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Acknowledgement—The authors thank Mrs Jacqui Hussain for the hard work involved in recruiting the patients.

Eur J Cancer, Vol. 29A, No. 1, pp. 21–23, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

Chemotherapy Induced Amenorrhoea in a Randomised Trial of Adjuvant Chemotherapy Duration in Breast Cancer

Leonard M. Reyno, Mark N. Levine, Peter Skingley, Andrew Arnold and H. Abu Zahra

We have previously reported the results of a clinical trial in patients with stage II breast cancer which compared a 12 week chemohormonal regimen with a 36 week chemotherapy regimen. Both pre and post menopausal women were entered. The 12 week regimen was inferior both in terms of disease-free survival and overall survival. The effect of chemotherapy on menstrual function was prospectively documented in 95 of 114 premenopausal women at 3 of the 4 participating centres. 67 of the 95 women (70.5%) developed permanent amenorrhoea. There was a statistically significant difference in the rate of induced amenorrhea between the 12 week and the 36 week groups; 23/42 vs. 44/53, respectively ($P = 0.003$). Recurrence and mortality rates were lower in the patients who became amenorrheic; 38% vs. 57% ($P = 0.03$) and 18% vs. 32% ($P = 0.17$), respectively. Similar trends were observed within treatment groups. The effect of induced amenorrhoea on outcome was seen predominantly in patients under 40 years old. These results suggest that the induction of ovarian failure is a potential mechanism for the observed effect of adjuvant chemotherapy in these patients. The difference in the ovarian failure rates between groups may be a possible explanation for the inferiority of the 12 week regimen.
Eur J Cancer, Vol. 29A, No. 1, pp. 21–23, 1993.

INTRODUCTION

WHILE POSTOPERATIVE adjuvant chemotherapy is standard practice for premenopausal patients with axillary node positive breast cancer, it is not known with certainty the mechanism by which such therapy prolongs remission and survival. Recent results of the Breast Cancer Trialists' Overview have demonstrated that ovarian ablation improves both relapse free survival and overall survival in women under the age of 50 [1]. It has been postulated that at least part of the benefit of cytotoxic therapy is derived from chemotherapy induced ovarian ablation [1–3]. No trial however has been designed in such a way and collected adequate data to answer this question directly.

We have previously reported the results of a clinical trial in stage II breast cancer which compared a 12 week adjuvant chemohormonal regimen which included tamoxifen with a standard 36 week chemotherapy regimen [4]. The 12 week regimen was inferior both in terms of disease-free survival and overall survival. The effect of chemotherapy on the patients' menstrual function was prospectively documented along with a questionnaire assessing quality of life [5]. We now report the ovarian

failure rates associated with these regimens and the relationship of ovarian failure to the outcomes of disease free survival and overall survival.

PATIENTS AND METHODS

Between 1984 and 1987, 437 women 70 years of age or younger with histologically confirmed axillary node positive breast cancer were randomised to receive either 12 or 36 weeks of treatment [4]. Briefly, the 12 week regimen consisted of cyclophosphamide, methotrexate, fluorouracil, vincristine, prednisone, doxorubicin, and tamoxifen. The tamoxifen was given for the 12 weeks only. The 36 week regimen consisted of cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone. Patients were stratified for number of involved axillary nodes and age.

A questionnaire assessing ovarian function was administered to patients enrolled at three of the four participating centres. These questionnaires were administered at the time of randomisation, every second week for the first 12 weeks and monthly thereafter for at least 12 months.

Women were defined as premenopausal if they reported a menstrual cycle in the 3 months prior to randomisation and six or more menstrual cycles in the preceding 12 months. Patients were considered to have developed permanent amenorrhoea if they reported cessation of menses on chemotherapy and menses did not return during the follow-up period.

The χ^2 test was used to compare rates of amenorrhoea. Recurrence and survival data were described by the Kaplan–Meier method and comparisons were made using the Mantel Cox test. Median follow-up was 40 months.

