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**ORIGINAL ARTICLE**

# Results of two randomized trials evaluating adjuvant anthracycline-based chemotherapy in 1 146 patients with early breast cancer

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**Abstract**

Two randomized trials evaluated the effect of 6 courses of anthracycline-based chemotherapy in early breast cancer. A total of 1 146 patients were included: 311 high-risk node-negative premenopausal patients and 835 high-risk node-negative or node-positive postmenopausal patients. Patients were randomized after surgery to receive either no chemotherapy (control group) or 6 courses of anthracycline-based chemotherapy (CT group). Postmenopausal patients received adjuvant tamoxifen for at least two years. Radiotherapy was delivered after completion of chemotherapy in the CT group. The 10-year disease-free survival (DFS) rates were 60% in the control group and 65% in the CT group (log-rank test, $p = 0.01$). The 10-year distant metastasis rates were 28% and 23% ($p = 0.02$), and the 10-year local recurrence rates were 12% and 10%, respectively ($p = 0.24$). Chemotherapy was significantly less effective in post-menopausal patients with estrogen receptor-positive tumors. Adjuvant anthracyclin-based chemotherapy yielded a significant benefit for DFS by lowering the risk of distant metastases. After up to 10 years of follow-up, deferring radiotherapy after chemotherapy did not compromise local control.

In the mid-1970s, adjuvant chemotherapy combining cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) became a standard treatment in young breast cancer patients with positive axillary nodes [1]. The results of the first trials were confirmed in a worldwide overview [2]. Adjuvant chemotherapy led to a 22% ($\pm 6$) decline in mortality among high-risk (mostly node-positive) premenopausal patients, but only a 4% ($\pm 5$) reduction in postmenopausal patients [2]. At the same time, adjuvant tamoxifen led to a 20% ($\pm 3$) reduction in mortality among postmenopausal patients but had no effect ($-1\% \pm 8$) in premenopausal patients. The resulting standard practice was to use adjuvant chemotherapy in node-positive premenopausal patients and adjuvant tamoxifen in postmenopausal patients. In 1989, one of the questions that remained unanswered regarding adjuvant treatment in early breast cancer was the effect of adjuvant chemotherapy both in young patients with negative axillary nodes, and in older patients receiving adjuvant tamoxifen [3]. Our group decided to investigate the potential benefit of 6 courses of anthracycline-based chemotherapy without tamoxifen in premenopausal patients with negative axillary nodes, and of anthracycline-based chemotherapy associated with tamoxifen in postmenopausal patients with either positive axillary nodes or negative axillary nodes and other high-risk prognostic factors. A secondary question was whether delaying postoperative radiotherapy up to 5 months in order to deliver adjuvant chemotherapy, would or would not reduce local control.

## Material and methods

### *Eligibility*

All women with primary infiltrating ductal or lobular breast carcinoma, without clinical distant metastasis

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were considered for inclusion. A postmenopausal status was defined as no menses for at least 12 months before the diagnosis. The main inclusion criteria for premenopausal patients were histologically-proven negative axillary lymph nodes and modified Scarff, Bloom and Richardson (SBR) histologic grade II or III tumors [4]. Inclusion criteria for postmenopausal patients were histologically proven positive or negative axillary lymph nodes associated with SBR histologic grade II or III tumors. All patients had laboratory tests, a chest x-ray and mammograms, and a liver ultrasound and bone scan were performed systematically in patients with positive axillary lymph nodes, and on request for other patients, according to laboratory signs or symptoms. All patients gave their informed consent prior to inclusion in the study according to current French regulations, and the Ethics Committee in Kremlin-Bicêtre, France, approved both protocols.

Exclusion criteria were as follows; age above 69, WHO performance status above 1, histology other than primary infiltrating carcinoma, inflammatory cancer, bilateral breast tumor, gestation or breast-feeding period, or a history of a previous cancer except basocellular skin or *in situ* cervix carcinoma. Patients with hepatic, renal or cardiac failure, or a previous myocardial infarction contraindicating anthracycline-based chemotherapy were also excluded.

