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Original Paper

Prognostic Impact of Amenorrhoea After Adjuvant Chemotherapy in Premenopausal Breast Cancer Patients with Axillary Node Involvement: Results of The International Breast Cancer Study Group (IBCSG) Trial VI

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Adjuvant chemotherapy-induced amenorrhoea has been shown to be associated with reduced relapses and improved survival for premenopausal breast cancer patients. Amenorrhoea was, therefore, studied to define features of chemotherapy (i.e. duration and timing) and disease-related factors which are associated with its treatment effects. We reviewed data from IBCSG Trial VI, in which accrual was between July 1986 and April 1993. 1196 of the 1475 eligible patients (81%) were evaluable for this analysis. The median follow-up was 60 months. Women who experienced amenorrhoea had a significantly better disease-free survival (DFS) than those who did not ($P = 0.0004$), although the magnitude of the effect was reduced when adjusted for other prognostic factors ($P = 0.09$). The largest treatment effect associated with amenorrhoea was seen in patients assigned to receive only three initial CMF courses (5-yr DFS: 67% versus 49%, no amenorrhoea; hazard ratio, 0.55; 95% confidence interval, 0.38 to 0.81; $P = 0.002$). DFS differences between amenorrhoea categories were larger for patients with ER/PR positive tumours (hazard ratio, 0.65; 95% confidence interval, 0.53 to 0.80; $P = 0.0001$). Furthermore, patients whose menses returned after brief amenorrhoea had a DFS similar to those whose menses ceased and did not recover (hazard ratio, 1.10; 95% confidence interval, 0.75 to 1.62; $P = 0.63$). The effects associated with a permanent or temporary chemotherapy-induced amenorrhoea are especially significant for node-positive breast cancer patients who receive a suboptimal duration of CMF chemotherapy. Cessation of menses, even for a limited time period after diagnosis of breast cancer, might be beneficial and should be prospectively investigated, especially in patients with oestrogen receptor-positive primaries.

Key words: breast cancer, adjuvant chemotherapy, amenorrhoea, premenopausal
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INTRODUCTION

AMENORRHEA IS observed in a substantial proportion of pre- and perimenopausal women who are treated with adjuvant chemotherapy for operable breast cancer; damage to the

ovaries can occur through impairment of follicular maturation and/or depletion of primordial follicles. Combination chemotherapy is used more often than single agents so it is, therefore, difficult to evaluate the role of each individual drug. Alkylating agents are most commonly associated with ovarian damage: these agents are not cell-cycle-specific and thus do not require cell proliferation for their cytotoxic action [1]. The most detailed information available is on the effects of cyclophosphamide: higher cumulative doses cause higher chemotherapy-induced amenorrhoea rates [2–5], but duration of treatment and route of administration as independent variables remain to be investigated. The antimetabolites, in contrast, cause little ovarian toxicity when used as adjuvant treatment for breast cancer and this could be explained by their cytotoxic effect on dividing cells [6]. The effect of anthracyclines and taxanes on the ovaries is still undetermined. Several chemotherapeutic combinations have been used, but reports on the incidence of chemotherapy-induced amenorrhoea have been rare: a recent review reported only 15 of 40 studies with this information in premenopausal women [7]. There is insufficient data available on which regimen causes the highest rate of ovarian failure: the reported incidence ranges from 0–100% and is probably related to different definitions of menopausal status and amenorrhoea and different age distributions and characteristics of the study population across different trials. The average percentage of chemotherapy-induced amenorrhoea in regimens based on cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) given for at least 3 months is 68% [8].

Since the beneficial effect of adjuvant multidrug chemotherapy in reducing relapse and mortality has been consistently larger for premenopausal patients, it has been postulated that at least part of this benefit is derived from chemotherapy-induced ovarian ablation. Several trials, not specifically designed to answer this question, have provided data relevant to this issue indirectly and retrospectively, by evaluating the relationship between outcome and menstrual status during or after chemotherapy. Amenorrhoea, however, was not consistently defined in these studies and differential analyses by permanent versus temporary amenorrhoea were not generally performed.

