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Chemotherapy versus Tamoxifen versus Chemotherapy plus Tamoxifen in Node-positive, Oestrogen-receptor Positive Breast Cancer Patients. An Update at 7 years of the 1st GROCTA (Breast Cancer Adjuvant Chemo-hormone Therapy Cooperative Group) Trial

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504 evaluable node positive oestrogen receptor (ER) positive breast cancer patients were randomly allocated to receive either 5 years tamoxifen treatment or chemotherapy [six courses of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) followed by 4 courses of epirubicin] or a combination of both treatments. At a median follow-up of 5 years tamoxifen appeared to be more effective than chemotherapy, the difference being highly significant in postmenopausal women. The addition of chemotherapy to tamoxifen was not able to significantly improve the results achieved by tamoxifen alone, irrespective of menopausal status. Trends were similar even after stratification for the number of involved nodes. The protective effect of tamoxifen in terms of reduction of the odds of death increased with time and no rebound phenomena on recurrence or death has occurred so far after the completion of tamoxifen treatment. Overall, the prognostic value of number of involved nodes and of progesterone receptor (PgR) status was confirmed by multivariate analysis. However, the predictive value of PgR was lost in patients receiving tamoxifen alone. Similarly, the degree of ER positivity was not predictive of the response to tamoxifen. Tamoxifen treatment should still be regarded as the gold standard for postmenopausal ER positive patients. In younger women the antioestrogen proved to be safe and at least as effective as chemotherapy. However, the analysis of the annual risks suggests that the concurrent or the sequential use of chemotherapy and tamoxifen might represent a more appropriate treatment for this patient subset, particularly for those with four or more involved nodes. Different cut-offs of ER and PgR assays from those we have arbitrarily employed in the present analysis should probably be used to select more properly the patients who can benefit from endocrine therapy.
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INTRODUCTION

In 1983, a prospective multicentric study was initiated in Italy by the Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group (GROCTA) to establish whether prolonged tamoxifen treatment might represent an alternative to adjuvant chemotherapy in patients with early breast cancer and with oestrogen receptor (ER) positive tumours. At that time, chemotherapy was the current treatment for all operated breast cancer patients with node positive tumours [1], although some concern about its possible usefulness in postmenopausal women was developing even in our Country [2]. Patients with ER positive tumours appeared to be specifically suitable for such a comparison for the following reasons: (1) they might be presumed to derive a substantial benefit from endocrine therapy; (2) a number of biological and clinical studies suggest that these patients might have a more indolent disease and, therefore, a better prognosis [3]. This and the fact that chemotherapy effectiveness in premenopausal women was ascribed, at least in part, to the endocrine effects induced by this treatment [4] allowed us to overcome the ethical problems raised by participating Centres in entering younger women.

Because some synergistic or at least subadditive effect between chemotherapy and endocrine therapy emerged from *in vitro* and *in vivo* studies [5], a third arm based on the concurrent administration of tamoxifen and chemotherapy was included in the study design with the purpose to investigate the ameliorative potential of combined treatment with respect both to chemotherapy and to tamoxifen alone.

A preliminary analysis, with a median follow-up of 40 months, has shown that in the group of patients selected for this study, tamoxifen might well represent a safe alternative to chemotherapy and that it should be preferred to the latter treatment

modality in postmenopausal women where it achieved significantly better results with less toxicity [6]. In addition, it showed that the results achieved by the combined use of tamoxifen and chemotherapy were better than those obtained by chemotherapy alone (although the advantage was significant only in postmenopausal women) but they were not so when compared with those yielded by tamoxifen alone [6].

Updated results are provided in this paper, more than 7 years after recruitment began when the median follow-up was 5 years.