### *Trial design*

Eligible patients who agreed to participate in the study were randomized after primary surgery between no adjuvant chemotherapy (control group) or 6 courses of anthracycline-based chemotherapy (CT group). In the CT group, chemotherapy was initiated within 6 weeks after surgery, and tamoxifen was given to postmenopausal patients at the end of chemotherapy. When required, postoperative radiotherapy was delivered within a month after surgery in the control group and after the completion of chemotherapy in the CT group. Radiotherapy was delivered concomitantly with adjuvant tamoxifen. All postmenopausal patients received adjuvant tamoxifen for at least two years and they were allowed to participate in a French trial comparing two years of tamoxifen with long-term treatment [5].

### *Treatment and follow-up*

The general treatment policy for primary surgery was a lumpectomy for patients with tumors measuring 3 cm or less (macroscopic diameter), and a total mastectomy for patients with larger tumors. All patients underwent axillary dissection. After surgery, postmenopausal patients started tamoxifen, as described above.

The chemotherapy regimen consisted of 6 courses of 5-fluorouracil (F) 500 mg/m$^2$, doxorubicin (A) or epirubicin (E) 50 mg/m$^2$, and cyclophosphamide (C) 500 mg/m$^2$, administered intravenously on day 1. The interval between each chemotherapy course varied between 21 and 28 days according to hematological tolerance. Doses were reduced by 20% and/or a further week was added to intervals between courses when the blood count at the time of each course showed less than 2 000 neutrophils or less than 100 000 platelets. Anti-emetic treatment was given according to the policy in each center.

Postoperative radiotherapy was delivered according to the protocol used in each center, but general principles were common to all participating centers. After a lumpectomy, a total dose of 45 to 50 Gy of radiotherapy was delivered to the breast using conventional fractionation, followed by a boost dose of approximately 15 Gy to the tumor bed. After a total mastectomy, postoperative radiotherapy was delivered to the 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 thereafter, with a yearly mammogram and a clinical examination at each visit. Complementary examinations were performed according to the policy in each center.

### *Statistical methods*

Randomization was computer generated with blocks of size 4, centralized at the Institut Gustave-Roussy by phone or fax, and stratified on each center.

In order to have a 90% chance of detecting a 7% difference in 5-year survival rates, from 76% to 83%, with a type 1 error of 5% (one-sided test), 1 154 postmenopausal patients were required. To detect a 10% difference in 5-year survival, from 65% to 75%, 724 premenopausal patients were needed.

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

Overall survival and disease-free survival (DFS) were the main endpoints. 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 the last follow-up or the date of death. DFS was defined as the time between the date of randomization and the date of the last follow-up or the date of the best available evidence for the first event: locoregional recurrence,

distant metastasis, contralateral breast tumor or death.

A secondary question was 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 [6], and compared with the log-rank test.

The heterogeneity of the treatment effect was tested for prognostic parameters in order to identify groups of patients differing from others according to their response to treatment. A test for trend was calculated for parameters with at least three ordered categories [7]. All tests were two-sided and a p value of 0.05 was considered significant, except for the heterogeneity and trend tests for which the p value for significance was 0.01.

## Results

### *Accrual*

Accrual started in March 1989. In March 1996, after accruing 1 150 patients (312 premenopausal and 838 postmenopausal patients), the group decided to close the trials when the fourth round of the EBCTCG overview demonstrated a benefit with adjuvant chemotherapy in high-risk node-negative younger patients and in older patients receiving adjuvant tamoxifen [8]. This decision was not based on the trial results that were not available at that time. Of these 1 150 patients, three were not evaluable because they decided not to be treated in the center after randomization and they were lost to follow-up. There were four ineligible patients; one was a man, one had had a previous breast cancer, one had bilateral breast cancer, and one had had a previous colon cancer. Among these patients, we excluded the man, and the three unevaluable patients. The three other patients were maintained in the analysis. Accrual according to centers is shown in Appendix I. Of the 1,146 patients included in the analysis, 573 were randomly allocated to each arm of the trial. The median follow-up is 9.0 years (range: 7–14 years), estimated by the inverted Kaplan-Meier method [9].

