

# Patterns of failure in a randomized trial of adjuvant chemotherapy in postmenopausal patients with early breast cancer treated with tamoxifen

R. Arriagada<sup>1,2</sup>, M. Spielmann<sup>1</sup>, S. Koscielny<sup>1</sup>, T. Le Chevalier<sup>1</sup>, T. Delozier<sup>3</sup>, M. Ducourtieux<sup>2</sup>, T. Tursz<sup>1</sup> & C. Hill<sup>1\*</sup>

<sup>1</sup>Institut Gustave-Roussy, Villejuif, France; <sup>2</sup>Instituto de Radiomedicina, Santiago, Chile; <sup>3</sup>Centre François Baclesse, Caen, France

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**Background:** We studied the effect of adjuvant anthracycline-based chemotherapy in postmenopausal patients with resected early breast cancer treated with adjuvant tamoxifen.

**Patients and methods:** The trial included 835 patients with either axillary lymph node involvement, or tumors with histological grade II or III. They were randomized after local surgery to receive either tamoxifen (TAM group) or tamoxifen plus chemotherapy (TAM-CT group) consisting of six courses of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), or 5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC). Radiotherapy was given after completion of adjuvant chemotherapy in the TAM-CT group and after surgery in the TAM group.

**Results:** The 5-year disease-free survival (DFS) rates were 73% in the TAM group and 79% in the TAM-CT group (log-rank test,  $P = 0.06$ ). The 5-year overall survival rates were 82% and 87%, respectively ( $P = 0.06$ ). The 5-year distant metastasis rates were 22% and 16% ( $P = 0.02$ ), and the 5-year local recurrence rates were 6% and 4%, respectively ( $P = 0.23$ ). There were no significant differences for contralateral breast cancer or other new primary malignancies. Chemotherapy tended to be more effective for patients who had tumors without estrogen receptors (trend test,  $P = 0.05$ ).

**Conclusions:** Anthracycline-based chemotherapy administered to postmenopausal patients receiving adjuvant tamoxifen gave a borderline significant benefit on overall and DFS, mainly by a reduction in distant metastases. Delaying radiotherapy after six courses of chemotherapy did not affect local control after up to 10 years of follow-up.

**Key words:** adjuvant chemotherapy, adjuvant tamoxifen, early breast cancer, postmenopausal patients, randomized trial

## Introduction

In the last 20 years, the therapy of early stage breast cancer has been extensively studied and the role of treatments adjuvant to surgery is becoming more clearly established. In 1989, the main question about the adjuvant treatment of early breast cancer in postmenopausal patients was whether adjuvant chemotherapy given in the presence of tamoxifen would lead to a survival benefit large enough to offset its toxicity. This question was valid for patients with node-positive axilla and for those who had node-negative axilla but other high-risk prognostic factors. The available results at that time showed a 20% [standard deviation (SD) 3] reduction in mortality with tamoxifen and a non-significant 4% (SD 5) reduction of

mortality with adjuvant chemotherapy [1]. Thus, the standard practice was to use tamoxifen and the benefit of additional chemotherapy was not considered to be established. Our group decided to investigate this question in a randomized trial evaluating six courses of anthracycline-based chemotherapy in the presence of tamoxifen. A subsidiary question was to determine whether or not delaying postoperative radiotherapy by 5 months to deliver adjuvant chemotherapy had a deleterious effect on local control.

## Patients and methods

### Eligibility

All women presenting with a primary infiltrating ductal or lobular breast carcinoma, without clinical distant metastasis, and with last menses at least 1 year before the diagnosis were considered for inclusion into the study. The two main inclusion criteria were positive histological axillary lymph nodes, or histological modified Scarff, Bloom and Richardson

\*Correspondence to: Dr C. Hill, Institut Gustave-Roussy, 39 Rue Camille Desmoulins, 94 805 Villejuif, France. Tel: +33-1-42-11-41-36; Fax: +33-1-42-11-51-58; E-mail: hill@igr.fr

grading [2] II or III. All patients had laboratory examinations, chest X-ray and mammograms. Liver ultrasound and bone scans were systematic for patients with positive axillary lymph nodes, and on request for other patients. All patients gave informed consent prior to inclusion in the study according to current French regulations, and the Ethics Committee of Kremlin-Bicêtre in France approved the protocol.