Evidence exists demonstrating that chemotherapy-induced amenorrhoea is associated with better outcomes among premenopausal patients and the effect of ovarian suppression is mainly observed in the subpopulations of patients with hormone receptor-positive tumours and in those younger than 40 years old [3]. The nature of the interaction between ovarian function suppression, age, receptor status and outcome has not yet been fully elucidated.

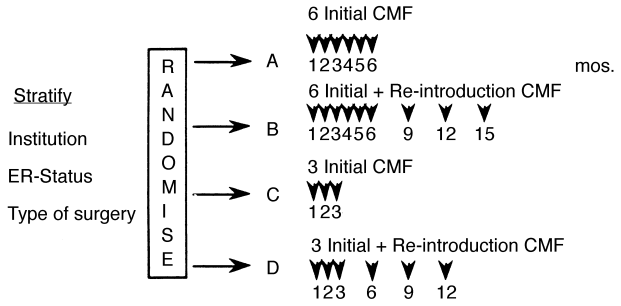

Figure 1. Schema for IBCSG Trial VI: pre and perimenopausal breast cancer patients with node-positive breast cancer.

We report the results of an extensive analysis of the relationship between amenorrhoea and outcome for a pre- and perimenopausal patient population with operable, node-positive breast cancer included in the International Breast Cancer Study Group Trial VI which compared CMF either for 3 or 6 initial cycles with or without a late re-introduction of 3 additional single cycles of CMF.

PATIENTS AND METHODS

From July 1986 to April 1993, 1554 pre- and perimenopausal patients were randomised and assigned to receive one of the treatments displayed in Figure 1. 1475 patients were eligible for the trial. 279 patients were not included in the analysis of amenorrhoea effects for a variety of reasons as shown in Table 1. Perimenopausal patients who had their most recent menstrual period more than 6 months prior to randomisation were excluded (182 women). In addition, 47 patients who were censored, relapsed, or died within the first 9 months following randomisation were excluded so that a landmark analysis could be performed [9]. These women were excluded to avoid possible misclassification bias due to either insufficient follow-up or the fact that the reported amenorrhoea could be due to treatments given at relapse. Nine months was selected as the landmark to allow sufficient time for the treatment to have an effect on cessation of menses. A total of 1196 patients were included in the landmark analyses.

After patients were randomised, menstrual status information was collected at baseline and every 3 months for the first 2 years and every 6 months thereafter. The present study includes data from the first 10 follow-up visits (i.e. 36 months). A woman was defined as having amenorrhoea if at

Table 1. *Reasons for exclusion of patients from effects of amenorrhoea analysis*

	CMF×6	CMF×6 + Reintroduction of CMF	CMF×3	CMF×3 + Reintroduction of CMF	Total
Total eligible	375	375	360	365	1475
Total evaluable	303	306	291	296	1196
Reasons not evaluable					
No chemotherapy received	2	1	2	4	9
Perimenopausal*	42	51	44	45	182
Became pregnant	1	1	—	—	2
Insufficient menses follow-up	2	1	—	2	5
Incorrect menopausal status	2	3	2	2	9
Event in first 9 months	12	8	17	10	47
Insufficient information at 9 months	11	4	4	6	25

*Most recent menses more than 6 months before randomisation.

the 9th month (± 1 month) from randomisation she reported 'no menses' for the past 3 months. Recovery was defined as the re-appearance of normal menstrual cycle or at least scanty bleeding at some point from the 12th month to the 36th month. From these two variables, 'amenorrhoea' and 'recovery', patients were classified into three categories: 'amenorrhoea/no recovery', 'amenorrhoea/recovery' and 'no amenorrhoea'.

Characteristics of the patients are described in Table 2. All patients had a histologically proven, node-positive unilateral breast cancer with either oestrogen receptor (ER)-positive or ER-negative status known. Surgery of the primary tumour was either a total mastectomy with axillary clearance or a breast conserving procedure (quadrantectomy or lumpectomy) with axillary lymph node dissection and subsequent local radiotherapy.

Age (40 years or more versus less than 40, range for this trial: 26–57) and ER status in the primary (concentrations ≥ 10 fmol per milligram of cytosol protein were considered positive; lower values negative) were considered important features due to observations in previous analyses [4]. We also considered the number of cycles of chemotherapy, 'ER/PR' status (where patients were classified as positive if either ER or progesterone receptor (PR) status was ≥ 10 and negative otherwise) and node group (4 or more versus 1–3 positive nodes).