### *Baseline characteristics*

The distribution of baseline characteristics according to treatment group is shown in Table I. There were no significant imbalances between the two groups. A negative hormone receptor value was defined as 9 fmol or less /mg of protein.

Table I. Patient characteristics according to treatment group.

| | Control group (n = 573) | | Adjuvant chemotherapy group (n = 573) | |
|---|---|---|---|---|
| Characteristic | n | % | n | % |
| Menopausal status | | | | |
| Pre- | 158 | 28 | 153 | 27 |
| Post | 415 | 72 | 420 | 73 |
| Age (years) | | | | |
| <45 | 89 | 16 | 85 | 15 |
| 45–50 | 66 | 12 | 60 | 10 |
| 51–55 | 88 | 15 | 93 | 16 |
| 56–60 | 130 | 23 | 121 | 21 |
| 61–65 | 106 | 18 | 129 | 23 |
| 65+ | 94 | 16 | 85 | 15 |
| Tumor size (cm) | | | | |
| ≤3 | 483 | 88 | 485 | 87 |
| >3 | 67 | 12 | 75 | 13 |
| Unknown | 23 | – | 13 | – |
| Positive lymph nodes | | | | |
| 0 | 308 | 54 | 315 | 55 |
| 1–3 | 181 | 32 | 189 | 33 |
| 4+ | 84 | 15 | 69 | 12 |
| Histological grade | | | | |
| I | 34 | 6 | 46 | 8 |
| II | 326 | 58 | 318 | 56 |
| III | 199 | 36 | 205 | 36 |
| Unknown | 14 | – | 4 | – |
| Estrogen receptor in fmol/mg of protein | | | | |
| Premenopausal* | | | | |
| 0–9 | 18 | 14 | 24 | 19 |
| 10–99 | 70 | 56 | 64 | 51 |
| 100+ | 37 | 30 | 37 | 30 |
| Unknown | 33 | – | 28 | – |
| Postmenopausal** | | | | |
| 0–9 | 58 | 16 | 55 | 15 |
| 10–99 | 91 | 25 | 95 | 26 |
| 100+ | 212 | 59 | 213 | 59 |
| Unknown | 54 | – | 57 | – |
| Progesterone receptor in fmol/mg of protein | | | | |
| 0–9 | 139 | 29 | 131 | 27 |
| 10–99 | 176 | 36 | 196 | 40 |
| 100+ | 170 | 35 | 160 | 33 |
| Unknown | 88 | – | 86 | – |

n: number of patients.
* in absence of tamoxifen
** in presence of tamoxifen

### *Surgery and radiotherapy*

Surgical treatment was a lumpectomy in 70% of patients, and a modified radical mastectomy in the remaining 30%. All patients had an axillary dissection with an average of 14 nodes removed in both the control group (range 1 to 43) and the CT group (range 1 to 37).

Radiotherapy was delivered according to the treatment policy in each center. Among the 798 patients who had a lumpectomy, all but 20 received breast

irradiation at a total dose ranging from 45 to 75 Gy, including the boost dose to the tumor bed. Among the 348 patients who had a mastectomy, 178 received radiotherapy to the chest wall at a dose ranging from 30 to 65 Gy, including a boost dose to the scar. Five percent of patients received axillary radiation at a dose ranging from 44 to 60 Gy. The internal mammary nodes received radiotherapy in 44% of cases at doses ranging between 30 and 65 Gy, and the supraclavicular area was irradiated in 41% of patients at doses ranging between 30 and 60 Gy.

*Treatment compliance*

Of the 573 patients in the CT group, 552 received chemotherapy and 20 did not (for one patient this information is missing). Among the 573 patients included in the control group, 9 received chemotherapy.

