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Effect of Chemotherapy with or without Buserelin on Serum Hormone Levels in Premenopausal Women with Breast Cancer

Carla I. Falkson, Hendré C. Falkson and Geoffrey Falkson

Serial determinations of serum oestradiol (E2), follicle-stimulating hormone (FSH) and luteinising hormone (LH) were done to assess the effect of chemotherapy, with or without a gonadotropin-releasing hormone analogue, buserelin, on ovarian function in 147 premenopausal women treated for breast cancer. Cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) plus buserelin was given to 81 women with metastatic disease, and 66 women were randomised to adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with buserelin or CMF alone. Baseline mean E2 of patients treated with cytostatics plus buserelin fell from premenopausal levels and remained low while patients were on study. E2 levels remained at premenopausal values in patients treated with CMF alone. Downregulation of FSH and LH occurred with cytostatics plus depot buserelin, but fluctuated with the nasal administration; on CMF alone, FSH and LH levels increased. Buserelin plus cytostatics more effectively caused ovarian ablation than cytostatic treatment alone. Depot buserelin was more effective than nasal buserelin.
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INTRODUCTION

OVARIAN ABLATION remains an important therapeutic manoeuvre in the management of premenopausal women with breast cancer. Oophorectomy is associated with morbidity and some psychological problems; the availability of a medical castration is therefore a useful addition to the oncologist's armamentarium. It has been demonstrated that intranasal administration of buserelin (D Ser[Bu] LHRH ethylamide) throughout the menstrual cycle will cause anovulation [1] and activity has been demonstrated with buserelin in premenopausal women with breast cancer [2]. Buserelin is well tolerated when given concomitantly with combination chemotherapy and therapeutic results are not adversely affected when buserelin is given with chemotherapy in premenopausal women with metastatic breast cancer [3].

This study was undertaken in order to assess the effect of chemotherapy with or without buserelin on ovarian function of premenopausal women with breast cancer.

PATIENTS AND METHODS

Serial determinations of serum oestradiol (E2), follicle-stimulating hormone (FSH) and luteinising hormone (LH) were done in 147 premenopausal women who received chemotherapy with or without buserelin. Hormone values were obtained by radioimmunoassays. All patients had histologically confirmed breast cancer. The median age of the patients was 43 (range 28–57) years. Of the 147 patients studied, 108 were still menstruating regularly, and 39 had had a hysterectomy with ovaries intact. All 147 were premenopausal as determined by pretreatment serum hormone levels. The normal range for a woman to be considered premenopausal was 50–1376 pmol/l for E2,

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Table 1. Characteristics of patients on different treatments

	Treatment			
	CAF	CAF	CMF + depot	CMF
Age mean (range)	41 (32–57)	45 (28–57)	40 (30–53)	42 (32–50)
Hysterectomy	5	15	8	11
Developed amenorrhoea	13/17	39/44	25/26	9/21
FSH (IU/l)	30.7 (10)*	23.3 (2.6)	16.2 (3.1)	17.3 (2.3)
LH (IU/l)	36.5 (9)	19.9 (19.9)	13.7 (3.5)	16.8 (1.9)

* Mean baseline (S.E.).

5–30 IU/l for FSH and 5–200 IU/l for LH; and the normal range for postmenopausal women was 0–50 pmol/l for E2; 50–100 IU/l for FSH and 50–100 IU/l for LH. Hormone values were obtained before treatment, monthly for the first 6 months and then at 3-monthly intervals.

The patients studied included 81 women treated for metastatic disease at first relapse, and 66 women randomised on an adjuvant study for node-positive operable disease. The patients with metastatic breast cancer were treated with CAF (cyclophosphamide 100 mg/m^2 orally per day on days 1–14, doxorubicin 30 mg/m^2 intravenously on days 1 and 8 plus 5-fluorouracil 500 mg/m^2 intravenously on days 1 and 8, repeated every 28 days) and buserelin. After six cycles of CAF plus buserelin, methotrexate 40 mg/m^2 intravenously was substituted for the doxorubicin on days 1 and 8. Buserelin was given intranasally to 22 patients, entered on a pilot study. When the depot formulation became available a new study was activated and 59 patients received the agent as a depot implant. The nasal spray was so constituted that a single inhalation delivered 100 μg of GnRHA. The dose administered was 2400 μg/day × 7 days (two inhalations in each nostril six times a day for a total of 24 inhalations per day). From day 8 onwards, the patients received 1200 μg/day of buserelin (two inhalations in each nostril three times a day for a total of 12 inhalations per day). Depot buserelin was given as a 6.6 mg subcutaneous implant every 28 days. (Initially monthly implants were considered necessary; subsequently the manufacturer, Hoechst laboratories, recommended one injection every 2 months.) There were 66 patients on the adjuvant study: 32 were randomised to receive CMF (cyclophosphamide 100 mg/m^2 orally per day on days 1–14, methotrexate 40 mg/m^2 intravenously on days 1 and 8, 5-fluorouracil 600 mg/m^2 intravenously on days 1 and 8 every 28 days) given for six cycles and 34 patients to CMF for six cycles plus monthly depot buserelin as a 6.6 mg subcutaneous implant continuously for 5 years.

