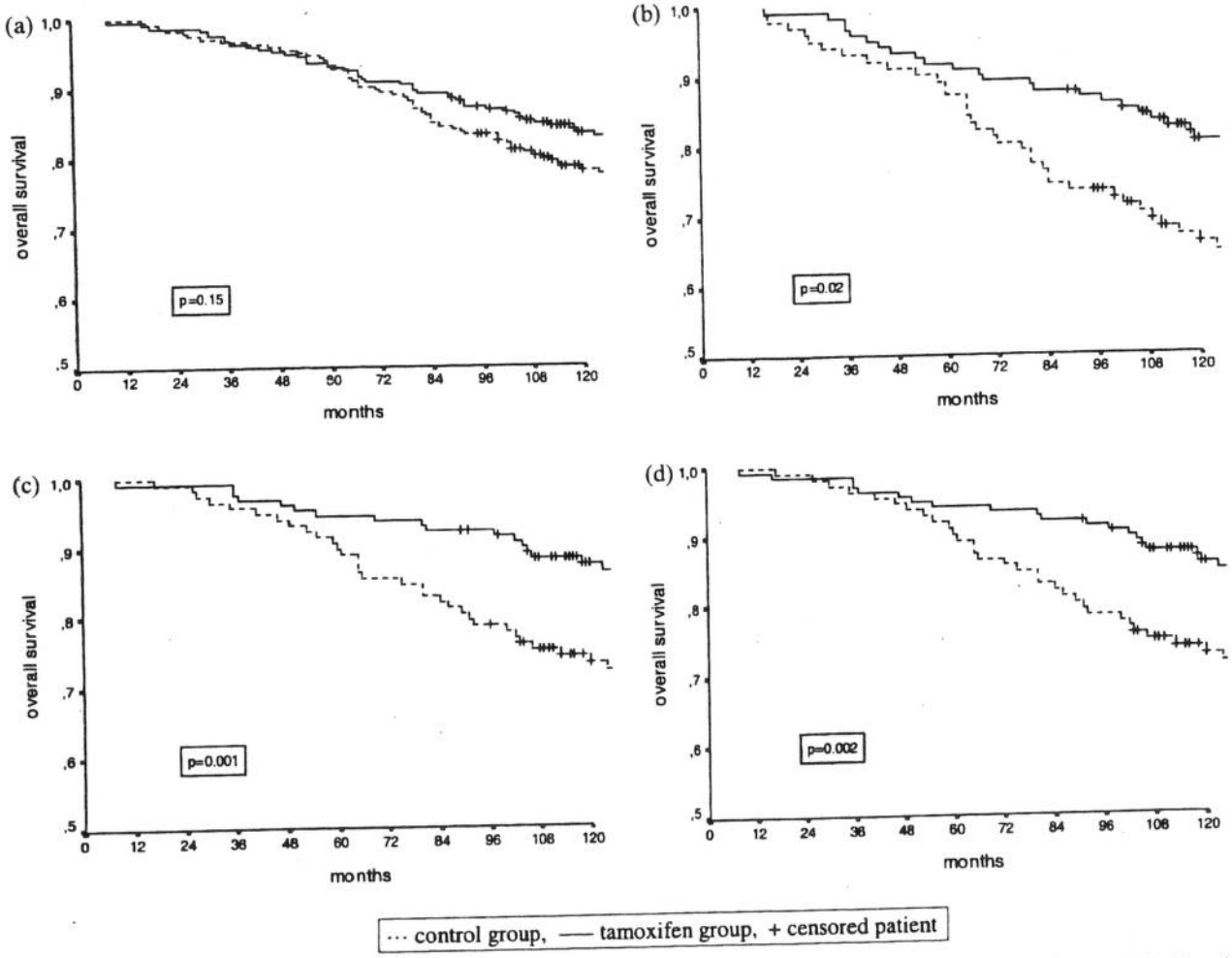

Figure 1. Overall survival in (a) entire population (control: 244; tamoxifen: 250 patients), (b) node-positive patients (c: 97; tam: 118), (c) patients with estrogen-receptor tumors (c: 90; tam: 92), and (d) patients with progesterone-receptor tumors (c: 111; tam: 137).