All postmenopausal patients received tamoxifen for two years, except 136 (60 in the control group and 76 in the CT group) who received long-term tamoxifen in the framework of a French tamoxifen trial [5].

In the CT group, chemotherapy consisted of FEC in 487 patients (85%), FAC in 49 patients and a mitoxantrone-based off-protocol regimen (12 mg/m$^2$) in 16 patients. Of the 552 women randomly allocated to the CT group who received the treatment, 525 (95%) received the six scheduled courses of chemotherapy, 16 (3%) received 5 courses, and 11 (2%) received three courses or less. Forty-one patients (7%) had an interval exceeding 28 days between two courses of chemotherapy. In addition, 27 patients had different doses from those planned in the protocol.

Forty-five patients (8%) experienced hematological toxicity, which led to delayed drug administration and a dose reduction in 7 patients, delayed drug administration only in 20 patients, and a dose reduction only in 9 patients.

*Survival and patterns of failure*

A total of 180 patients in the CT group experienced at least one event (locoregional or distant metastasis, contralateral breast cancer or death from any cause), as compared to 218 in the control group. Kaplan-Meier curves for disease-free survival are shown in Figure 1; the difference was statistically significant ($p = 0.01$).

A total of 124 deaths were observed in the CT group versus 150 in the control group (Figure 3); the difference was not significant ($p = 0.09$). The 10-year disease-free survival, overall survival and event rates are shown in Table II. The 10-year actuarial

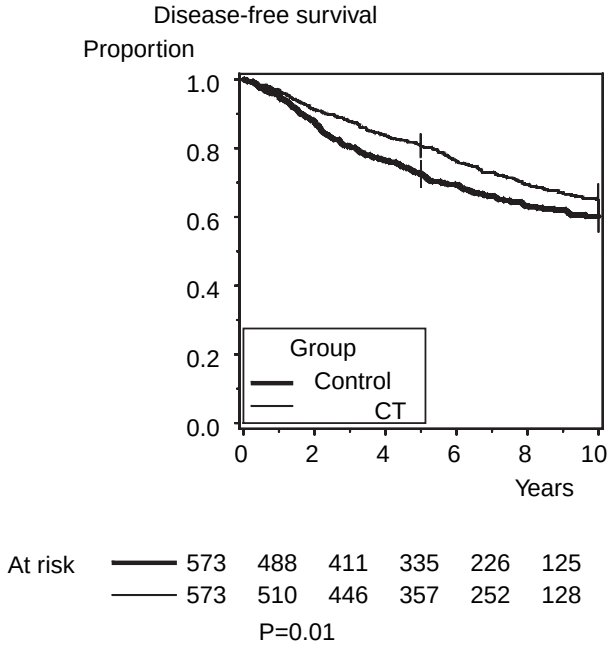


Figure 1. Disease-free survival according to treatment groups (log-rank test, $p = 0.01$).

locoregional recurrence rate was 10% in the CT group and 12% in the control group ($p = 0.24$). The 10-year actuarial distant metastasis rate was 23% in the CT group and 28% in the control group ($p = 0.02$). The incidence curves 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 10-year actuarial CBC rate was 6% in CT group and 7% in control group ($p = 0.30$). Thirty-nine patients developed a NPM, 18 in the CT group and 21 in the control group. The 10-year actuarial NPM rates were 4% in the CT group and 5% in the control group ($p = 0.59$). The most frequent tumor sites were the colon or rectum (7), the endometrium (6) and there were 4 cases of leukemia (1 acute myeloid leukemia and 2 chronic lymphoid leukemia in the control group, and 1 acute myeloid leukemia in the CT group).

Figure 4 shows the relative treatment effect for each type of event. The size of the effect was similar for all evaluation criteria, and significance levels depended on the number of events in each category.