Statistics

A non-parametric statistical analysis, the Mann–Whitney U test, was used to compare baseline serum hormone values. One-way analyses of variance were done on the serial means of the three hormones to test if differences between the curves were significant. Differences were considered significant if $P < 0.05$.

RESULTS

Table 1 shows the age, menstrual status and baseline serum hormone values for the patients in the different treatment groups. There were no significant differences between baseline values of E2, FSH and LH in the four groups of patients. There was no significant correlation between pretreatment serum E2 levels and age of the 147 patients studied (Pearson's correlation, $P = 0.76$).

CAF and nasal buserelin

Of the 22 patients, 17 were still menstruating regularly when entered on study. 5 had hysterectomies with ovaries intact, but were still premenopausal as judged by prestudy serum E2, FSH and LH. Amenorrhoea occurred in 13/17 women: in 6 patients after 1 month on treatment, in 3 after 2 months, in 1 after 3 months and in 3 after more than 10 months. After 3 months on treatment, the mean (S.E.) serum E2 baseline value of 281.9 (62.4) pmol/l decreased to a mean of 37.7 (13.1) pmol/l and remained low while patients were on study. The mean FSH baseline value was 30.7 (10) IU/l; after an initial increase during the first month on treatment it gradually decreased. The mean LH baseline value was 36.5 (9.5) IU/l. It decreased after treatment, then rose again and dropped sharply after 4 months, then remained at about 10 IU/l.

CAF and depot buserelin

Of the 59 patients 15 had had a hysterectomy. Of the others, 39/44 developed amenorrhoea: in 30 patients after one cycle, in 7 after two cycles, in 1 after four cycles and in 1 after five cycles. After 1 month on treatment the mean (S.E.) serum E2 baseline value of 292 (46.3) pmol/l decreased to a mean of 43.6 (18.6) pmol/l and remained at postmenopausal levels while patients were on study. The mean baseline FSH was 23.3 (2.6) IU/l; it decreased to 11 IU/l after 1 month and remained at about 15 IU/l while patients were on study. LH dropped from a baseline of 19.9 (2.3) IU/l and remained at about 12 IU/l.

Randomised adjuvant study

CMF. Of 32 patients randomised to six cycles of CMF, 11 had a hysterectomy and 9/21 developed amenorrhoea: 1 patient after one cycle, 2 patients after two cycles, 3 patients after three cycles, 1 patient after four cycles, 1 patient after six cycles and 1 patient 12 months after entry on study. 2 of these 9 patients started menstruating again after the six cycles of chemotherapy. The mean (S.E.) serum E2 baseline value was 322.8 (49.6) pmol/l. The decrease of serum E2 was insufficient in patients treated with CMF alone; not only did the level remain over

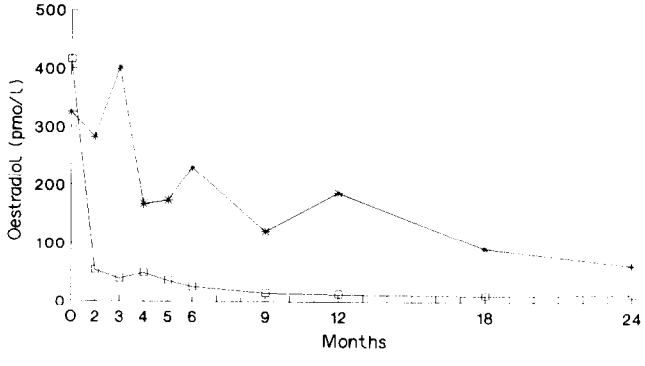

Fig. 1. Mean serum E2 for patients on randomised adjuvant study. * = CMF for six cycles, —□— = CMF for six cycles plus continuous buserelin.