PATIENTS AND METHODS

Patient eligibility, allocated treatments and follow-up studies

Details about patient eligibility, treatment of primary tumour, treatments allocated after mastectomy, hormonal receptor assay, method of randomisation and follow-up studies have been previously reported [6, 7]. In brief, patients aged 35–65 years with node positive, ER positive (≥ 10 fmol/mg protein) tumours were entered into the study. Patients with amenorrhea for 2 years or more were considered to be postmenopausal. Within 6 weeks from mastectomy, patients were randomised by phone to receive one of the following treatments: group T: tamoxifen, 30 mg daily for 5 years; group CT: six courses of CMF (cyclophosphamide: 500 mg/m^2, methotrexate: 40 mg/m^2 and 5-fluorouracil: 600 mg/m^2) followed by four courses of epirubicin: 75 mg/m^2. All drugs were administered intravenously every 3 weeks; group CTT: a combination of both treatments, according to the same dosages and schedules. Patients were clinically examined at different intervals during the first 3 years, from the third up to the fifth year and thereafter (every 3, 4 and 6 months, respectively). They continued to be submitted yearly to bone scan, chest X-ray and liver scan or ultrasonography (if liver enzymes were altered). The vital status of any patient failing to present for examination was checked by phone.

Statistical analysis

The major end-points of the study were recurrence and death. Recurrence included: local-regional and distant metastases, recurrence in the ipsilateral breast (in patients submitted to lumpectomy or quadrantectomy), controlateral breast cancer, second malignancy and death, irrespective of its cause. Times to recurrence or death were measured from the date of randomisation. In accordance with accepted statistical practice [8], all patients were analysed (including 25 inelegible patients) except 6 who were entered by a centre that did not ensure an adequate adherence to the study.

Relapse free survival and overall survival curves were drawn using the method of Kaplan and Meier [9] and the significance of the differences between curves assessed using the log-rank test [8]. Treatment comparisons were made in all patients and after stratification by menopausal and nodal status. In addition, the annual odds of recurrence and death have been calculated [10], overall and in each menopausal subset (1) to determine the follow-up period during which maximum contribution to overall treatment benefit (with respect to chemotherapy) was achieved and (2) to document the possible occurrence of "rebound" phenomena on recurrence or death at the completion of treatment, in patients allocated to receive tamoxifen (either alone or combined with chemotherapy).

Finally, Cox multivariate analysis [11] was used both to adjust comparisons for the major known prognostic factors and to confirm the predictive value of those factors, overall and within each treatment arm. All P values were derived from a 2-sided test for significance.

Table 1. Analysis of all events: overall and by menopausal and nodal status

	No. of patients	No. of events	O/E	P =	Pairwise P
All patients					
T	168	63	0.89		0.002*
CT	165	90	1.49	0.000	0.23†
CTT	171	57	0.72		0.000‡
Premenopausal					
T	79	30	0.96		0.31*
CT	81	39	1.25	0.19	0.5†
CTT	77	26	0.79		0.07‡
Postmenopausal					
T	89	33	0.84		0.0006*
CT	84	51	1.8	0.000	0.27†
CTT	94	31	0.65		0.000‡
Nodes ≤ 3					
T	96	23	0.84		0.015*
CT	88	35	1.58	0.0058	0.71†
CTT	106	25	0.76		0.0037‡
Nodes > 3					
T	72	40	0.92		0.0068*
CT	77	55	1.36	0.015	0.36†
CTT	65	32	0.74		0.0046‡

T = tamoxifen; CT = chemotherapy; CTT = chemohormonetherapy.
* T vs. CT; † T vs. CTT; ‡ CT vs. CTT.
O/E = observed/expected ratio.

RESULTS

The main characteristics of study patients have been described in detail elsewhere [6]. Nevertheless, it is noteworthy to recall that treatment arms were well balanced as for the following factors: patients' age and menopausal status; treatment of primary; tumour size (pT category); number of involved nodes; degree of ER positivity and progesterone receptor (PgR) status.