*Treatment interactions with patient, tumor or treatment characteristics*

There was no difference in the treatment effect between premenopausal and postmenopausal patients. The relative risks of events were similar in premenopausal and postmenopausal patients: 0.66

Table II. Ten-year actuarial survival and event rates according to treatment groups.

| | Control group | | Chemotherapy group | | Odds Ratio* | |
|---|---|---|---|---|---|---|
| Survival/events | 10-year rate | 95% CI | 10-year rate | 95% CI | (95% CI) | P value |
| Disease-free survival | 60% | 56–64% | 65% | 60–69% | 0.77 (0.63–0.94) | 0.01 |
| Overall survival | 71% | 67–75% | 75% | 70–79% | 0.81 (0.64–1.03) | 0.09 |
| Locoregional recurrence | 12% | 9–16% | 10% | 8–14% | 0.80 (0.55–1.17) | 0.24 |
| Distant metastasis | 28% | 24–32% | 23% | 19–27% | 0.75 (0.59–0.96) | 0.02 |
| Contralateral breast cancer | 7% | 5–10% | 6% | 4–10% | 0.75 (0.44–1.28) | 0.30 |
| New primary malignancy | 5% | 3–9% | 4% | 2–6% | 0.84 (0.45–1.58) | 0.59 |

*The control group is the reference.

(0.45–0.96, p = 0.03) and 0.82 (0.65–1.03, p = 0.09), respectively.

We studied possible variations in the effect of chemotherapy on disease-free survival according to tumor or patient characteristics such as axillary lymph node involvement, estrogen receptor (ER) status, histologic grade, menopausal status and age. No significant variations were evidenced. For instance, Figure 5 shows that there was no heterogeneity or any trend in the treatment effect according to age (heterogeneity and trend tests: 0.69 and 0.36, respectively).

There were no significant differences in the treatment effect according to the number of involved axillary lymph nodes (Figure 6). We have analysed the effect of chemotherapy by menopausal status i.e. separately in pre-menopausal women who did not receive tamoxifen and in postmenopausal women who received tamoxifen systematically. As shown in Figure 7, the benefit of chemotherapy is somewhat larger among pre-menopausal than among post menopausal women (risk reduction with chemotherapy equal to 44% SD 17% versus 13% SD 12%). This figure also shows the results by level of estrogen receptors. In pre-menopausal women, chemotherapy is associated with a highly significant 44% risk reduction (P = 0.008) and this risk reduction does not vary significantly between ER groups (test for heterogeneity P = 0.95). In postmenopausal patients, the overall risk reduction is not statistically significant (13%, p = 0.27), the heterogeneity test is

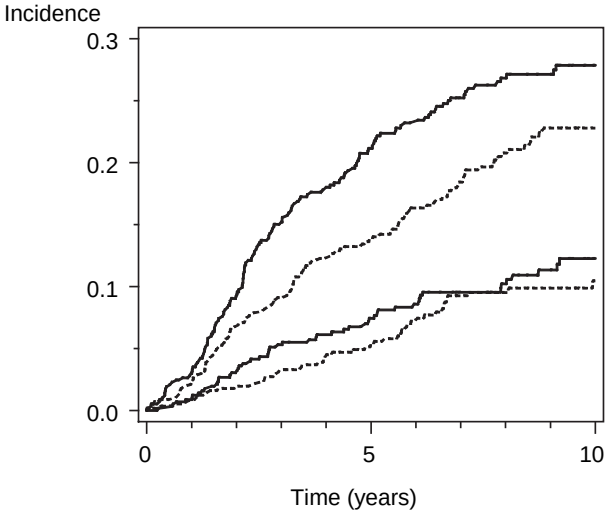


Figure 2. Incidence (estimated by 1-Kaplan Meier) of distant metastases (two top curves; log-rank, p = 0.02) and locoregional recurrences (two bottom curves; log-rank, p = 0.24) according to treatment groups. Continuous lines represent the control group and dotted lines the CT group.