Disease-free survival (DFS) for this landmark analysis was defined as the length of time from the date of randomisation to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. The Kaplan–Meier method [10] was used to estimate survival distributions for DFS and a two-sided logrank test was used to assess the statistical significance of differences between the DFS distributions [11]. Cox proportional hazards regression models were used to estimate the magnitude of differences in DFS rates adjusting for covariates and to test for interactions [12]. The data were analysed at a median observation time of 60 months and the 5-year DFS percentages are presented.

RESULTS

Overall, 62% of patients (736 out of 1196) became amenorrheic. Tables 3 and 4 show the incidence of amenorrhoea in each of the treatment groups and for patient subpopulations defined by age and ER/PR status. The average incidence of reported amenorrhoea in patients who received prolonged adjuvant chemotherapy (at least 6 cycles) was 66%. The incidence of reported amenorrhoea was lower in patients receiving only 3 cycles of treatment (48%). Eighteen per cent of the women younger than 40 and 74% of the women 40 years or older reported amenorrhoea.

Table 2. Patient characteristics according to treatment group

	CMF×6	CMF×6 + Reintroduction of CMF	CMF×3	CMF×3 + Reintroduction of CMF	Total
Total evaluable	303	306	291	296	1196
Age					
< 40 years	61	69	73	63	266
≥ 40 years	242	237	218	233	930
ER/PR status*					
Negative	57	61	53	61	232
Positive	246	245	238	235	964

*ER/PR patients were classified as positive if either ER or progesterone receptor (PR) status was ≥ 10 fmol/mg protein and negative otherwise.

Table 3. Incidence of amenorrhoea at 9 month landmark and recovery according to treatment group

	CMF×6	CMF×6 + Reintroduction of CMF	CMF×3	CMF×3 + Reintroduction of CMF	Total
Total evaluable	303	306	291	296	1196
Amenorrhoea (%)					
No	93 (31)	102 (33)	152 (52)	113 (38)	460 (38)
Yes	210 (69)	204 (67)	139 (48)	183 (62)	736 (62)
No recovery	182 (87)	180 (88)	124 (89)	170 (93)	656 (89)
Recovery	28 (13)	24 (12)	15 (11)	13 (7)	80 (11)

Table 4. Incidence of amenorrhoea according to age and ER/PR status

	Amenorrhoea/Recovery (%)	Amenorrhoea/No recovery (%)	No amenorrhoea (%)
Age			
< 40 years ($n = 266$)	21 (8)	28 (10)	217 (82)
≥ 40 years ($n = 930$)	59 (6)	628 (68)	243 (26)
ER/PR status*			
< 10 ($n = 232$)	18 (8)	114 (49)	100 (43)
≥ 10 ($n = 964$)	62 (7)	542 (56)	360 (37)

*ER/PR patients were classified as positive if either ER or progesterone receptor (PR) status was ≥ 10 fmol/mg protein and negative otherwise.

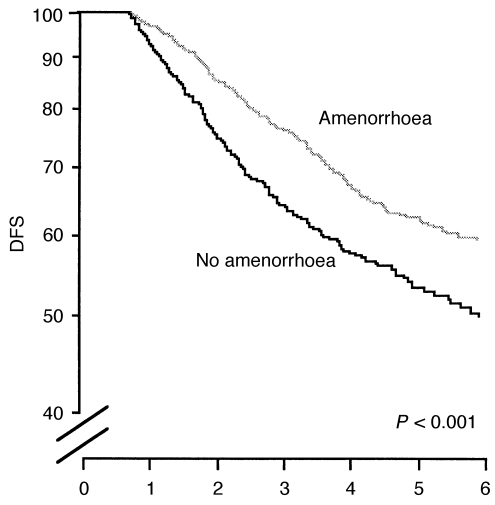

Figure 2. Kaplan–Meier plots for landmark analysis of disease-free survival according to amenorrhoea status for premenopausal patients with node-positive breast cancer in IBCSG Trial VI: all patients ($n = 1196$).