Thus, women with no nodal involvement and grade I tumors were excluded. Other criteria for exclusion were age >69 years, World Health Organization (WHO) performance status >1, histology other than primary infiltrating carcinoma, inflammatory cancer, bilateral breast tumor or history of previous cancer, except skin basal-cell carcinoma or *in situ* carcinoma of the cervix. Patients with hepatic, renal or cardiac failure, or previous myocardial infarction contra-indicating anthracycline-based chemotherapy were also excluded.

### Trial design

Eligible patients who consented to participate in the study were randomized after primary surgery between the two following arms: tamoxifen 20 mg/day for at least 2 years (TAM group) or the same tamoxifen schedule plus six courses of anthracycline-based chemotherapy (TAM-CT group). In the TAM-CT group, chemotherapy was to start within 6 weeks of surgery, and tamoxifen was given at the end of chemotherapy. When postoperative radiotherapy was indicated, it was given within 1 month of surgery in the TAM group and after completion of chemotherapy in the TAM-CT group. Radiotherapy was given concomitantly with adjuvant tamoxifen. Patients included were allowed to participate in the French trial on tamoxifen treatment duration [3] comparing 2 years versus long-term treatment.

### Treatment and follow-up

The general treatment policy for primary surgery was a tumorectomy for patients with tumors of a macroscopic diameter of  $\leq 3$  cm and a mastectomy for patients with larger tumors. All patients underwent axillary dissection. After surgery, they started tamoxifen as described above.

Patients allocated to the TAM-CT arm started chemotherapy 2–4 weeks after surgery. The chemotherapy regimen consisted of six courses of 5-fluorouracil (F) 500 mg/m<sup>2</sup>, doxorubicin (A) or epirubicin (E) 50 mg/m<sup>2</sup>, and cyclophosphamide (C) 500 mg/m<sup>2</sup>, delivered intravenously on day 1. The interval between each chemotherapy course varied from 21 to 28 days according to hematological tolerance. Doses were reduced by 20% and/or intervals between courses were increased by 1 week when blood count showed <2000/ $\mu$ l neutrophils or <100 000/ $\mu$ l platelets. Anti-emetic treatment was given according to each center's policy.

Postoperative radiotherapy was given according to the protocol of each center, but general principles were common. Radiotherapy was always given to the breast after tumorectomy at a total dose of 45–50 Gy in conventional fractionation, followed by a boost dose (~15 Gy) to the tumor bed. Supraclavicular and internal mammary chain were irradiated only in patients with positive axillary nodes. Also, patients treated with total mastectomy received postoperative radiotherapy (chest wall, supraclavicular and internal mammary chain) only if the axillary nodes were positive.

After treatment completion, patients were seen every 6 months for the first 5 years, and yearly afterwards, with a yearly mammogram and a clinical examination at each visit. Complementary examinations were conducted according to each center's policy.

### Statistical methods

Central randomization was done at the Institut Gustave-Roussy by phone or fax and stratified on each center.

A sample size of 1200 patients was planned for, in order to have a 90% chance of detecting a 7% difference in 5-year overall survival (OS) rates, from 76% to 83%, with a type I error of 5% (one-sided test).

All evaluable patients were included in the analysis in the randomly allocated treatment group (intention-to-treat analysis).

Overall survival and disease-free survival (DFS) were the main end points. They were analyzed by the Kaplan–Meier method (Rothman confidence interval) and compared using the log-rank test. Overall survival was defined as the time between the date of randomization and the date of last follow-up or death. Disease-free survival was defined as the time between date of randomization and date of last follow-up or date of best available evidence of the first unfavorable event: locoregional recurrence, distant metastasis, contralateral breast tumor or death.

A subsidiary question was to determine whether postponing radiation therapy after adjuvant chemotherapy might or might not have an effect on local control. Local recurrence and distant metastasis rates were determined using Kaplan–Meier estimators ignoring the occurrence of other events except death [4], and compared with the log-rank test.

The heterogeneity of treatment effect was tested for all prognostic parameters to detect groups of patients differing from others by their response to treatment. For parameters with at least three ordered categories, a test for trend was calculated [5]. To account for multiple comparisons, tests performed in the different categories used a 0.01 significance level. The significance tests for the overall population are at the 0.05 significance level. All *P* values are two-sided.