RESULTS

114 patients at the three centres where questionnaires were administered were premenopausal at the time of randomisation. Serial questionnaires were available for 95 of them; 42 of these women were from the 12 week group and 53 from the 36 week group. The mean age of these patients was 43 years (S.D. 5.8).

Of the 95 women 67 (70%) developed permanent amenorrhoea. 28 women continued to report menses during the follow-up period, although 14 of these patients reported a transient cessation of menstrual activity. In these 14 women, the median disruption of menses was 26 weeks (range 16–57 weeks). Only patients who did not report a resumption of menstrual cycles are classified as developing permanent amenorrhoea in the current analysis.

There was a statistically significant difference in the rate of induced permanent amenorrhoea between the 12 week and the 36 week treatment groups, 23/42 (55%) vs. 44/53 (83%) respectively, $P = 0.003$.

Of the 67 patients who developed permanent amenorrhoea, 22 (33%) developed recurrent breast cancer compared with 16 (57%) in the 28 patients who continued to menstruate. This difference is statistically significant, $P = 0.03$ (see Fig. 1). There was also a trend towards lower mortality in the patients who developed permanent amenorrhoea, 18% vs. 32%, respectively, $P = 0.17$. When the results concerning menstrual status were analysed within treatment groups, these trends were maintained (see Table 1).

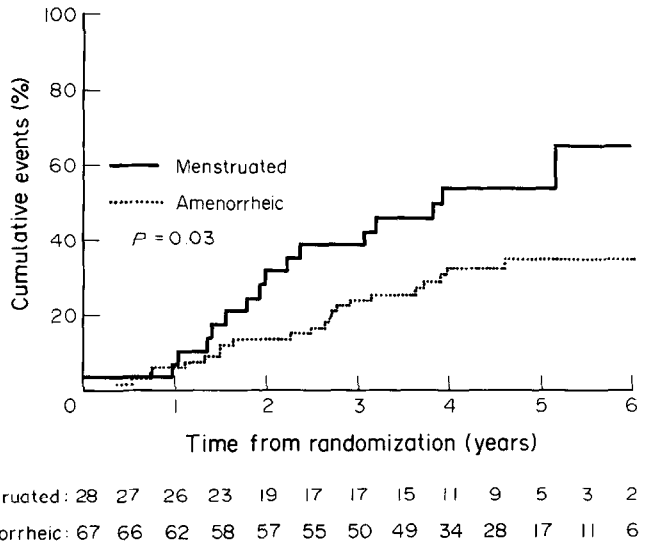

Fig. 1. Cumulative recurrence rates in patients who developed amenorrhoea compared with those who did not develop amenorrhoea.

Table 1. Outcomes by treatment groups

	12 week Amenorrhea			36 week Amenorrhea		
	Yes ($n = 23$)	No ($n = 19$)		Yes ($n = 44$)	No ($n = 9$)	
Recurrence	8 (35%)	11 (58%)	$P = 0.15$	14 (32%)	5 (56%)	$P = 0.25$
Mortality	4 (17%)	7 (37%)	$P = 0.2$	8 (18%)	2 (22%)	$P = 0.9$

Patient age and the development of permanent amenorrhoea may be closely related. We therefore compared the recurrence rates in patients 40 years or less with those in patients over 40 based on the presence or absence of amenorrhoea (Table 2). In the ≤ 40 group only 3 of 11 amenorrheic patients recurred compared with 11 of 14 in the patients who continued to menstruate, $P = 0.07$. Conversely, in the over 40 group, 9 of 46 amenorrheic patients recurred compared with 5 of the 24 patients who continued to menstruate, $P = 0.8$.