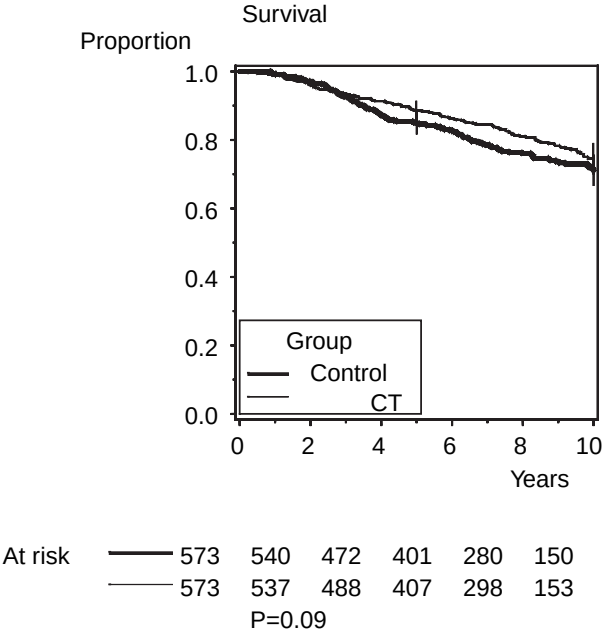


Figure 3. Overall survival according to treatment groups (p = 0.09).

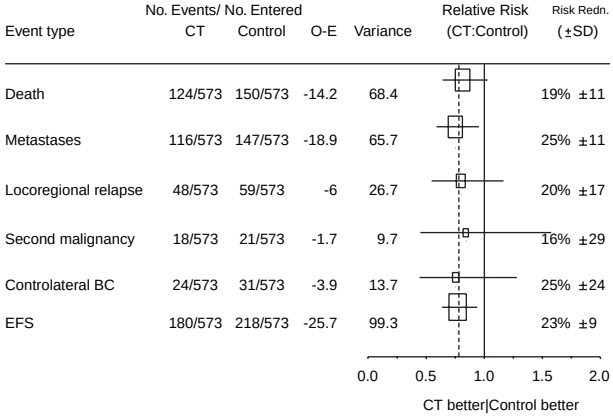


Figure 4. Effect of chemotherapy on different types of events. EFS: event-free survival.

not significant, and the trend test shows that the effect of chemotherapy is larger in patients with tumor with less ER receptors ($p = 0.03$). There seems to be no effect of chemotherapy in postmenopausal women treated by tamoxifen when their tumor has a high level of estrogen receptors. In premenopausal women, the overall absolute benefits in terms of 10-year DFS was 13% (95CI: 2–22%), in postmenopausal women, the absolute benefits in terms of 10-year DFS were: 17% (95% CI: −3%–32%) for ER-, 9% for ER+ (−5%–20%), and −3% (−13%–5%) for ER++ tumors.

## Discussion

The results of these trials confirm the beneficial effect of adjuvant chemotherapy in patients with early breast cancer. They mainly demonstrate that the treatment effect was similar for different age groups (Figure 4). This is at variance with the original hypotheses of both trials which assumed that the effect of chemotherapy in older patients receiving adjuvant tamoxifen would be minor com-

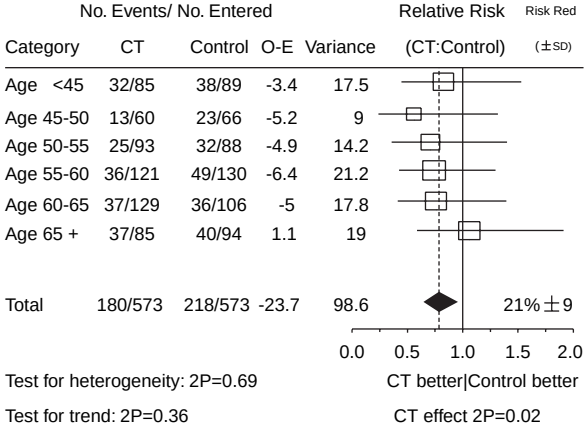


Figure 5. Effect of chemotherapy on DFS according to age groups. Differences were not significant.