Women who experienced amenorrhoea had a significantly better DFS overall than those women who did not ($P = 0.0004$; Figure 2). Women who did not experience amenorrhoea were younger than those who did: 47% (217/460) of the women in the 'no amenorrhoea' group were less than 40 years old compared with 7% (49/736) in the 'amenorrhoea' group. When age was considered in a model with amenorrhoea status, the significance of the amenorrhoea effect was reduced ($P = 0.11$). There was no significant difference in DFS between those women who experienced amenorrhoea and those who did not within either subgroup of age, although, for those women 40 years and older, the rate of disease recurrence was lower (Figure 3).

Table 5 shows the 5-year DFS percentages and the estimated crude and adjusted hazard ratios and confidence intervals for the entire study population as well as for subgroups defined by age, treatment, receptor status and nodes. To evaluate if the effect of experiencing amenorrhoea was different across patient subgroups, all possible two-way interactions with amenorrhoea status were considered. The interaction with ER/PR status was significant ($P = 0.03$ for the interaction term). Experiencing amenorrhoea was associated with a significant effect on DFS among patients with ER/PR-positive tumours ($P = 0.0001$). The same association was not found for the patients with ER/PR negative tumours ($P = 0.78$; Table 5 and Figure 4).

The interaction between amenorrhoea status and duration of treatment was borderline significant ($P = 0.09$ for the interaction term). For the subgroup of women who received only 3 initial cycles of CMF, those who experienced amenorrhoea had a significantly better DFS than those women who did not experience amenorrhoea ($P = 0.002$). Amenorrhoea status was also a significant prognostic factor for the subgroup of women who received at least 6 cycles of CMF ($P = 0.04$), but the magnitude of the effect was less than for the CMF×3 group (Table 5 and Figure 5).

When age, duration of treatment, ER/PR status and node group were considered in a multivariate model with amenorrhoea status, the difference in DFS for those women who experienced amenorrhoea versus those who did not was reduced as compared to the crude analysis ($P = 0.09$; Table 5).

Duration of amenorrhoea did not affect outcome: a pairwise test between the 'amenorrhoea/no recovery' and 'amenorrhoea/recovery' categories showed no significant difference in DFS overall (HR 1.10, 95% CI 0.75–1.62, $P = 0.63$, 5-year DFS 63 ± 2% for the 656 women who did not recover and 60 ± 6% for the 80 women who recovered). In addition, no significant effect of recovery on DFS was observed in any subset of patients examined (older versus younger women, short versus prolonged treatment, ER/PR + versus ER/PR − primaries, ER + versus ER − primaries, or 4 + nodes versus 1–3 nodes).

DISCUSSION

The effect of chemotherapy-induced amenorrhoea on survival from breast cancer remains controversial. Analysis and comparison of the available data are difficult because of differences in trial design and definition of the variables. The overview of the Early Breast Cancer Trialists' Collaborative