Treatment results are summarised in Tables 1 and 2 and in Figs 1–4. Overall, the best results were achieved in patients receiving combined treatment and the worst ones in those receiving chemotherapy. However, no significant difference was observed between the clinical outcome of patients receiving combined treatment and of those treated with tamoxifen alone. These trends were maintained even after stratification by menopausal status or number of involved nodes, both after univariate

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Table 2. Analysis of all deaths: overall and by menopausal and nodal status

	No. of patients	No. of deaths	O/E	P =	Pairwise P
All patients					
T	168	40	0.81		0.0008*
CT	165	67	1.57	0.000	0.56†
CTT	171	37	0.71		0.000‡
Premenopausal					
T	79	19	0.93		0.21*
CT	81	27	1.35	0.11	0.42†
CTT	77	14	0.71		0.045‡
Postmenopausal					
T	89	21	0.72		0.0004*
CT	84	40	1.82	0.000	0.96†
CTT	94	23	0.71		0.0001‡
Nodes ≤ 3					
T	96	11	0.64		0.012*
CT	88	22	1.59	0.026	0.42†
CTT	106	17	0.88		0.07‡
Nodes > 3					
T	72	29	0.88		0.028*
CT	77	45	1.48	0.0037	0.31†
CTT	65	20	0.65		0.0015‡

T = tamoxifen; CT = chemotherapy; CTT = chemohormonetherapy.
* T vs. CT; † T vs. CTT; ‡ CT vs. CTT.
O/E = observed/expected ratio.

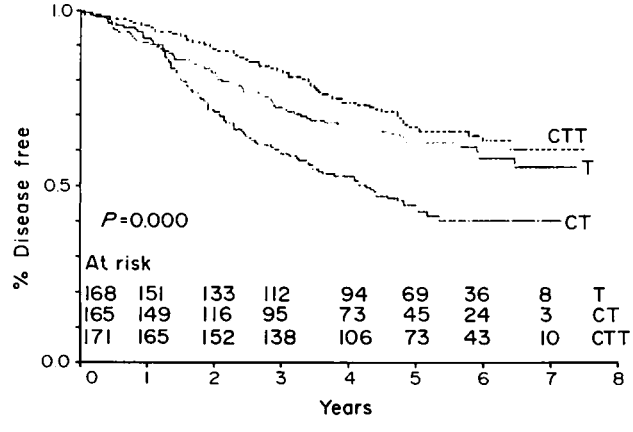

Fig. 1. Disease-free probability for all patients. Patients at risk are indicated at the bottom. Test for heterogeneity: P = 0.000. Pairwise P values are as follows: T vs. CT, P = 0.002; T vs. CTT, P = 0.23; CT vs. CTT, P = 0.000.

analysis (Tables 1 and 2) and after multivariate analysis (data not shown).

In accordance with previous analysis, the concurrent use of chemotherapy and tamoxifen was more effective than tamoxifen alone only in preventing the development of local–regional metastasis (Table 3).

Figure 5 shows the annual odds of recurrence or death according to menopausal status. When the odds of recurrence were considered, it appeared that the protective effect of tamoxifen over chemotherapy differed in the menopausal subsets. In postmenopausal women it reached its maximum in the second year and remained unchanged thereafter, up to the 6th year. In

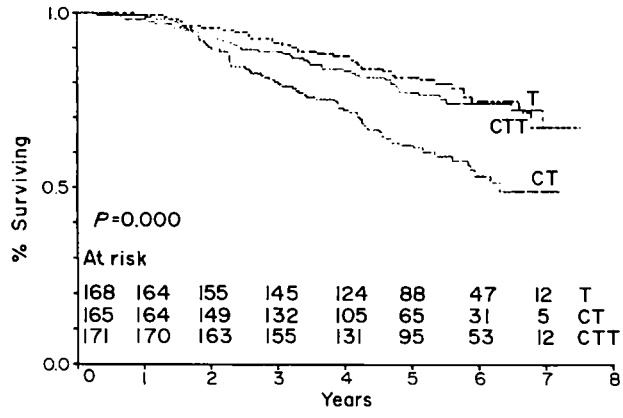

Fig. 2. Probability of surviving for all patients. Patients at risk are indicated at the bottom. Test for heterogeneity: P = 0.000. Pairwise P values are as follows: T vs. CT, P = 0.0008; T vs. CTT, P = 0.56; CT vs. CTT, P = 0.003.