## Results

### Accrual

Accrual started in March 1989. During 1995, this accrual began to slow down and, in March 1996, after inclusion of 838 patients, the group decided to close the trial after results of the fourth round of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview that showed a benefit with adjuvant chemotherapy in the presence of tamoxifen [6]. Of these 838 patients, two were not evaluable because they decided not to be treated at the center after randomization and were lost to follow-up. Six patients were ineligible: one was a man, two were premenopausal, one had a previous breast cancer, one had bilateral breast cancer and one had a previous colon cancer. Among these patients, we excluded from the analysis the man and the two patients who were not evaluable for whom we had no information. Accrual according to each participating center is shown in Appendix A. Of the 835 patients included in the analysis, 415 were randomized to the TAM group and 420 to the TAM-CT group. The median follow-up was 8.2 years, estimated by inverted Kaplan–Meier [7].

### Patient characteristics

The distribution of baseline characteristics according to treatment group is shown in Table 1. There are no significant

**Table 1.** Patient characteristics according to treatment group

Characteristic	TAM group ( <i>n</i> = 415)		TAM-CT group ( <i>n</i> = 420)	
	<i>n</i>	%	<i>n</i>	%
Age (years)				
<55	85	20	86	20
55–65	236	57	248	59
65+	94	23	86	20
Tumor size (cm)				
≤3	342	86	354	87
>3	56	14	55	13
Unknown	17	–	11	–
Positive lymph nodes				
0	153	37	162	39
1–3	178	43	189	45
4+	84	20	69	16
Histological grade				
I	33	8	45	11
II	232	58	240	58
III	138	34	132	31
Unknown	12	–	3	–
ER level (fmol/mg)				
0	13	4	9	2
1–9	45	12	46	13
10–99	91	25	95	26
100+	212	59	213	59
Unknown	54	–	57	–
PR level (fmol/mg)				
0	17	5	17	5
1–9	95	26	89	25
10–99	124	34	136	37
100+	124	34	120	33
Unknown	55	–	58	–

ER, estrogen receptor; *n*, number of patients; PR, progesterone receptor; TAM, tamoxifen; TAM-CT, adjuvant chemotherapy [six courses of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), or 5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC)] added to tamoxifen.

imbalances between the two groups. Hormone receptor determination with a value of  $\leq 9$  fmol/mg was defined as negative.

### Surgery and radiotherapy

Surgical treatment was a tumorectomy in 68% of patients, and modified radical mastectomy in the remaining 32%. All patients had an axillary dissection with an average and median number of 14 nodes removed both in the TAM group (range 2–43 nodes) and in the TAM-CT group (range 1–37 nodes).

Radiotherapy was delivered according to the practice of each center. Among the 568 patients who had a tumorectomy, all but one received breast irradiation at a total dose ranging from 45 to 75 Gy, including the boost dose on the tumor bed. Among the 267 patients who had a mastectomy, 156 received radiotherapy to the chest wall at a dose ranging from 45 to 65 Gy, including boost dose to the scar. Seven per cent of patients received axillary radiation at a dose ranging from 45 to 60 Gy. The internal mammary nodes received radiotherapy in 55% of cases at doses between 45 and 65 Gy, and the supraclavicular area was irradiated in 54% of patients at doses

between 45 and 60 Gy. The proportions of patients who received radiotherapy were 85% and 87% for the TAM and TAM-CT groups, respectively.

### Treatment compliance

Of 420 patients in the TAM-CT group, 409 received chemotherapy and 11 patients did not (nine refused treatment, one was not given chemotherapy by mistake, one was not treated according to the protocol because of a bilateral tumor).

Among the 415 patients included in the TAM group, eight received chemotherapy: four had distant metastases diagnosed after randomization, three received chemotherapy by mistake and one had her treatment changed from tamoxifen to chemotherapy after developing a phlebitis.

In the TAM-CT group, chemotherapy included epirubicin in 375 patients (89%), doxorubicin in 20 patients and mitoxantrone (12 mg/m<sup>2</sup>) in 11 patients. One patient received three courses of FAC followed by three courses of FEC, one patient received six courses of CMF, and another six courses of EV (vincristine) CF.