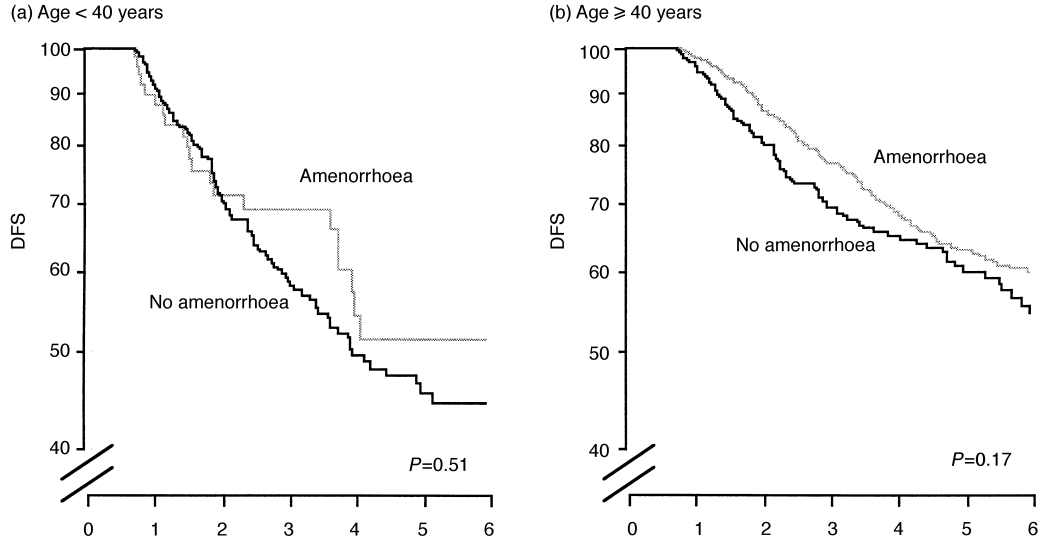

Figure 3. Kaplan–Meier plots for landmark analysis of DFS according to amenorrhoea status by age: 266 patients < 40 years of age (a) and 930 patients ≥ 40 years of age (b).

Table 5. *Estimated 5 year DFS percentages and hazard ratios (HR) according to amenorrhoea status*

			Unadjusted			Adjusted for covariates		
Amenorrhoea status	*n*	5 yr DFS%	HR	95% CI	*P*-value	HR	95% CI	*P*-value
All patients								
Amenorrhoea	736	62	0.72	0.60, 0.86	0.0004	0.84*	0.67, 1.03	0.09
No amenorrhoea	460	54						
Age ≥ 40								
Amenorrhoea	687	63	0.86	0.66, 1.07	0.17	0.84†	0.66, 1.06	0.14
No amenorrhoea	243	60						
Age < 40								
Amenorrhoea	49	51	0.85	0.54, 1.36	0.51	0.82†	0.50, 133	0.42
No amenorrhoea	217	46						
Three CMF cycles								
Amenorrhoea	139	67	0.55	0.38, 0.81	0.002	0.69‡	0.44, 1.07	0.09
No amenorrhoea	152	49						
At least 6 CMF cycles								
Amenorrhoea	597	61	0.80	0.64, 0.98	0.04	0.90‡	0.70, 1.14	0.38
No amenorrhoea	308	56						
ER/PR +								
Amenorrhoea	604	65	0.65	0.53, 0.80	0.0001	0.76§	0.61, 0.96	0.02
No amenorrhoea	360	52						
ER/PR –								
Amenorrhoea	132	52	1.06	0.70, 1.61	0.78	1.22§	0.71, 2.13	0.46
No amenorrhoea	100	60						
ER +								
Amenorrhoea	533	65	0.68	0.55, 0.85	0.0006	0.79§	0.61, 1.00	0.05
No amenorrhoea	309	53						
ER –								
Amenorrhoea	203	57	0.81	0.58, 1.13	0.23	0.94§	0.62, 1.42	0.78
No amenorrhoea	151	56						
Node group 4 +								
Amenorrhoea	232	48	0.60	0.45, 0.77	0.0001	0.75‖	0.56, 1.02	0.06
No amenorrhoea	157	33						
Node group 1–3								
Amenorrhoea	504	69	0.83	0.64, 1.07	0.15	0.92‖	0.68, 1.24	0.58
No amenorrhoea	303	65						

*Adjusted for age (≥ 40 versus < 40), duration of treatment (3 versus at least 6 cycles of CMF), ER/PR (+ versus −), and node group (4 + versus 1–3). †Adjusted for duration of treatment (3 versus at least 6 cycles of CMF), ER/PR (+ versus −) and node group (4 + versus 1–3). ‡Adjusted for age (≥ 40 versus < 40), ER/PR (+ versus −) and node group (4 + versus 1–3). §Adjusted for age (≥ 40 versus < 40), duration of treatment (3 versus at least 6 cycles of CMF), and node group (4 + versus 1–3). ‖Adjusted for age (≥ 40 versus < 40), duration of treatment (3 versus at least 6 cycles of CMF), and ER/PR (+ versus −). *n* = number of patients, DFS = disease-free survival, 95% CI = 95% confidence interval, HR = hazard ratio: amenorrhoea versus no amenorrhoea.

