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Effect of Anti-Cancer Chemotherapy on the Circulating Levels of Follicle Stimulating Hormone, Luteinizing Hormone and Prolactin in Postoperative Premenopausal Breast Cancer Patients

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Abstract.- The levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) were determined in postoperative premenopausal breast cancer patients. In the patients which received CMF-therapy there was a marked increase in the circulating FSH and LH levels following the initiation of chemotherapy, while in controls the hormone levels remained considerably lower. In contrast, the levels of prolactin decreased appreciably following administration of anticancer drugs to breast cancer patients. A positive correlation was found in these hormonal changes and the regression of tumor size following chemotherapy. The hormone levels in the serum of breast cancer patients can, therefore, serve as clinical tools in monitoring the disease and response to drug treatment.

Key words: Anti-cancer chemotherapy, follicle stimulating hormone, luteinizing hormone, prolactin, breast cancer.

INTRODUCTION

Several previous investigations (Bani *et al.*, 1986; Pearson, 1976; Sheth *et al.*, 1975) have suggested an involvement of hormones with the development of breast cancer. Although there is no direct evidence that hormones themselves can convert a normal cell into a malignant cell, there is reason to believe that a complex interplay of hormonal and other factors result in a proliferation effect (Mittra *et al.*, 1974; Bird *et al.*, 1981). The mammary tissue is a target for a number of hormones including gonadotrophins and sex steroids; therefore it is relevant to determine the relationship of hormonal changes which are associated with the breast carcinoma. There have been conflicting reports regarding the circulating levels of pituitary gonadotrophins (LH and FSH) and prolactin (PRL) in breast cancer patients (Borkowski *et al.*, 1977; Adami *et al.*, 1979; Bird *et al.*, 1981). It has been shown that experimental mammary cancer is dependnet on PRL (Pearson *et al.*, 1969; Boot, 1970; Meites *et al.*, 1972). Hypophysectomy in some cases may lead to remission of metastatic breast cancer in patients whose cancers have shown no response to oophorectomy and adrenalectomy (Sheth *et al.*, 1975). This has been attributed to the reduction in mammatropic action ascribed to several anterior pituitary hormones.

Adjuvant chemotherapy or chemotherapy coupled with endocrine therapy has proved to be an effective tool in controlling the carcinoma of breast. In this report, we have investigated the relationship of chemotherapy and hormonal levels (FSH, LH and PRL) in postoperative premenopausal breast cancer patients so that the progress of disease following drug treatment can be monitored in specific biological terms.

MATERIALS AND METHODS

Patients and methods

One hundred patients aged 26-44 years were selected for this study. All the patients had undergone mastectomy for infiltrating ductal carcinoma. Fifty patients (therapy group) were given CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil) therapy according to a preset regimen of 0, 8, 20 and 28 days of each month for 5 months. Blood sampling was carried out between 9-11 AM overlapping with the drug regimen. The other 50 patients did not receive chemotherapy and served as controls (control group). Other risk factors in breast cancer were also taken into consideration e.g. family history, parity, menstrual history, prior endometrial or ovarian cancer, any hormonal drugs or contraceptive used in past. These patients were examined monthly by blood picture, liver and brain scan for disease progression (micrometastasis) and mammography was also performed.

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Analytical methods

Blood samples were collected according to the drug regimen from both control and therapy group and were allowed to clot. The serum was separated by centrifugation at 2000 g for 30 min at -20°C until used for assays.

The concentration of FSH, LH and PRL in the serum of both therapy and control groups was measured by radioimmunoassay using the Amerlex RIA kits (Amersham, U.K.). Comparisons of hormone levels between therapy and control group and at various time points were made by determining the coefficients of correlation with the corresponding P values and using the T test. The inter and intra assay coefficients of variation were 2.0 ng/ml, 7.6% and 10.5% for PRL, FSH and LH respectively.

RESULTS

The serum concentration of FSH in therapy group (breast cancer patients receiving chemotherapy) showed a steady increase from day 0-28 of the drug regimen (Table I). The mean value on day 0 was 12.3±3.1 mIU/ml which increased significantly to 52.1±9.2 on day 28 with a corresponding P value of <0.01. When the mean values of FSH on 28th day were compared between therapy and control group, they were significantly different (P<0.075).