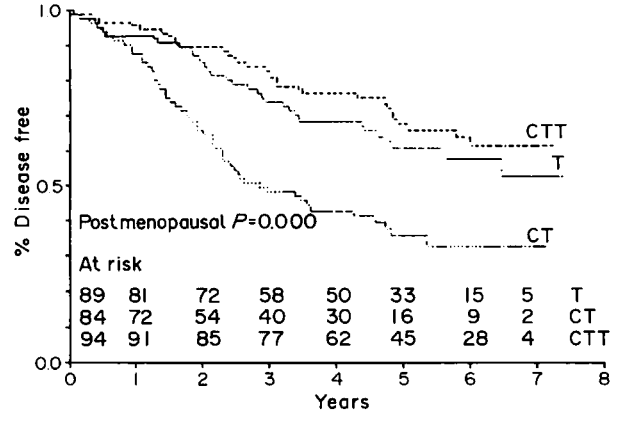

Fig. 3. Disease-free probability for postmenopausal patients. Patients at risk are indicated at the bottom. Test for heterogeneity: P = 0.000. Pairwise P values are as follows: T vs. CT, P = 0.0006; T vs. CTT, P = 0.27; CT vs. CTT, P = 0.000.

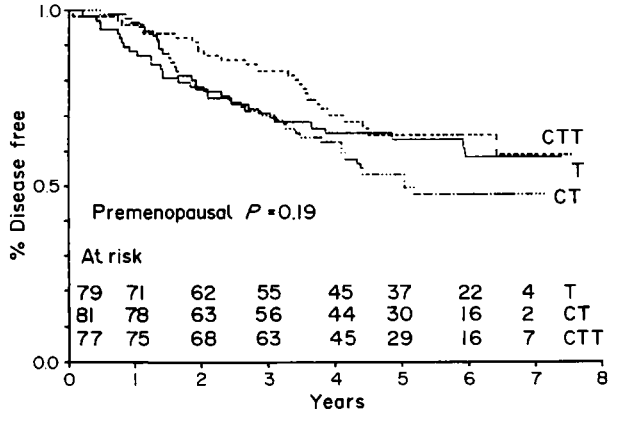

Fig. 4. Disease-free probability for premenopausal patients. Patients at risk are indicated at the bottom. Test for heterogeneity: P = 0.19. Pairwise P values are as follows: T vs. CT, P = 0.31; T vs. CTT, P = 0.5; CT vs. CTT, P = 0.07.

Table 3. Number of patients with recurrence according to sites of relapse

	Treatment arm		
Site of relapse	T	CT	CTT
Second malignancy	1	2	2
Opposite breast	—	4	1
Local-regional*	20	22	8
Distant†	34	49	37
Local-regional and distant	7	8	7
†Dead without cancer	1	5	2
Total	63	90	57

T = tamoxifen; CT = chemotherapy; CTT = chemo-hormonetherapy. * T vs. CT $P = 0.82$, T vs. CTT $P = 0.026$, CT vs. CTT $P = 0.0095$. † Distant plus distant and local regional: T vs. CT $P = 0.056$, T vs. CTT $P = 0.87$, CT vs. CTT $P = 0.1$.

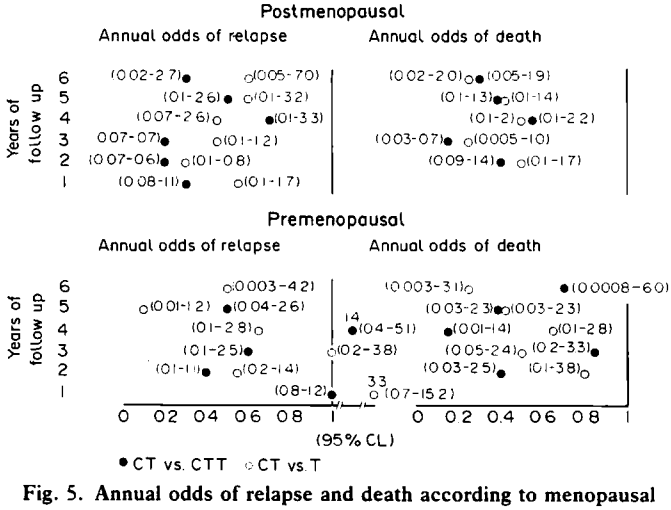

Fig. 5. Annual odds of relapse and death according to menopausal status.

younger women treated with tamoxifen there was an excess of recurrences in the first year, although the absolute recurrence rate was very low: three events in the T arm as compared with none in the CT arm. Furthermore there was a decrease in the protective effect of tamoxifen also in the third year. No "rebound" effect upon recurrence was seen in the 6th year, i.e. after the completion of tamoxifen treatment, in any of the menopausal subsets. Furthermore, the protective effect of tamoxifen with respect to death was independent of menopausal status and increased with time.