Of 409 women randomized to the TAM-CT group who received chemotherapy, 387 women (95%) received the scheduled six courses of chemotherapy, 12 (3%) five courses and 10 (2%) three courses or less. Thirty-three patients (8%) had an interval period between two courses of chemotherapy of more than 28 days (10% in two or three cycles and 90% in one cycle). In addition, 20 patients had doses different from the doses planned in the protocol (30% in five cycles, 35% in two or three cycles and 35% in one cycle).

Twenty-nine patients (7%) had hematological toxicity which induced delayed administration and a dose reduction in seven patients, delayed administration in 15 patients and a dose reduction in seven patients.

### Disease-free survival and overall survival

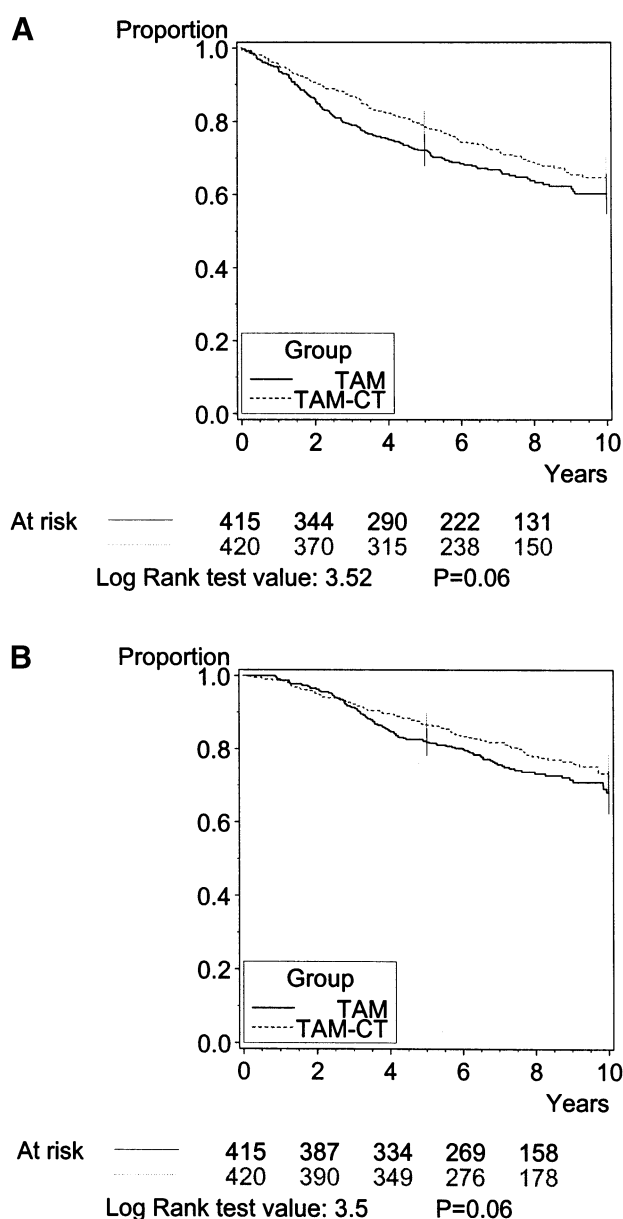
A total of 147 patients in the TAM group experienced at least one event (locoregional or distant metastasis, contralateral breast cancer or death from any cause), compared with 126 in the TAM-CT group. Kaplan–Meier curves for DFS are shown in Figure 1A; the difference is statistically borderline significant ( $P = 0.06$ ).

A total of 112 deaths were observed in the TAM group versus 89 in the TAM-CT group. The OS curves according to treatment groups are shown in Figure 1B; the difference is borderline significant ( $P = 0.06$ ).

The 5-year DFS and OS rates are shown in Table 2.

### Patterns of failure

The 5-year event rates are shown in Table 2. The 5-year actuarial loco-regional recurrence rate was 6% in the TAM group and 4% in the TAM-CT group ( $P = 0.23$ ). The 5-year actuarial distant metastasis rate was 22% in the TAM group



**Figure 1.** (A) Disease-free survival according to treatment groups (log-rank test,  $P = 0.06$ ). (B) Overall survival according to treatment groups (log-rank test,  $P = 0.06$ ).

and 16% in the TAM-CT group ( $P = 0.02$ ). The cumulative incidences for these two events are shown in Figure 2.

