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Adjuvant Chemotherapy in Premenopausal Patients with Primary Breast Cancer; Relation to Drug-induced Amenorrhoea, Age and the Progesterone Receptor Status of the Tumour

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Abstract—*Adjuvant chemotherapy with cyclophosphamide, 5-fluorouracil and methotrexate (CMF)-induced permanent ovarian suppression in 47 of 77 (61%) premenopausal patients with axillary node positive breast cancer. After a median observation time of 37 months the relapse-free and overall survival times were significantly longer for patients with permanent amenorrhoea.*

A strongly positive correlation between CMF-induced amenorrhoea and age of the patients, as well as between age and the tumour PgR status, was found. The induction of ovarian suppression predominantly occurs in patients wih PgR positive tumours and may add an endocrine effect to the cytotoxic action of adjuvant chemotherapy in this particular group of older premenopausal women.

PATIENTS AND METHODS

BETWEEN 1976 and 1987 85 premenopausal patients with primary breast cancer and involved axillary lymph nodes received adjuvant chemotherapy consisting of 24 courses of low dose or nine or six courses of conventional dose of CMF. No additional endocrine therapy was given. The patients subsequently were followed at intervals up to 6 months for tumour recurrence and ovarian function, including measurement of serum LH and FSH levels. Patients with an observation period of less than 12 months, who did not get a recurrence, were excluded from this analysis. Assays for oestradiol (ER) and progesterone receptors (PgR) were done using the dextran-coated charcoal method with multiple point Scatchard plot analysis, with cut off values of 10 fmol/mg cytosol protein [1].

Statistical comparisons of the estimated relapse free survival (RFS) and overall survival curves (Kaplan–Meier) were made using the Gehan–Wilcoxon non-parametric test (P denoted by p) and the log rank test (P denoted by p^*) [2].

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RESULTS

Forty-seven of the 77 patients (61%) who were eligible for this analysis became permanently amenorrhoeic with a corresponding rise in serum gonadotrophins. Of these patients 89% were aged 40 years or older. The mean interval between the start of chemotherapy and the permanent cessation of ovarian function was 8 months and 3 months for patients < 40 years and ≥ 40 years respectively. Patients with permanant ovarian suppression were older ($P < 0.0001$), more often had PgR positive tumours ($P < 0.05$) and had less involved axillary lymph nodes ($P < 0.05$) than patients without permanent amenorrhoea.

No statistically significant differences were found between both groups of patients in tumor ER status, tumour stage, type of primary treatment, interval between surgical therapy and start of chemotherapy, CMF regimen and average relative dose of chemotherapy.

Within the group of patients with known PgR status ($n = 59$) the relations between the occurrence of CMF-induced amenorrhoea, the axillary nodal involvement at first treatment and the age of the patients was analysed. Table 1 shows that patients with PgR positive tumours had a significantly smaller number of involved axillary lymph nodes,

Table 1. Progesterone receptor activity related to age, axillary node involvement and induction of permanent amenorrhoea

	PgR positive $n = 47$	PgR negative $n = 12$	P value	PgR unknown $n = 18$
Age (years)	44 ± 5	39 ± 6	<0.02	39 ± 6
Axillary nodes involved				
1–3	32 (68)*	4 (33)		8 (44)
≥ 4	12 (26)	4 (33)	<0.025	3 (17)
infraclavicular	3 (6)	4 (33)		7 (39)
Amenorrhoea				
permanent	34 (72)	4 (33)		9 (50)
no (permanent)	13 (28)	8 (67)	<0.05	9 (50)

*Numbers in parentheses are the percentages of the 47, 12 and 18 patients in each group.

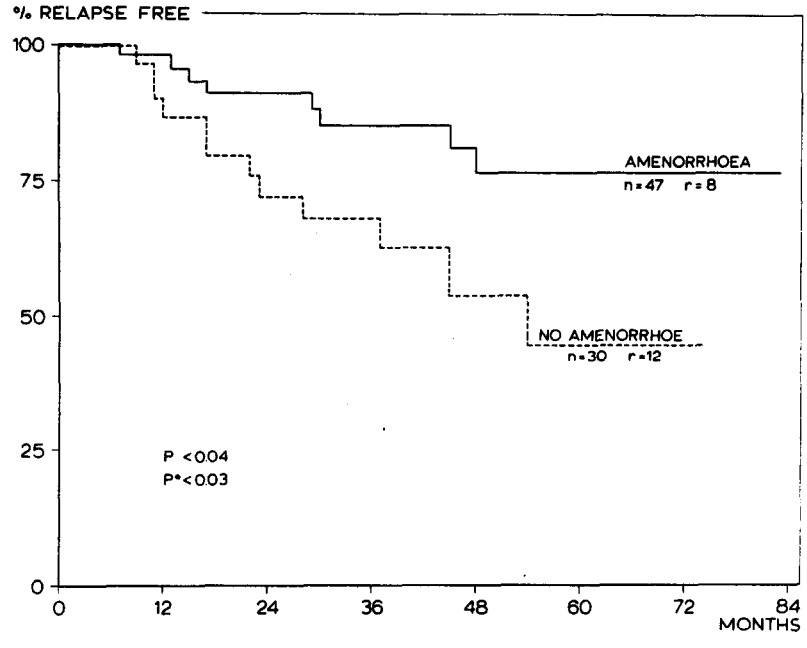

Fig. 1. Estimated relapse-free survival of patients with and without a CMF-induced permanent amenorrhoea.

had a significantly higher age and had significantly more often CMF-induced amenorrhoea than patients with PgR negative tumours.

Relapse-free survival (RFS) and overall survival

After a median observation period of 37 months (range 11–131 months), 85% and 68% of the patients with and without a CMF-induced permanent amenorrhoea respectively were estimated to be relapse-free ($p^* < 0.03$; Fig. 1). The corresponding values for the overall survival were 90% and 69% respectively ($p^* = 0.03$). The estimated RFS as well as the overall survival were significantly longer for patients with a PgR positive than with a PgR negative tumour ($p^* < 0.01$ and $p^* < 0.01$).

DISCUSSION

In accordance with literature data, older premenopausal patients more often had a CMF-induced permanent ovarian suppression with a corresponding rise in serum gonadotrophin levels than younger ones [3–5]. The inverse correlation between age and the interval between start of chemotherapy and onset of amenorrhoea has also been described earlier [3]. Both phenomena can be explained by a decreasing number of active ovarian follicles with increasing age [6]. Older premenopausal women more often have PgR positive tumours than younger ones [7, 8]. An inverse relation has been described between the tumour PgR status and axillary lymph-node involvement [9]. In accordance, Table 1 shows that patients with PgR positive tumours were older and had less involved axillary nodes than patients with PgR negative tumours. Permanent CMF-induced amenorrhoea occurred most frequently in the former group.

In accordance with our data, induction of permanent amenorrhoea and tumour PgR positivity have been related with an optimal beneficial effect of adjuvant chemotherapy [10, 11]. In addition, adjuvant chemotherapy is a prerequisite for the prognos-

tic benefit of tumour PgR positivity [12].

In conclusion, a rapid induction of ovarian suppression by adjuvant chemotherapy occurs predominantly in older premenopausal women preeminently being the patients with hormone dependent (PgR positive) tumours and less involved axillary nodes. The beneficial outcome of adjuvant chemotherapy in this particular group of patients may be explained by the combined cytotoxic and endocrine potential of this treatment.

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