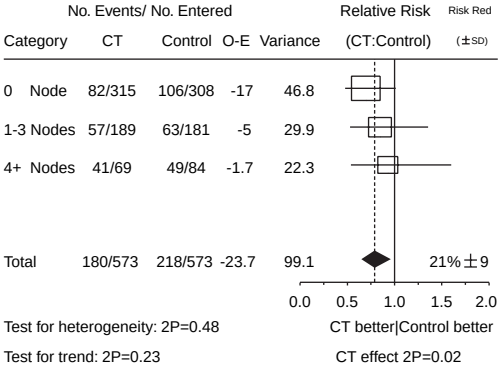


Figure 6. Effect of chemotherapy on DFS according to lymph node involvement. Differences were not significant.

pared to that occurring in younger patients [10], as stated in the statistical methods. Indeed, the 5-year disease-free survival rate in the control group was about 72% and the absolute treatment benefit was about 8%. Had the same hypothesis been put forward for the calculation of the sample size (type 1 and 2 risks of 5% and 10%, respectively), approximately 800 patients would have been necessary.

Another finding is that the effect of chemotherapy in terms of the relative reduction in different events was roughly the same (about 20%), as shown in Figure 3. The low frequency of events such as locoregional recurrences, contralateral breast cancer and other new primary malignancies (about 5% or less at 5 years) probably explain the lack of statistical significance. This low incidence contrasts with that of distant metastases (about 20%), which weighs heavily in the difference in disease-free survival. These trials evaluated the role of anthracycline-based chemotherapy (mostly FEC) given in a single

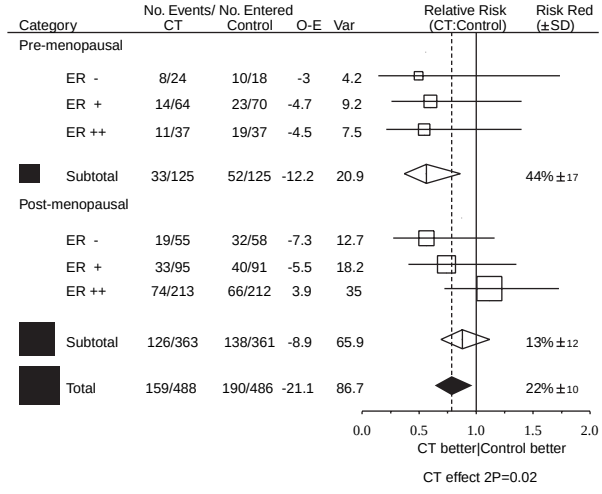


Figure 7. Effect of chemotherapy on DFS according to estrogen receptors and menopausal status.

2–3-hour perfusion per cycle. The rationale was to avoid potential dose adaptation during the course of the treatment that can occur with the classic CMF regime. Indeed, when we planned the trials, there was concern about decreasing the beneficial effect of adjuvant CMF related to the likelihood of administering lower doses mainly in older patients [11,12].

Anthracycline-based chemotherapy regimens have been proven more effective than CMF-like regimes [8], even if the difference is moderate. However, a controversy persists concerning the different CMF schedules with some authors [11,12] claiming that the best effect is obtained with the classic CMF regimen, as initially described [1]. It was purported that the smaller effect of adjuvant chemotherapy in postmenopausal patients was linked to poorer tolerance which dictated a decrease in the CMF doses administered in the classic schedule. Having allowed for the likelihood of this dose effect when planning the current trials, we decided to use a one-course-per-day anthracycline-based regimen, so that dose adaptation would be avoided during the chemotherapy cycle. Indeed, compliance to chemotherapy in our trials was quite satisfactory as 95% of patients received the six planned courses, most of which were FEC. The other issue regarding the anthracycline dose is the level of the epirubicin dose. When we were planning the study, three randomized trials evaluating dose equivalence between doxorubicin and epirubicin in advanced breast cancer [13–15] had shown that a similar tumor effect could be obtained with equi-molar doses of both anthracyclines. These results were confirmed later by four other studies in the same type of patient population [16–19].