The protective effect with respect to recurrence or death of combined tamoxifen–chemotherapy treatment in postmenopausal women was quite similar to that exerted by tamoxifen alone, specifically in the last 3 years (4th–6th).

In premenopausal women the protective effect of chemo-hormonetherapy or tamoxifen alone was more variable, in particular when the odds of death were considered; this is most likely an effect of the small number of deaths occurring at the beginning and in the last years of follow-up.

However, the concurrent use of chemotherapy and tamoxifen was able to minimise both the increased risk observed with tamoxifen alone in the first year and the decrease in the protective effect of the antioestrogen in the third year of follow-up.

Table 4. Relative risk (RR) of recurrence after multivariate analysis

Variable	RR	(95% CL)	P =
Menopausal status			
Pre	1		
Post	1.2	(0.86–1.69)	0.78
Nodal status			
1–3	1		
> 3	2.95	(2.2–4.1)	0.0000
PgR			
≤ 30 fmol/mg	1		
> 30 fmol	0.71	(0.52–0.97)	0.0002
ER			
≤ 100 fmol/mg	1		
> 100 fmol/mg	1.01	(0.71–1.43)	0.83
Allocated treatment			
CT	1		
T	0.68	(0.49–0.95)	0.0000
CTT	0.40	(0.27–0.59)	

CT = chemotherapy; T = tamoxifen; CTT = chemo-hormonetherapy.

Table 4 shows the overall predictive value (with respect to recurrence) of a number of factors including: menopausal status, number of involved nodes, degree of ER positivity, PgR status and allocated treatments, as it was disclosed by Cox multivariate analysis.

Because PgR assay was not performed in all participating centres only 468 patients were included in this analysis. Furthermore a cut-off value of 30 fm/mg protein (which corresponded with the third percentile) was arbitrarily chosen to define PgR assay as positive. Also, an arbitrary cut-off value of 100 fm/mg protein was chosen to discriminate between patients with moderately or highly positive ER assays.

Allocated treatment, number of involved nodes and positivity of PgR assay were the only discriminating factors.

The predictive value of these variables was investigated also within each treatment arm (Table 5) and again the number of involved nodes showed a strong discriminating power, while PgR status lost its predictivity in patients treated with tamoxifen alone. Major drug-related side effects were described in detail in our previous report [6]. Acute side effects were significantly more numerous and heavy in patients receiving chemotherapy. In fact, most of them experienced nausea, vomiting, alopecia and mielotoxicity to some degree. In the present analysis we have investigated in detail the incidence of gynaecological disease in each treatment arm (Table 6). Premenopausal patients receiving tamoxifen alone experienced a significantly higher incidence of uterine fibroids and/or foliculinic ovarian cysts. However, no increase in the clinical occurrence of endometrial hyperplasia and/or endometrial carcinoma was seen in patients receiving tamoxifen as compared with those treated with chemotherapy alone.

DISCUSSION

The present analysis confirms previous findings and provides additional information. The overall results and those achieved in each menopausal subset confirm that an appropriate endocrine therapy, such as the use of tamoxifen for 5 years, might be considered a safe way (i.e. the most effective and the less toxic one) to manage breast cancer patients with ER positive tumours.