(P = 0.002). Disease-free survival also differed significantly in several subpopulations, i.e., in patients with involved lymph nodes (P = 0.008), estrogen receptor-positive tumors (P = 0.01), and progesterone receptor-positive tumors (P = 0.01). Moreover, it differed significantly in the overall population (P = 0.01). The overall survival curves are shown in panels (a–d) of Figure 1; the disease-free survival curves are shown in panels (a–d) of Figure 2.

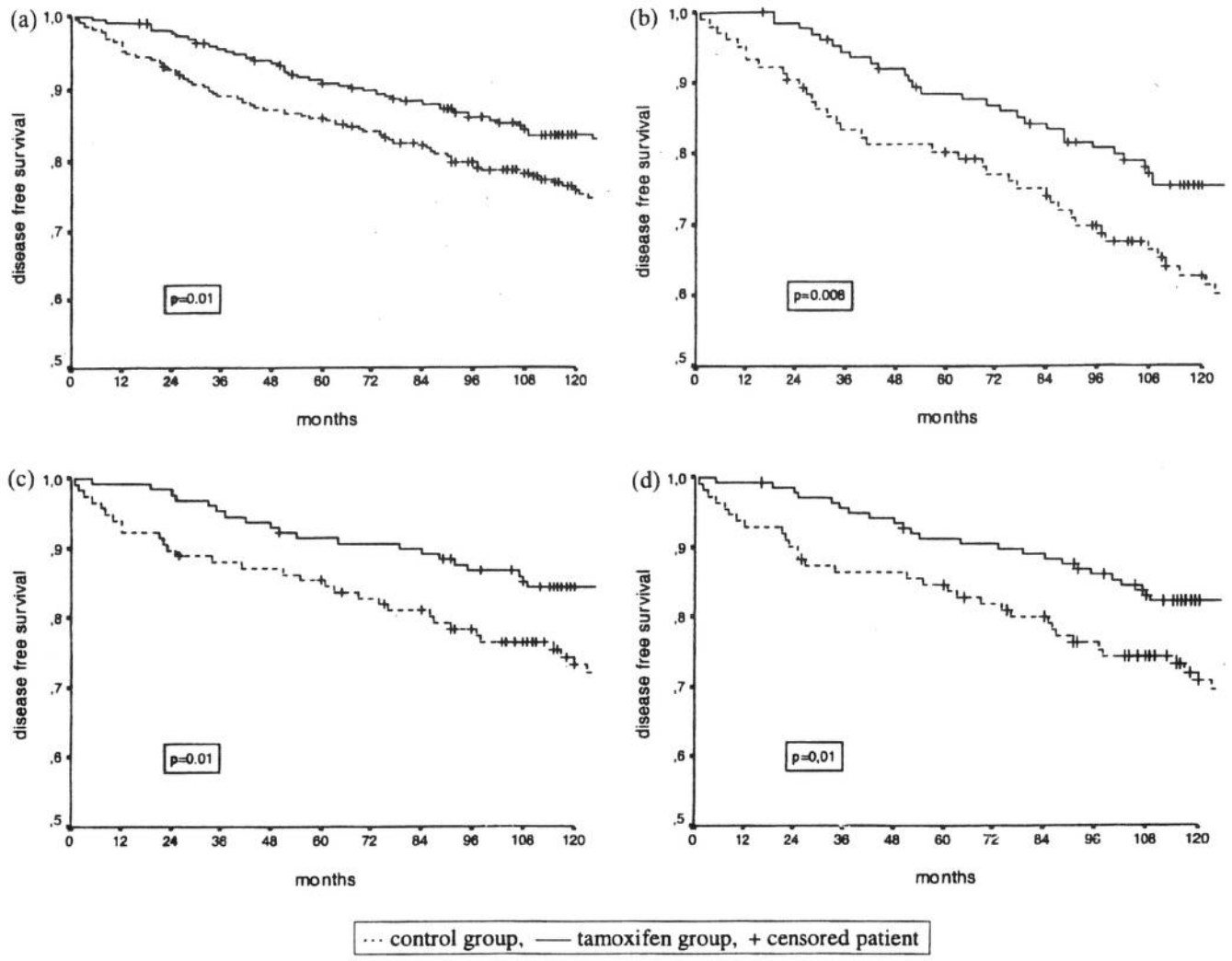

Figure 2. Disease-free survival in (a) entire population (control: 244; tamoxifen: 250 patients), (b) node-positive patients (c: 97; tam: 118), (c) patients with estrogen-receptor tumors (c: 90; tam: 92), and (d) patients with progesterone-receptor tumors (c: 111; tam: 137).