	1	6	9	12	18	24	Months
CMF alone:	32	23	16	13	8	7	**Patients**
CMF + depot buserelin:	34	29	24	18	15	13	**Patients**

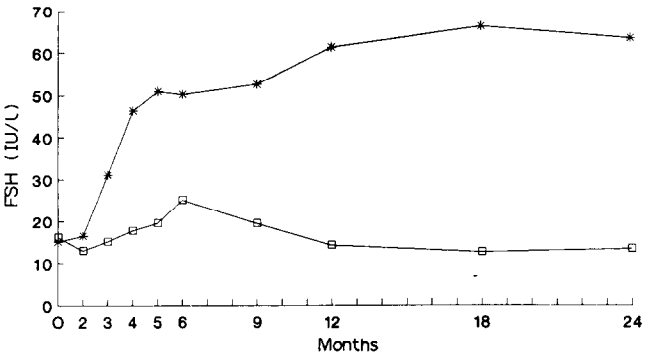

Fig. 2. Mean serum FSH for patients on randomised adjuvant study. See details, Fig. 1.

50 pmol/l, but until the fourth month it was over 200 pmol/l and at the 18th month was over 100 pmol/l (Fig. 1). The mean baseline values for FSH was 17.3 (3.1) IU/l and for LH 16.8 (3.5) IU/l; both FSH and LH values rose while patients received CMF (Figs 2 and 3).

CMF plus monthly depot buserelin continuously. Of 34 patients randomised to six cycles of CMF plus monthly buserelin, 8 had had a hysterectomy, and 25/26 developed amenorrhoea: 22 patients after one cycle, 2 patients after two cycles and 1 patient after four cycles. After 1 month on treatment the mean (S.E.) serum E2 baseline value of 414.9 (163.7) pmol/l decreased to 53.7 (16.1); after 2 months on treatment, it was 43.8 (15.9) and remained at postmenopausal levels while patients were on study (Fig. 1). The mean baseline value for FSH was 16.2 (2.3) IU/l and for LH 13.7 (1.9) IU/l. A decrease of FSH and LH was seen during the first 2 months, followed by a slight increase until levels gradually decreased after 6 months (Figs 2 and 3). Pretreatment serum hormone values of patients randomised on the two treatment arms were not significantly different. The serial mean values of patients treated with CMF alone were significantly different compared to the values of patients on CMF plus buserelin: E2 ($P < 0.01$) FSH ($P < 0.0001$) and LH ($P < 0.00001$).

DISCUSSION

The isolation and synthesis of luteinising hormone-releasing hormone (LHRH) in 1971 [4] introduced a method of medical castration. Synthetic gonadotropin-releasing hormone analogues (GnRHA), of which buserelin is one, have been shown to result in supraphysiological gonadotrophin release. With repeated administration their effect is paradoxical; the synthesis and secretion of gonadotropins are decreased and gonadal hormone concentrations fall [5]. Experimental studies in animals have shown that supraphysiological doses of GnRhA results, after a period of pituitary stimulation, in desensitisation of the gonadothrophs with consequent downregulation of FSH and LH synthesis [6]. In males, GnRhA administration inhibits FSH and LH production [7, 8]. Klijn and de Jong [2], reporting on 4 premenopausal patients treated with nasal buserelin only for metastatic breast cancer, noted that all 4 patients became anovulatory; however, FSH and LH fell but rose again and very low LH levels were not reached during their brief observation period.

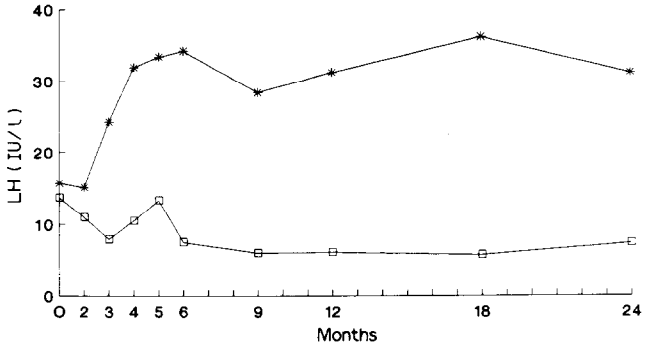

Fig. 3. Mean serum LH for patients on randomised adjuvant study. See details, Fig. 1.

In the current study, we investigated the effect of chemotherapy with or without buserelin in ovarian function in 147 premenopausal women with breast cancer. While serum E2 levels decreased to postmenopausal levels in patients who received CAF or CMF plus buserelin, this was not the case while patients received CMF alone. The decrease to postmenopausal E2 levels occurred after 1 cycle of CAF or CMF plus depot buserelin and after 3 months of CAF plus nasal buserelin. Downregulation of FSH and LH occurred with chemotherapy plus depot buserelin. Amenorrhoea developed rapidly in patients who received buserelin: 66.7% developed amenorrhoea after the first month, 80.4% before the end of the second month and 81.6% before the end of the third month. Among those patients treated solely with CMF, 4.7% developed amenorrhoea the first month, 14.2% before the end of the second month and 28.6% before the end of the third month.