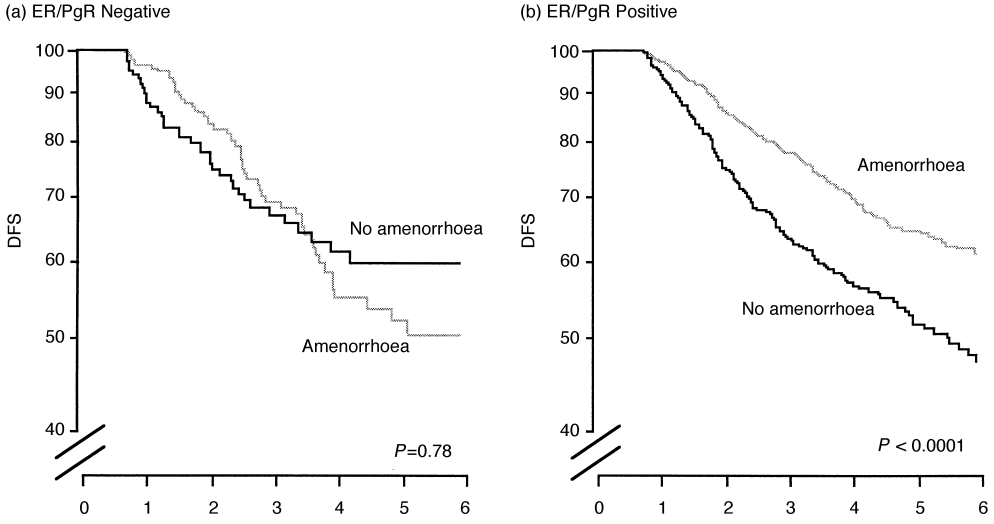

Figure 4. Kaplan–Meier plots for landmark analysis of DFS according to amenorrhoea status by ER/PR status: 232 patients with ER/PR – status (a) and 964 patients with ER/PR + status (b).

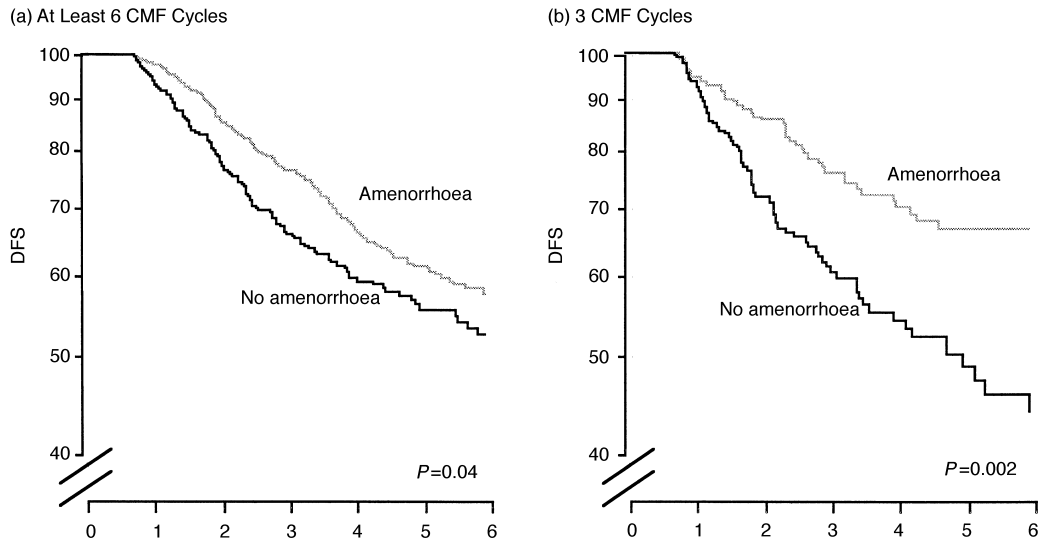

Figure 5. Kaplan–Meier plots for landmark analysis of DFS according to amenorrhoea status by duration of treatment: 905 patients who received at least 6 cycles of CMF (a) and 291 patients who received 3 cycles of CMF (b).

Group [13] reported a beneficial effect of adjuvant ovarian ablation similar in magnitude to that of cytotoxic chemotherapy. Furthermore, the new data (not shown) show that chemotherapy plus ovarian ablation is not more effective than chemotherapy alone.