Most patients were 50 years old or older at randomization. No analysis was performed according to age.

There was a significant difference in disease-free survival between the two groups when tamoxifen treatment was initiated more than five years, rather than less than five years, after primary treatment.

Discussion

In this trial, delayed adjuvant tamoxifen treatment led to a significant improvement in disease-free survival in breast cancer patients. This effect was more obvious in some patient subgroups: (i) the most eligible patients for hormonal treatment (ER-positive and/or PR-positive patients) and (ii) patients with a higher risk of recurrence (node-positive patients). We did notice that most patients were ER-positive or ER-unknown, so the results are essentially valid in this population.

Delayed adjuvant tamoxifen caused no significant improvement in overall survival in the global population. However, it did significantly improve overall survival in node-positive patients and in patients whose tumors were estrogen receptor- or progesterone receptor-positive. These results found in selected subgroups but not in the global population may be due to the lack of power of our trial in the global population: a too-small population and a low death rate. On the whole, our study population had a good prognosis as indicated by the relatively low number of events recorded. This was probably because (i) patients with a poor prognosis had already received tamoxifen in most centers, therefore mostly patients with a good prognosis had not been offered adjuvant therapy; and (ii) patients with fast-growing tumors already had metastatic disease at two years, therefore only patients with slow disease progression could be included. This bias is reflected in the rather good results for the node-positive subpopulation.

The hypothesis that delayed adjuvant tamoxifen therapy after mastectomy for node-negative disease could delay recurrence was raised by Jordan [4, 5]. He speculated that the time of mastectomy is arbitrary and may have no relevance for the growth of an occult metastasis. Therefore, a course of tamoxifen could be

effective no matter when it is administered. Our results support this hypothesis.

Finally, our results are in accordance with those of the Wisconsin tamoxifen trial [6]. This placebo-controlled randomized trial recruited 140 women previously treated for axillary node-negative breast cancer. The mean time since breast cancer diagnosis was 7–8 years. Patients were randomized to receive tamoxifen or placebo. At 10-year analysis, there were 3 deaths in the tamoxifen group and 11 deaths in the control group ($P = 0.03$). There were, however, no differences in the disease-free survival.

We did not find a limit in the interval to initiate delayed adjuvant tamoxifen treatment. Furthermore, there was a significant improvement in disease-free survival when tamoxifen treatment was initiated more than five years, rather than less than five years, after primary treatment. This interesting point may be a chance finding based on our small sample size. Nevertheless, within the limits of 10 years, we demonstrated that delayed adjuvant tamoxifen reduced relapses in early breast cancer.

This trial does not directly compare delayed adjuvant treatment to immediate adjuvant treatment. However, the reductions in the recurrence rate were of the same order for delayed and immediate adjuvant treatment.

Side effects were quite frequent, i.e., 18%. It is difficult to establish how genuine these side effects were in the absence of placebo in the control group. It may be that some patients unconsciously rejected delayed treatment. Perhaps they considered themselves cured; perhaps they did not wish to be reminded of their disease.

Conclusions

In women who did not receive adjuvant tamoxifen immediately after surgery or radiotherapy, subsequent long-term tamoxifen administration reduces recurrence and death, even if the treatment is initiated two or more years after surgery. This treatment should be offered to all patients with ER+ and/or PR+ tumors who did not receive it previously, regardless of the interval since primary diagnosis, but within the limits of 10 years.

Furthermore, this delayed adjuvant tamoxifen treatment may reduce contralateral breast cancer in this high-risk population.

The EBCTCG overview [7] suggested no clinical advantage to tamoxifen use in receptor-negative patients. As our trial included only 24 ER-negative patients, we could not look for any effect in this small group. Therefore, delayed adjuvant tamoxifen should not be proposed for these patients to reduce recurrences. Only the preventive effect on contralateral breast cancer should be considered.

It has been reported that the combination of chemotherapy and tamoxifen increases the risk of thrombosis. For this reason, some physicians tend to begin tamoxifen immediately or some months after the completion of chemotherapy. Considering our results, this careful attitude does not seem noxious. Tamoxifen can, in such cases, be delayed without significantly increasing the risks of relapse.

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