There were no significant differences for contralateral breast cancer (CBC) or other new primary malignancies (NPM). The 5-year actuarial CBC rate was 2% in each group ( $P = 0.24$ ). Thirty one patients developed NPM: 18 and 13 patients in the TAM and TAM-CT groups, respectively. The 5-year actuarial NPM rates were 2.5% in each group ( $P = 0.30$ ). The most frequent tumor sites were as follows: colon or rectum, seven; endometrium, six; and leukemias, four (three in the TAM group and one in the TAM-CT group).

**Table 2.** Five-year actuarial survival and event rates according to treatment group

Survival /events	TAM group		TAM-CT group		OR (95% CI)	P value
	5-year rate (%)	95% CI	5-year rate (%)	95% CI		
Disease-free survival	73	68–77	79	75–83	0.80 (0.63–1.01)	0.06
Overall survival	82	78–85	87	83–90	0.77 (0.58–1.01)	0.06
Locoregional recurrence	6	4–9	4	2–6	0.73 (0.43–1.23)	0.23
Distant metastasis	22	19–27	16	13–20	0.72 (0.55–0.95)	0.02
Contralateral breast cancer	2	1–4	2	1–4	0.69 (0.34–1.40)	0.24
New primary malignancy	2.5	1–5	2.5	1–5	1.55 (0.75–3.21)	0.30

CI, confidence interval; OR, odds ratio; TAM, tamoxifen; TAM-CT, adjuvant chemotherapy [six courses of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), or 5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC)] added to tamoxifen. The TAM group is the reference group.

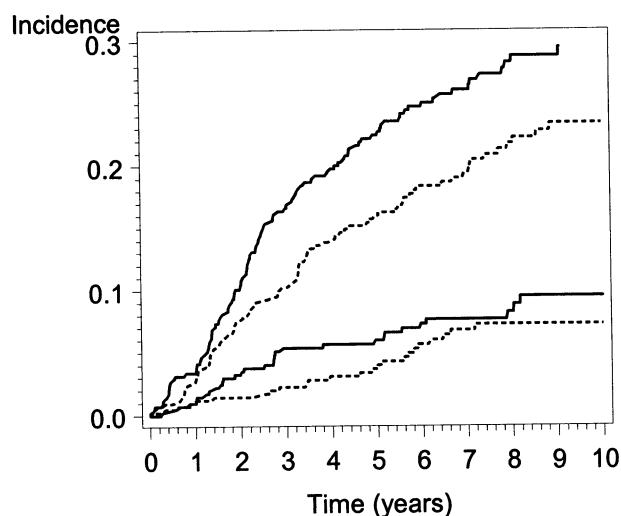
### Treatment interactions with tumor or patient parameters

We studied the variations of chemotherapy effect according to tumor or patient characteristics—such as axillary lymph node involvement, estrogen receptor (ER) status, histological grade and age—in terms of DFS. Treatment interaction was borderline significant only for ER status (trend test,  $P = 0.05$ ) and not significant for the other factors. For instance, age was analyzed in 2-year categories and no differential treatment effect was found (heterogeneity test, 0.98; trend test, 0.92). Chemotherapy seemed to be more effective for patients with ER-negative tumors. However, the  $P$  value is not formally significant, as a value of 0.01 was defined for multiple com-

parisons. Results according to ER and lymph node involvement are shown in Figure 3.