Table I.- Mean values for circulating follicle stimulating hormone (FSH) in premenopausal breast cancer patients receiving chemotherapy (therapy, group) and patients without chemotherapy (control group).

Sampling regimen (days)	Therapy group* (mIU/ml)	Control group** mIU/ml)
0	12.3±3.1	10.9±1.4
8	31.4±2.1	17.6±3.1
20	36.2±8.6	18.2±5.1
28	52.1±9.2	26.4±2.1

*The values between day 0 and day 28 differed significantly (P = <0.01)

**The values between day 0 and day 28 did not differ significantly (P< =0.05)

Mean values for serum LH in both therapy and control groups are presented in Table II. A marked increase in the LH levels was observed following chemotherapy. The LH values prior to the initation of therapy were 29.2±4.1 mIU/ml which increased to 83.1±11.6 mIU/ml on day 28 of the treatment (P<0.005).

Table II.- Mean values for circulating luteinizing hormone (LH) in premenopausal breast cancer patients receiving chemotherapy (therapy, group) and patients without chemotherapy (control group).

Sampling regimen (days)	Therapy group* (mIU/ml)	Control group** mIU/ml)
0	29.23±4.1	14.6±9.1
8	33.0±6.1	22.3±11.2
20	56.2±4.3	23.5±6.1
28	83.1±11.6	43.8±4.1

*The values between day 0 and day 28 differed significantly (P = <0.005)

**The values between day 0 and day 28 did not differ significantly (P< =0.075)

Mean values for PRL in both the therapy and control groups are presented in Table III. In contrast to serum LH and FSH, the PRL levels decreased considerably in the therapy group, while they remained steady in the corresponding controls. The drop in plasma PRL levels was significant between day 0 (26.4±3.1 ng/ml) and day 28 (3.2±1.2 ng/ml) with P<0.001. Following administration of the anticancer drugs, the tumor size decreased considerably in the therapy group.

Table III.- Mean values for circulating prolactin (PRL) in premenopausal breast cancer patients receiving chemotherapy (therapy, group) and patients without chemotherapy (control group).

Sampling regimen (days)	Therapy group* (mIU/ml)	Control group** mIU/ml)
0	26.4±3.1	13.8±4.1
8	21.2±1.3	10.7±1.6
20	14.3±1.2	6.0±0.96
28	3.2±1.2	7.2±.51

*The values between day 0 and day 28 differed significantly (P = <0.001)

**The values between day 0 and day 28 did not differ significantly

DISCUSSION

Our results indicate an increase in the mean values for FSH and LH following the administration of CMF-therapy to premenopausal breast cancer patients. This rise in plasma FSH and LH concentration can be attributed to an interference of these anticancer drugs with the hypothalmo-hypophysial gonadal axis, possibly through a positive feedback resulting from lowering of estrogen levels (Anjum, unpublished data). These anticancer drugs have been shown to cause ovarian ablation affecting the estradiol and progesterone levels (Jordan and Anjum, unpublished). Although it is not clear, at present, whether this interference of the axis is at the level of the pituitary or the hypothalmus.

In contrast to FSH and LH, the concentration of PRL in circulation decreased significantly following CMF therapy. Previous literature has conflicting reports on the PRL levels in breast cancer patients. Kwa *et al.* (1974) could not find any significant difference in PRL level of breast cancer patients while others have shown that prolactin is higher in normal subjects than in breast cancer patients (Bird *et al.*, 1981; Bhatavdekar *et al.*, 1990). Robyn *et al.* (1973) indicated that there is variation in PRL levels during the menstrual cycle and increased values were recorded during luteal phase rather than the follicular phase. Prolactin in any case has a major role in the growth, development and function of breast cancer in both rodents and humans. Another recent study have shown that prolactin had a linear correlation with histologic grade and an inverse correlation with estrogen receptor and pogesterone receptor levels and survival (Bhatavdekar *et al.*, 1990; Nicoll, 1974; Welsch and Nagasawa, 1977). The anticancer drugs have an ablative effect on the ovaries and subequently reduce the blood estrogen levels. Since the estrogens have a prolactogenic effect, in the case of their lower stimulus, the PRL levels decrease. The drop in the levels of PRL, following drug therapy do however, have a clinical use, in identifying the presence of recurrent disease which is often difficult to evaluate. Our data further suggest that blood levels of FSH, LH and PRL can serve as useful tools in monitoring the response of chemotherapy and the progress of disease.

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