DISCUSSION

The results of our study confirm that a substantial proportion of premenopausal women who receive prolonged adjuvant systemic chemotherapy will experience chemotherapy induced ovarian ablation. The overall proportion of patients developing

Table 2. Recurrence by age

	≤ 40 Years Amenorrhea			> 40 Years Amenorrhea		
	Yes ($n = 11$)	No ($n = 14$)		Yes ($n = 46$)	No ($n = 24$)	
Recurrence	3 (27%)	11 (79%)	$P = 0.07$	9 (20%)	5 (21%)	$P = 0.8$

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Received 5 May 1992; accepted 8 July 1992.

amenorrhoea (70%) is consistent with the observations made in other trials [2,3,6–8]. The proportion of patients rendered amenorrheic was lower in the patients randomised to the relatively less effective 12 week treatment arm which contained tamoxifen. We have previously postulated that the inferiority of the 12 week arm could be explained by its shorter duration and/or a negative interaction of tamoxifen with cytotoxic chemotherapy [3].

The data presented now suggests a third possible mechanism for the inferiority of the shorter arm which relates to the disparate rates of ovarian failure between the two treatment groups. In addition, it was only in the group of patients ≤ 40 years that the differences were both statistically significant and clinically impressive. It should be noted that in a previous analysis the 12 week treatment was inferior both in women < 50 years and ≥ 50 years [3]. Thus, the difference in ovarian failure rates between groups cannot be postulated as the only mechanism for the inferiority of the shorter arm.

The current analysis is subject to obvious criticism not the least of which is the number of patients available for analysis and the absence of data from one participating centre. It is unlikely that the inclusion of data from the fourth centre would change the results significantly, but this cannot be excluded. Ultimately however, the number of patients and the event rates make it difficult if not impossible to reach conventional levels of statistical significance beyond the observation that the induced rates of amenorrhoea are different on the two regimens and the recurrence rate is higher in patients who continued to menstruate.

The mature results of the Guy's/Manchester trial are interesting in this regard [6]. The trial, now with a median follow-up of 8 years, compared 12 cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) to observation alone in women with stage II disease. Data regarding ovarian failure rates was available for 90 of 97 premenopausal CMF treated women on the trial. 77% of women treated with CMF developed amenorrhoea. The rate was highest in women older than age 40 compared with women under age 40 (58/60 vs. 11/30). Patients who developed amenorrhoea did better as a whole, but the effect was greatest in the cohort of women older than age 40. In contrast to our own results, the authors could not detect an effect in women younger than age 40, an observation which has been suggested by other investigators [8].

The mechanism by which adjuvant chemotherapy prolongs remission and survival remains controversial but likely includes both cytotoxic and endocrine effects. The most recent overview analysis supports the concept of a dual mechanism of action and our own results are consistent with this observation [1]. However, we are unable to fully characterise the interaction of the two effects. The current results suggest that in premenopausal women "effective chemotherapy" will be associated with ovarian ablation in most women. However, if the cytotoxic and endocrine effect confer benefit independently (i.e. rather than the endocrine outcome simply serving as a marker for cytotoxic therapy) it will be difficult to separate the effect of ovarian ablation from chemotherapy in the analysis of any trial if all patients receive chemotherapy. The Intergroup Study comparing 12 months of CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone) to the same chemotherapy plus adjuvant oophorectomy in premenopausal women with ostrogen receptor positive tumours perhaps illustrates this difficulty [9]. 314 patients were randomised and at a median follow-up of 5 years no significant differences in relapse free survival or overall survival are apparent. The authors point out that the sample size is too small to rule out moderate differences in outcome and to date, the ovarian failure rate in the control arm has not been reported.

Given the well defined role of adjuvant cytotoxic therapy in improving both relapse free and overall survival in premenopausal women with node positive breast cancer, it is unlikely that a prospective trial comparing ovarian ablation to standard chemotherapy will be undertaken. The current results and the results of others suggest that at least part of the benefit of chemotherapy is related to ovarian ablation but the nature of the interaction with known prognostic variables such as age and oestrogen receptor content has not been fully characterised. Ideally, on going trials in premenopausal patients should prospectively collect data regarding menstrual function so that more powerful analyses can be completed in the future.

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