The effect of chemotherapy plus intranasal buserelin on FSH and LH appears to be less consistent in women, as can be seen from our results. While the intranasal route is an easy and non-invasive way to administer the agent, the depot implant had a more consistent effect on the secretion of gonadotropins in women. Long-term follow-up analysis of the Eastern Cooperative Oncology Group and Cancer and Acute Leukemia Group B studies in premenopausal women with metastatic breast cancer has shown very high response rates to treatment with cytostatics. Using multivariate regression models, it was shown that not receiving cytostatics soon after oophorectomy is associated with significantly poorer survival [9]. It is therefore important to consider ovarian ablation as part of the treatment of premenopausal women with advanced breast cancer. The exact role of ovarian ablation in the adjuvant situation has not been completely elucidated. Some evidence exists that amenorrhoea is beneficial for premenopausal patients. In analysing the magnitude of endocrine effects of adjuvant chemotherapy for premenopausal women with breast cancer, Goldhirsch *et al.* [10] concluded that it is unlikely that cytotoxic-induced ovarian suppression is the main mechanism of response to adjuvant systemic chemotherapy.

Results from the current study show that LHRH plus cytostatic treatment was more effective in causing ovarian ablation than cytostatic treatment alone. The addition of buserelin to chemotherapy rapidly resulted in ovarian ablation, this effect being more rapid and consistent with depot buserelin than with buserelin administered nasally.

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Adjuvant Cisplatin-based Chemotherapy for Stage I and II Ovarian Cancer: a 7-year Experience

S. Chiara, S. Mammoliti, C. Oliva, L. Merlini, M. Bruzzone, M.R. Sertoli, G.C. Parodi, N. Ragni, G. Foglia, F. Odicino, G. Parodi, L. Iskra, F. Carnino, E. Guercio, P.F. Conte and R. Rosso

87 patients with high risk of recurrence FIGO stage I and II ovarian carcinoma were treated with adjuvant chemotherapy consisting of cisplatin 50 mg/m^2 plus cyclophosphamide 600 mg/m^2 on day 1 every 28 days for 6 courses. Toxicity and efficacy of the regimen was evaluated after a median follow-up of 45 months. Treatment-related toxicity was mild and reversible, consisting chiefly of acute WHO grade 2 myelosuppression (10% of patients) and controllable grade 3 emesis (55%). No late toxicity was observed. Actuarial 7-year survival and relapse-free survival (RFS) were 76% and 61%, respectively; a statistically significant difference in outcome was observed for undifferentiated grade tumour (G1 vs. G2 vs. G3: $P < 0.01$) but not for FIGO stage disease (stage I vs. stage II). In our opinion, short-term chemotherapy including the most active single agent, i.e. cisplatin, appears a tolerable and effective treatment which deserves further evaluation in large randomised trials.
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INTRODUCTION

IN A REVIEW of literature from 1960 to 1975, the 5-year survival of FIGO stage I and II patients was only 70% and 32%, respectively, in spite of appropriate treatment for localised disease. The explanation of this failure was both related to the lack of accurate assessment of the extent of disease, and the poor understanding of the influence of prognostic factors on outcome of ovarian cancer. Results from staging studies indicated frequent understaging of early ovarian cancer with postsurgical residual disease in 33% and intraabdominal spread of disease in 75% of patients [1, 2]. Likewise, careful analyses about the prognostic importance of histological grade, positive peritoneal cytology and other factors demonstrated that conclusions of earlier clinical trials could be inaccurate because of maldistribution or poor definition of prognostic groups [3].

Thereafter, in the later 1970s it became apparent from natural history of "early" ovarian cancer that any form of adjuvant treatment must encompass the entire abdominal cavity. This finding accounted for the poor results achieved by surgery alone or postoperative pelvic irradiation [4].

Abdominopelvic radiotherapy, intraperitoneal chromic phosphate and alkyl-based chemotherapy have been employed to treat high-risk patients; results from these trials are conflicting [5, 6]. Cisplatin-based chemotherapy has proved to be the most effective treatment for advanced ovarian cancer, resulting in objective response rates up to 60–80% [7]. Therefore, chemotherapeutic regimens including the most active agent, i.e. cisplatin, are the best candidates to be tested in an adjuvant setting. Moreover, chemosensitivity of tumour cells correlates with growth fraction, which is particularly high in microscopic disease and is inversely proportional to tumour burden [8].