Table 5. Results achieved by multivariate analysis in each treatment arm

Variable	T RR (95% CL)	*P*	CT RR (95% CL)	*P*	CTT RR (95% CL)	*P*
Menopausal status						
Pre	1		1		1	
Post	1.2 (0.7–2.3)	0.97	1.4 (0.8–2.3)	0.78	1.1 (0.5–2.1)	0.69
Nodal status						
1–3	1		1		1	
> 3	3.5 (2.1–6.1)	0.001	2.3 (1.5–3.7)	0.000	3.4 (1.8–6.6)	0.004
PgR						
≤ 30 fmol/mg	1		1		1	
> 30 fmol/mg	1.1 (0.6–2.0)	0.11	0.5 (0.3–1.2)	0.015	0.7 (0.4–1.3)	0.019
ER						
≤ 100 fmol/mg	1		1		1	
> 100 fmol/mg	0.6 (0.3–1.2)	0.10	1.3 (0.8–2.2)	0.17	1.1 (0.5–2.2)	0.99

T = tamoxifen; CT = chemotherapy; CTT = chemohormonetherapy; RR = relative risk; CL = confidence limit.

Table 6. Incidence of gynaecological disease by menopausal status and allocated treatment

	T (n = 168)	CT (n = 165)	CTT (n = 171)
Premenopausal			
Uterine fibroids*	14/79	2/81	1/77
Ovarian cyst*	3/79	—	—
Endometrial hyperplasia	1/79	1/81	—
Postmenopausal			
Uterine fibroids	1/89	1/84	3/94
Ovarian cyst	—	—	—
Endometrial hyperplasia	—	—	1/94
Endometrial cancer	—	—	1/94

* T vs. CT vs. CTT: P = 0.0000.

This appeared particularly true in postmenopausal women. In this patient subset, tamoxifen therapy achieved better results than chemotherapy, irrespective of the end-point considered, and it yielded comparable results with those achieved by combined chemo-tamoxifen therapy, particularly when patient death was the considered end-point.

The analysis of disease-free survival curves, as well as that of the annual odds of recurrence and of recurrence patterns suggests that the combined use of chemotherapy and tamoxifen can provide a small additional benefit (over tamoxifen alone), mainly in the first years after mastectomy, constituted by a more effective prevention of local-regional relapses. This advantage has not yet been translated into a distant disease-free or an overall survival advantage. For this reason, we do not believe that it can justify the routine use of such combined treatment in postmenopausal women. The findings emerging from the Stockholm trial might suggest that a similar improvement of tamoxifen efficacy on local-regional relapses could be achieved by combining the antioestrogen with post-operative radiotherapy [12]. However, there is again no evidence that radiotherapy can impact on patient survival [13].

Therefore, we believe that previous statements of the 1985 NIH Consensus Conference regarding postmenopausal ER positive breast cancer patients [14] still retain their value, and that prolonged tamoxifen treatment should be regarded as the gold standard for this patient subset.

Two recent reports seem to be in contrast with our conclusions. The NSABP-B16 study has shown that the concurrent use of four cycles of doxorubicin plus cyclophosphamide and of tamoxifen achieved a significant improvement of the therapeutic results over tamoxifen alone in a selected group of postmenopausal breast cancer patients arbitrarily defined as "tamoxifen-responsive" [15].

However, the results of this trial have raised a certain criticism in the scientific community [16–18]. In fact, at least 20% of the patients enrolled into the NSABP study had ER negative tumours and those patients had little chance to benefit from tamoxifen treatment. Furthermore, the results of this study are still preliminary and it is not easy to understand why no major advantage was achieved by NSABP investigators with the other chemo-hormonal regimens despite the fact that one of them also included doxorubicin. An improper selection might also have biased the results achieved by Pearson *et al.* [19] in a small group of postmenopausal ER positive patients. Again, an inappropriate cut-off (3 fmol/mg protein) was chosen by these investigators to select patients suitable for a comparison of tamoxifen alone versus tamoxifen plus a five-drug regimen. Indeed, these investigators failed to find any significant survival advantage which could be related to the use of chemo-endocrine therapy.

Furthermore, no clear-cut advantage of chemo-tamoxifen therapy over tamoxifen alone emerged from the previous studies in postmenopausal women which have addressed this issue [20–22].