Since then, two adjuvant trials [20,21] have shown that a dose effect exists for epirubicin and a dose of 100 mg/m$^2$ is now considered more effective than 50 mg/m$^2$. Even if the French trial [20] included only 276 and the Belgian trial [21] 217 postmenopausal patients, neither of these trials showed a differential chemotherapy effect according to age. The results of our trials could therefore have been improved with a higher dose of epirubicin or even the use of the classic CMF regimen. However, the team conducting the Belgian trial reported an excess of acute myeloid leukemia in the high-dose epidoxorubicin group [22]. This usually fatal disease offsets the potential treatment benefit and indications should be limited to high-risk populations [23]. In our trial, there was no difference in the incidence of acute myeloid leukemia between the two groups with and without chemotherapy (one case in each group).

Regarding the exploratory subgroup analyses, a larger treatment effect in terms of DFS was suggested for patients with ER-negative tumors, and this result is in keeping with that found in the EBCTCG overview [8]. In our trial, the effect of chemotherapy varied according to ER subgroups only in postmenopausal patients (Figure 7). These findings are consistent with those of the IBCSG IX trial that evaluated the role of 3 CMF in the presence of tamoxifen in node-negative postmenopausal patients [24]. The analysis of the trial failed to show a beneficial treatment effect of 3 CMF in patients with tumors containing more than 10 fmol/mg of protein. We did not find any other interaction between the chemotherapy effect and patient or tumor characteristics in our trial.

The study of the patterns of failure showed that chemotherapy mainly affected the distant metastasis rate, without a clear effect on other tumor events (Table II). However, the size of the effect was similar for all events (Figure 4). It is important to note that long-term locoregional control was not significantly decreased by the deferral of local (regional) radiotherapy in order to administer 6 courses of chemotherapy. This is in agreement with findings in the IBCSG studies [25] and contradicts the results of a small randomized study evaluating the chronology of radiotherapy and chemotherapy in early breast cancer [26]. At this point in time, there is no evidence that postponing radiotherapy to administer active adjuvant chemotherapy may have a deleterious effect. These findings suggest that systemic treatments have a beneficial, albeit moderate effect on local control [27] compared to that yielded by radiotherapy since the relative reduction in the locoregional recurrence rate was about 18% compared to 66% with radiotherapy. The relative reduction in the recurrence and death rates evidenced in the current trials and other similar studies [8] may be weighed against the small absolute benefit obtained in patients with a relatively good prognosis (ER-positive and node-negative tumors of less than 30 mm) [28]. In the decision-making process, it is advisable to consider the risk factors affecting each patient and to weigh the expected benefit against the adverse early toxicity of adjuvant chemotherapy [29]. A large-scale review of almost 7 000 patients included in IBCSG trials [30] showed that lethal toxicity is related to age and mainly affects patients aged 65 years or older. It should be borne in mind that premenopausal patients with positive hormonal receptors also benefit from hormonal treatments, such as ovarian suppression and/or adjuvant tamoxifen [31,32].

In conclusion, overall treatment effects are in favor of adjuvant chemotherapy in pre- and postmenopausal patients in different subgroups even if they are some quantitative differences according to the ER status. A more precise definition of hormonal

responsiveness in breast tumors could allow a decrease in the indications for adjuvant chemotherapy in selected patients and thus avoid over-treatment.

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## Appendix I

List of participants, all in France

| Institution | N patients | Investigators |
|---|---|---|
| Institut Gustave-Roussy (IGR), Villejuif | 935 | Rodrigo Arriagada, Geneviève Contesso, 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, Odile Switsers, Christelle Levy |
| Centre Val d'Aurelle, Montpellier | 51 | Monique Rémé-Saumon |
| CHU Jean Bernard, Poitiers | 38 | Thierry Germain |
| Centre d'Oncologie du Pays Basque, Bayonne | 24 | Marc Lipinski |
| CHU, Orléans | 11 | Noël Breteau |
| CHU, Limoges | 9 | Bernard Roullet |

CHU: Centre Hospitalier Universitaire.