### Analysis of tamoxifen treatment duration

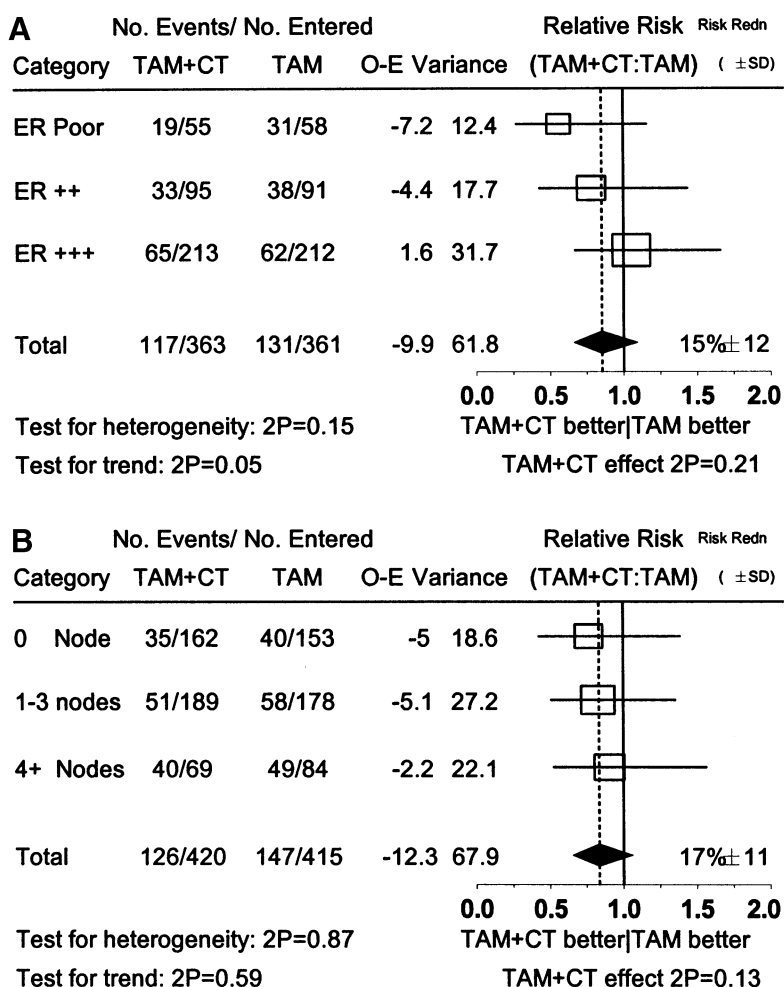
Two hundred and sixty-seven patients were randomized at the Institut Gustave-Roussy after 2 years of tamoxifen either to stop tamoxifen (131 patients) or to continue a long-term treatment with tamoxifen (136 patients). Among these 267 patients, 121 and 146 were in the TAM and TAM-CT groups, respectively. There was no significant difference (trend test,  $P = 0.31$ ) in the chemotherapy effect among patients who received tamoxifen for only 2 years [hazard ratio (HR), 0.52; 99% CI 0.17–1.61] as compared with those who received long-term tamoxifen (HR, 0.97; 99% CI 0.32–2.92).



**Figure 2.** Incidence (estimated by 1 – Kaplan–Meier) of distant metastases (two top curves; log-rank,  $P = 0.02$ ) and locoregional recurrences (two bottom curves; log-rank,  $P = 0.23$ ) according to treatment group. Continuous lines correspond to the tamoxifen (TAM) group and dotted lines to the TAM-CT group [tamoxifen plus chemotherapy consisting of six courses of FAC (5-fluorouracil, doxorubicin, cyclophosphamide) or FEC (5-fluorouracil, epidoxorubicin, cyclophosphamide)].

### Discussion

This trial confirms the beneficial effect of adjuvant chemotherapy in postmenopausal patients with early breast cancer receiving adjuvant tamoxifen. In the EBCTCG overview which includes a high proportion of postmenopausal women (among 18 000 patients, about 75% were  $\geq 50$  years of age [6]) adjuvant chemotherapy was demonstrated to have a small effect as compared with the effect observed in premenopausal patients [8, 9]. A controversy arose when the hypothesis of a hormonal-related mechanism (ovarian suppression) was proposed to explain the differential effect between younger and older patients [10, 11]. A similar argument was proposed for postmenopausal patients who received tamoxifen: the effect of chemotherapy would be observed mainly in the absence of hormonal treatment. The latter argument was the rationale for planning the current study, as it was questionable whether adjuvant chemotherapy added a beneficial effect to adjuvant tamoxifen in these patients. In the trial, patients with ER-negative tumors were included, as at the time the EBCTCG overview results showed that the beneficial effect of tamoxifen also existed in this subgroup of postmenopausal patients [1]. In the present analysis, chemotherapy seemed



**Figure 3.** Chemotherapy effect according to (A) estrogen receptor (ER) status and (B) axillary lymph node involvement. End point is disease-free survival. The test of heterogeneity tests for equality of treatment effect between the three categories. The test for trend evaluates the slope of the relationship between the ordered categories and the odd ratios.

more effective in patients with ER-negative tumors, probably accounting for a lesser effect of adjuvant tamoxifen as shown by Rutqvist et al. [12] and corroborated by the EBCTCG overview [13].