Our results in premenopausal women confirm that tamoxifen might represent a safe alternative to chemotherapy even in this subset of patients. As we have previously discussed [6], it cannot be excluded that these conclusions might be biased by the use of a less intensive chemotherapeutic regimen. However, this is not likely. In fact, in the discussion section of a recent paper by Bonadonna's Group [23] it is clearly stated that equivalent results can be achieved either with 12 cycles of "classical" CMF or with six cycles of the same regimen, or with 12 cycles of intravenous CMF. Furthermore, in the aforementioned paper [23] similar results have been obtained in patients with one to three positive nodes by using 12 courses of intravenous CMF or eight courses of intravenous CMF followed by four courses of

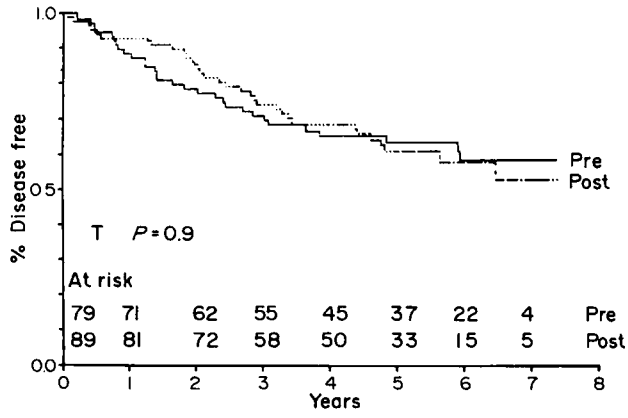

Fig. 6. Disease-free probability by menopausal status for patients allocated to tamoxifen. Patients at risk are indicated at the bottom. $P = 0.9$.

intravenous doxorubicin, i.e. a regimen almost identical to that that we employed. These findings and those previously achieved by the same group with six cycles of "classical" CMF followed by four cycles of doxorubicin plus vincristine [24] can rule out that the sequential use of CMF and doxorubicin can exert a detrimental effect, although more recent results obtained in patients with four or more involved nodes can suggest that the use of doxorubicin before rather than after CMF might be even more appropriate [25].

Figures 6 and 7 clearly show that premenopausal women have the same overall responsiveness to tamoxifen, but that they are significantly more sensitive to chemotherapy than postmenopausal patients. This difference, which emerged from univariate comparisons, seemed to disappear when multivariate analysis was applied. However, it should be taken into appropriate account that a smaller number of patients was considered for multivariate analysis (which was limited to patients with available PgR assays) and that a positive PgR assay (a condition more frequent in postmenopausal women) was predictive of a better response to chemotherapy.

The different sensitivity to chemotherapy of pre- and postmenopausal women was observed in several trials and emerged also from the EBCTCG overview [26]. This difference was ascribed at least in part to the endocrine effects that this treatment modality induces in premenopausal women. However, the role played by chemotherapy induced amenorrhea is still controversial [27]. We have previously found that both chemotherapy and tamoxifen induced a persistent amenorrhea in about 70% of premenopausal women [6]. However, drug-induced amenorrhea was not found to influence the response of these women to chemotherapy or tamoxifen.

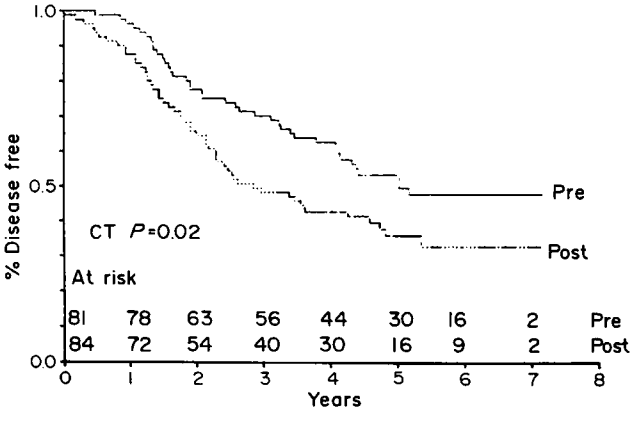

Fig. 7. Disease-free probability by menopausal status for patients allocated to chemotherapy. Patients at risk are indicated at the bottom. $P = 0.02$.

Therefore, it might be hypothesised that ER assay allows identifying a subpopulation of pre- and postmenopausal breast cancer patients who have the same overall sensitivity to tamoxifen but a different sensitivity to chemotherapy. It is also possible to hypothesise that tumour kinetics and genetics contribute in a different way to both tamoxifen and chemotherapy sensitivity in pre- and in postmenopausal women, respectively [28].