In two NSABP trials [6], with a total of 96 patients who received either melphalan alone or in combination with 5-fluorouracil (5-FU), no relationship was observed between amenorrhoea and treatment effect. However, this statement was exclusively based upon the observation that improvement of DFS was better in younger patients, who had a lower incidence of chemotherapy-induced amenorrhoea, without further analysis undertaken.

The recently updated results at 20 years of follow-up of the Milan trial, in which 78 premenopausal, node-positive patients were treated with CMF, confirm the previous finding of no significant difference in outcome between women with and without chemotherapy-induced amenorrhoea [14, 15]. Again, this refers to a small number of cases since only 6% of patients older than 40 maintained normal menses.

Subsequent trials with a greater number of patients reported some differences in DFS favouring women who ceased menses. The mature results (median follow-up 8 years) of the Guy's/Manchester trial [16], comparing 12 cycles of CMF to observation alone, confirmed the previously reported trend [17] toward a better DFS for premenopausal patients with chemotherapy-induced amenorrhoea (69 patients) when compared with patients who continued to menstruate (21 patients) ($P = 0.005$). This effect, in agreement with the Milan results, was not detectable in patients aged 40 years or less.

In the Danish premenopausal trial [2], exploring the differential effect of cyclophosphamide alone versus CMF, patients treated with cyclophosphamide alone ($n = 321$) had a significantly better DFS if they had experienced amenorrhoea ($n = 264$) or had ER positive tumours ($n = 59$), while patients treated with CMF ($n = 315$) had the same DFS regardless of menstrual or ER status. Assuming that cyclophosphamide is a less tumoricidal treatment than CMF, these data suggest that the effect of adjuvant cytotoxic therapy is mediated partly through chemical castration and partly through a pure cytotoxic effect.

In the ECOG premenopausal study (CMF versus CMF plus prednisone (p) versus CMFp plus tamoxifen) menstrual status was available for 506 patients: the time to relapse of patients experiencing amenorrhoea and whose tumours were ER-positive was significantly longer than for patients who had no amenorrhoea or who had ER-negative tumours [18].

Levine and associates [3] recently reported the results of a Canadian multicentre randomised trial comparing a 12-week chemohormonal regimen with a 36-week chemotherapy regimen in node-positive breast cancer patients. The effect of chemotherapy on menstrual function was prospectively documented in the majority of patients (95 of 114 premenopausal women). The recurrence rate was significantly lower in patients who became amenorrheic and there was a trend towards lower mortality in women developing permanent amenorrhoea. In this trial, however, the benefit was apparent only in patients 40 years or less.

Two trials (I and V) of the International (Ludwig) Breast Cancer Study Group (IBCSG) addressed the relationship between amenorrhoea and outcome. In IBCSG Trial I, 491 pre- and perimenopausal patients with operable, node-positive breast cancer were randomised to receive CMF or CMF plus low-dose prednisone (p) for 1 year [19]. In 399 patients with menstrual status known and monitored, induced amenorrhoea was associated with a longer DFS for younger patients (≤ 39 years old), patients who received lower CMF doses ($< 80\%$ of the planned dose) and patients with ER-positive tumours. In IBCSG Trial V, 1127 premenopausal patients received either no adjuvant therapy (node-negative only), one course of peri-operative CMF (node-negative and node-positive), or a prolonged 6-month CMFp treatment (node-positive only) [20, 21]. The incidence of amenorrhoea was related to the duration of adjuvant therapy: 21% for patients receiving no adjuvant therapy, 31% for patients receiving a single cycle, and 68% for patients treated with prolonged chemotherapy [4]. Amenorrhoea was not significantly associated with DFS outcome for patients who received a single cycle or no adjuvant chemotherapy; this might be explained by the relatively low number of patients who achieved amenorrhoea and by the overall poor outcome

for premenopausal node-positive patients who received only a single cycle of CMF. Cessation of menses was associated with a statistically significant improvement in DFS for the subset of 387 patients that received the prolonged treatment ($P = 0.05$ logrank test), but the absolute difference in 4-year DFS percentage was modest ($68 \pm 3\%$ for the amenorrhoea group versus $61 \pm 5\%$ for the no amenorrhoea group) [4].