Seven other large trials (each including more than 500 patients) have evaluated the role of adjuvant chemotherapy in postmenopausal patients or in patients over 50 years of age, all treated with adjuvant tamoxifen. They are summarized in Table 3 [14–20].

The International Breast Cancer Study Group (IBCSG) VII study [14] showed a significant effect of three courses of CMF chemotherapy in terms of DFS, but this beneficial effect was limited to patients <65 years of age. This age effect was not confirmed in our trial. The South West Oncology Group (SWOG) 7827 study [15] did not show a significant effect of CMFVP chemotherapy, nor did the National Cancer Institute of Canada (NCIC) trial [16] that in addition reported an increased toxicity for the combined arm with eight CMF.

The two National Surgical Adjuvant Breast and Bowel Project (NSABP) trials [17, 18] showed a beneficial effect of six CMF or four AC, the first schedule only in terms of OS. The other trial evaluating anthracycline-based chemotherapy is the SWOG 8814 trial [19] that showed a beneficial effect on DFS and OS. Finally, the International Collaborative Cancer Group (ICCG) study [20] evaluated mono-chemotherapy with epirubicin (50 mg/m<sup>2</sup> twice in each cycle) and the results showed a significant effect on DFS. Overall, >7000 patients were included in these large trials and, in general, they favor the use of chemotherapy. The overall effect of chemotherapy is a 23% reduction in the risk of relapse or death (odds ratio 0.77, 95% CI 0.71–0.84), which is highly significant. Of course, a publication bias is possible, since trials that included less than 500 postmenopausal patients and unpublished trials were excluded. This publication bias would tend to increase the overall treatment effect [21].

If we consider the overall results according to the type of chemotherapy, two of the four trials evaluating CMF showed a

**Table 3.** Published randomized trials<sup>a</sup>

Trial [reference]	<i>n</i>	Chemotherapy	Inclusion criteria	DFS: OR (95% CI)	<i>P</i> value
IBCSG VII [14]	608	3 CMFc	N+	0.78 (0.62–0.97)	0.03
SWOG 7827 [15]	598	12 CMFVp	N+, ER+	0.89 (0.71–1.12)	0.32
NCIC [16]	705	8 CMF	N+, ER+ or PR+	0.97 (0.77–1.23)	0.80
NSABP B-20 [17]	1264	6 MF/6 CMFc	N–, ER+	0.74 (0.52–1.05)	0.09
NSABP B-16 [18]	1124	4 AC60/PF-PFA30	N+, PR+	0.52 (0.37–0.72)	0.0001
SWOG 8814 [19]	1470	6 C A30 d 1 & 8 F seq. or conc.	N+, ER+	0.70 (0.58–0.85)	0.0002
ICCG [20]	604	6 E50 d1 & 8	N+	0.72 (0.54–0.96)	0.02
Current trial	835	6 FEC50	N+, or grade II–III	0.80 (0.63–1.01)	0.06
Overall results	7208	–	–	0.77 (0.71–0.84)	<10 <sup>–4</sup>

<sup>a</sup>Including more than 500 postmenopausal patients or patients >50 year of age that evaluated the effect of adjuvant chemotherapy in the presence of tamoxifen.

IBCSG, International Breast Cancer Study Group; ICCG, International Collaborative Cancer Group; NCIC, National Cancer Institute of Canada; NSABP, National Surgical Adjuvant Breast and Bowel Project; SWOG, South West Oncology Group; A, doxorubicin; C, cyclophosphamide; CMFc, classical CMF; E, epirubicin; F, 5-fluorouracil; M, methotrexate; p, prednisone; P, L-phenylalanine mustard; V, vincristine; DFS, disease-free survival; OR, odds ratio, adjuvant tamoxifen alone is the reference group; N, node; ER, estrogen receptor; PR, progesterone receptor.

beneficial significant effect, and the four trials that evaluated an anthracycline-based chemotherapy showed a significant treatment effect. If this difference between the effects of these regimens was real, three kinds of explanations should be discussed: the major effect of anthracyclines, the type of CMF and the dose effect.

Anthracycline-based chemotherapy regimens have been shown to be more effective than CMF-like chemotherapy [6]; even if the difference is moderate it could explain the apparent better results in trials summarized in Table 3. However, a controversy is still ongoing on the different modalities of CMF, and some authors [22, 23] claim that the best effect is obtained with a classical CMF regimen as originally described [8]. Indeed, in Table 3, the two trials evaluating classical CMF [14, 17] found a significant beneficial treatment effect. However, there is no heterogeneity on treatment effects among trials in terms of DFS (heterogeneity test,  $P = 0.08$ ).