This seems to be suggested also by the analysis of the annual odds of recurrence in the menopausal subsets. In fact, premenopausal patients showed an increased risk of relapse during the first year of treatment with tamoxifen, which was prevented by the concurrent use of chemotherapy. This might indicate that there was a small proportion of young patients with very aggressive disease that did not benefit from endocrinetherapy but did respond to chemotherapy. Younger women showed another "peak" of risk during the third year that is not easy to explain. In fact, while this second "peak" could also be related to the existence of another group of patients with an intermediate aggressive disease, it might represent rather an effect of the hyperoestrogenic stimulation which is known to occur in fertile women treated with tamoxifen [29]. The occurrence of hyperoestrogenic stimulation phenomena in our study was documented by the increased incidence of gynaecological disease in tamoxifen-treated patients. Indeed, the protective effect of the concurrent use of chemotherapy on this second peak of rise was accompanied by a sharp reduction in the incidence of gynaecological disease. Unfortunately, we had not planned to monitor our patients from the endocrinological point of view and therefore, we cannot say whether these hypotheses might be plausible and which role, if any, might have been played by hyperoestrogenic stimulation. Some clarification in this regard will probably derive from the comparison *a posteriori* of the patients in the actual series and of those who are presently randomised within the second GROCTA study to receive either CMF chemotherapy or tamoxifen plus an LH–RH analogue. In fact, the concurrent use of tamoxifen and of an LH–RH analogue should prevent all hyperoestrogenic stimulation phenomena.

The protective effect of tamoxifen with respect to chemotherapy, and in particular the reduction in the odds of death it induced, increased with time. This trend is comparable with the trends emerging from EBCTCG metanalysis of tamoxifen trials [26]. Moreover, no rebound effects on recurrence (or death) were seen in patients who were given tamoxifen (either alone or in combination with chemotherapy). However, this finding should be considered as a preliminary one, inasmuch as a small proportion of patients was still on active treatment at the time of the present analysis (28 and 32 patients in T and CTT arms, respectively).

Finally, the temporal patterns of relapse or death of patients treated with combined tamoxifen and cytotoxics were more variable in pre- than in postmenopausal patients, suggesting that stronger interactions among these drugs probably do occur in younger women as was previously suggested [30]. Nevertheless, the concurrent use of chemotherapy and tamoxifen showed to exert a subadditive effect in this patient subset. In our opinion, this positive yet not significant trend along with the better control of disease achieved by chemotherapy in the first year of

follow-up and its preventive effect on the hyperoestrogenic stimulation phenomena induced by tamoxifen, in our opinion suggest that chemo-hormonal therapy might be a more appropriate treatment for these women. This might be particularly advisable in women with four or more involved nodes since a positive, even not significant, trend favoured the use of chemotherapy and tamoxifen in this nodal subset, irrespective of menopausal status. Furthermore, some benefit has been revealed in ER positive premenopausal women with four or more involved nodes treated with CMF and oophorectomy in the Ludwig II study [31]. However, whether chemotherapy and tamoxifen should be given in a sequential way rather than concurrently remains an open issue, even though our findings seem to suggest that this latter schedule might be more appropriate. Overall, allocated treatments, number of involved nodes and PgR status emerged as the most predictive factors in our study, already confirming previous observations [32, 33].

However, it is noteworthy that neither PgR status nor the degree of positivity of ER assay appeared to be major predictors of response to tamoxifen. This might be explained by the lack of a linear relationship between steroid hormone receptors concentration and response to hormonetherapy in early disease. Should this be the case, the cut-off arbitrarily chosen in the present analysis might not be the more appropriate one.

Finally, it is noteworthy that no excess in endometrial carcinoma or hyperplasia was observed in our patients treated with tamoxifen. Our findings are in contrast with those coming from Swedish studies [34], but contribute to corroborate the safety of prolonged antioestrogenic treatment as previously suggested by a retrospective analysis of the Scottish trials [35].

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APPENDIX

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