The current results presented from Trial VI are consistent with these earlier findings and support the proposition that a portion of the effect of adjuvant cytotoxics for premenopausal breast cancer patients is due to chemotherapy-induced ovarian function suppression. The relationship between the effect of amenorrhoea and dose of CMF received was confirmed in the current study, which indicates that the anti-tumour effect of ovarian function suppression is more important when a shorter duration of CMF provides less direct cytotoxic effect of chemotherapy. Amenorrhoea might be a marker for selection of sensitive cells by independent mechanisms of tumour cell kill. Alternatively, the induced amenorrhoea might be a signal that antitumour CMF levels had been delivered despite the lower dose.

Based on the observation of no difference in DFS outcome according to the status of recovery of menses, we showed that even a temporarily limited ovarian function suppression with menses cessation provides some benefit in terms of DFS. The biological explanation underlying this observation is speculative: complex interactions exist between circulating hormone levels, their regulatory mechanisms and normal and/or neoplastic breast cell growth. Consistent evidence is emerging, however, to suggest strict relationships between growth factors, oncogenes and hormones in regulation of breast cancer cell growth [22]; even transient modifications of this milieu could be responsible for significant differences in antitumour activity. Furthermore, the fact that the effect of amenorrhoea was observed mainly in the sub-population of patients with steroid hormone receptor-positive primaries (ER/PR+) reinforces the hypothesis that the relative contributions of both the castration and the cytotoxic antitumour effect of chemotherapy differ for different patient subgroups.

It is also important to recognise that the results presented are based on a retrospective analysis of data. The fact that a lower percentage of women younger than 40 experienced amenorrhoea as compared with women 40 years or older (18 versus 74%, respectively) could also partly explain the poorer results in patients without ovarian function suppression. Young age represents an unfavourable prognostic factor in breast cancer patients.

These findings, nevertheless, are reassuring for the conduct of two ongoing IBCSG trials, Trial VIII and Trial 11–93. In Trial VIII, pre and perimenopausal patients with node-negative breast cancer are randomised to receive one of three therapies: (1) Zoladex $\times$ 24 months, (2) CMF $\times$ 6, or (3) CMF $\times$ 6 followed by Zoladex $\times$ 18 months (the 4th arm, no therapy, was discontinued 2 April 1992). It is to be expected that the amenorrhoea induced by Zoladex will be reversible in many patients, so the observation that reversible chemotherapy-induced amenorrhoea still confers protection is reassuring. For this trial, menses status is collected every month for the first 3 years following randomisation. As of 31 July 1997, 936 patients have been randomised to this trial with 45 patients randomised to the no therapy arm and the rest of the patients divided evenly among the other 3 arms. The Zoladex alone arm thus far has the highest percentage of patients ceasing menses in the shortest amount of time.

In Trial 11–93 premenopausal women with node-positive breast cancer and receptor positive tumours are randomised to receive, after surgical, radio- or chemically-induced ovarian ablation, (1) doxorubicin, cyclophosphamide (AC)$\times$4 followed by tamoxifen for 5 years or (2) tamoxifen alone. As of 31 July 1997, 148 patients have been randomised.

Both of these trials, in different patient populations and together with other ongoing studies, address the fundamental issue of the relative role of chemotherapy and endocrine manipulations in premenopausal breast cancer patients. The fact that adjuvant cytotoxic therapy is also effective in patients with tumours containing no oestrogen receptors and the observation of an early onset of its effects as opposed to the delayed effect observed in trials with surgical or radiation-induced ovarian ablation [23], argue for the complementarity of the two approaches.

In conclusion, the effect of ovarian ablation on survival from breast cancer remains controversial, but increasing evidence favours the hypothesis that cytotoxics-induced castration improves disease-free survival and perhaps prolongs overall survival. Many questions are still to be answered: does tamoxifen, when given sequentially after chemotherapy in premenopausal patients, improve treatment outcome in terms of reduced disease occurrence? Are the consequences of early menopause, especially in patients with node-negative disease, outweighed by improved treatment results? Is there a combination of drugs which yields equal relapse-free survival and is associated with a lower rate of cytotoxics-induced castration? The results presented in this analysis and emerging from other ongoing studies may help oncologists in the near future to offer their patients the safest and most effective treatment.

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APPENDIX

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