An alternative explanation would be a dose effect. It has been claimed that the smaller effect of adjuvant chemotherapy in postmenopausal patients was related to a poorer tolerance leading to a decrease in the delivered CMF doses within the classical schedule. Taking into account the possibility of this dose effect during the planning of the current trial, we decided to use an anthracycline-based regimen given in one day per course, thus avoiding dose adaptation during the chemotherapy cycle. Indeed, the chemotherapy compliance was quite good, as 95% of patients received the six planned courses, most using epirubicin, and only in 7% of patients was there an alteration in the chemotherapy delivery schedule. The other issue regarding the anthracycline dose is the chosen level of epirubicin dose. When planning the study, three randomized trials evaluating dose equivalence between doxorubicin and

epirubicin in advanced breast cancer [24–26] showed that a similar tumor effect was obtained with equi-doses of both anthracyclines. Since then, two adjuvant trials [27, 28] have shown that a dose effect exists for epirubicin and now a dose of 100 mg/m<sup>2</sup> is considered more effective than 50 mg/m<sup>2</sup>. Even though the French [27] and Belgian trials [28] included only 276 and 217 postmenopausal patients, respectively, neither of these trials showed a differential chemotherapy effect according to age. It can then be hypothesized that the results of our trial could have been improved with a higher dose of epirubicin or even the use of a classical CMF regimen. In any case, these arguments favor the use of adjuvant chemotherapy in the population studied.

Regarding the exploratory subgroup analyses, in our trial a larger treatment effect was suggested for patients with ER-negative tumors in terms of DFS. This result agrees with those found in the EBCTCG overview [6]. We did not find any other interaction between chemotherapy effect and patient or tumor characteristics. We emphasise, however, that these analyses are only exploratory.

The study of the pattern of failure showed that chemotherapy mainly affected the distant metastasis rate, without a clear effect on the rate of other types of event (Table 2) in the presence of local or locoregional radiotherapy among >85% of patients. It is of importance that long-term control was not affected by the delay of local (regional) radiotherapy introduced by the administration of six courses of chemotherapy. These findings are in agreement with those of the IBCSG studies [29] and contradict the results of a small randomized study evaluating the chronology of radiotherapy and chemotherapy in early breast cancer [30]. At the present time, there is no evidence that a delay of radiotherapy when active adjuvant

chemotherapy is given has a deleterious effect. This finding favors the hypothesis that systemic treatments have a beneficial effect on local control [31], even if this effect is rather moderate when compared with that provided by radiotherapy.

The relative reduction of recurrence and death found in the current and other similar trials (Table 3) may be challenged by the small absolute benefit that is obtained in patients with relatively good prognosis with tumors of <30 mm, with positive-ER and node-negative axilla [32]. In this decision-making process, it is advisable to take into account the particular risk factors of each patient to balance the expected benefit with the early toxicity of adjuvant chemotherapy [33].

In conclusion, overall treatment effects are in favor of adjuvant chemotherapy in postmenopausal patients in different subgroups even if there are some quantitative differences. It seems that the beneficial effects of chemotherapy and tamoxifen are at least partially independent.

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## Appendix A. List of participants<sup>a</sup>

Institution	No. of patients	Investigators
Institut Gustave-Roussy (IGR), Villejuif	688	Rodrigo Arriagada, Françoise Fontaine, Axel Le Cesne, Thierry Le Chevalier, Françoise May-Levin, France Rochard, Marc Spielmann, Danièle Sarrazin, Thomas Tursz
Data management, IGR, Villejuif		Muriel Ducourtieux
Biostatistics, IGR, Villejuif		Catherine Hill, Serge Koscielny
Centre François Baclesse, Caen	81	Thierry Delozier, Alain Rivière
CHU Jean Bernard, Poitiers	34	Thierry Germain
Centre d'Oncologie du Pays Basque, Bayonne	23	Marc Lipinski
CHU, Limoges	9	Bernard Roullet

<sup>a</sup>All participating centers are located in France.  
CHU, Centre Hospitalier Universitaire.