EFFECT OF CHEMOTHERAPY ON CIRCULATING STEROID HORMONE LEVELS IN POSTOPERATIVE PREMENOPAUSAL BREAST CANCER PATIENTS

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ABSTRACT

Serum levels of 17-B oestradiol, testosterone and progesterone were determined in postoperative premenopausal breast cancer patients. In patients receiving chemotherapy circulating 17-fl oestradiol values decreased significantly compared to control group during the sampling/drug regimes employed. Among the control group, however, the oestradiol levels remained high throughout the sampling period. Testosterone levels in patients were also significantly low compatred to control group throughout the sampling regimen upto 28 days. In contrast the levels of progesterone in patients were elevated and remained high compared to the corresponding controls. A positive correlation was found between the drop in serum oestradiol and testosterone levels following the initiation of chemotherapy and the regression of the tumour size. Steroid hormone levels in the serum of breast cancer patients receiving chemotherapy can serve as clinical tools to monitor the progress of the disease and response to therapy. (JPMA 41: 296, 1991).

INTRODUCTION

Carcinoma of breast is a commonly occurring malignant disease among women with sex hormones implicated in its etiology and, development[1]. Steroid hormones like estrogen and androgen are involved in all types of breast cancer at various stages[2]. Although hormones cannot initiate the malignant response in normal cells, but they might play a proliferative role in breast cancer. Surgical ablation (Ovariectomy) causes regression of breast tumours[3]. Stoll reported that hormone-sensitive tumours later may become hormone-independent and exhibit continuous independent growth, irrespective of hormonal changes in the serum. These hormonal changes can be induced via endocrine or chemotherapy and result in the regression of breast tumour. These therapies may manifest their effects in a number of possible ways which include, (i) direct inhibition of tumour growth, (ii) suppression of pituitary hormone secretion, (iii) anti-oestrogenic effects of the peripheral as well as the target organ conversion of androgens to oestrogens[4]. It is, therefore, of interest to determine the endocrine status (especially the steroid hormones) of breast cancer patients in response to chemotherapy to monitor the progression or regression of the disease. Classically, measurements of urinary metabolites of ovarian hormones were used in such studies[5] but have been proved unsatisfactory. Sensitive radioimmunoassay methods to determine the circulating levels of steroid hormones in postoperative premenopausal breast cancer patients receiving chemotherapy have been used in this study to monitor the effectiveness of the drugs.

PATIENTS AND METHODS

Fifty premenopausal patients aged 26-44 years were selected for the study. All patients were suffering

from unilateral infiltrating ductal carcinoma of breast and were in stage II and III. Twenty five patients were given CMF (cyclophosphamide, methotrexate and 5-fluorouracil) therapy (patients group) and other 25 patients did not receive chemotherapy (control group). Other risk factors, e.g., family history, parity, menstrual history, prior endometrial or ovarian cancer, any hormonal drugs or contraceptives used in past were also recorded. Patients were examined monthly and blood picture, liver, brain scan and mammography were performed for disease progression (micrometastases). Serum levels of 17-B oestradiol, testosterone and progesterone were measured 4 times a month i.e., according to chemotherapeutic drug regimen 0,8,20 and 28th day of each month for five months. The sampling regimen overlapped with drug regimen. Blood samples were collected at corresponding intervals from both the patients and the control group according to the drug regimen for hormonal determination. Hormonal determination was performed on peripheral blood samples drawn between 9AM to 11AM. Blood was allowed to clot at 4°C, serum was separated by centrifugation and stored at -20°C until assayed. Serum oestradiol, testosterone and progesterone concentrations were determined using Coat-A-count solid phase radioimmunoassay kits (Diagnostic Products Corporation, USA). The sensitivity of the assays were 8 pg/mi for oestradiol, 0.4 ng/ml for progesterone and 0.4 nmol/ml for testosterone. The inter and intra assay coefficients of variation were 10.5 and 9.3% for oestradiol, 7.3 and 9.5% for testosterone and 6.9 and 11% for progesterone respectively. Comparisons of hormone levels between patients and control groups were performed by Duncan's multiple ranged test. Three way Anova was used to determine P values used for all statistical analysis.

RESULTS

The mean oestradiol levels did not differ but mean testosterone levels were significantly ($P < 0.05$) lower in patients than controls on day 0. There was a sharp decline in the mean oestradiol ($P < 0.01$) and testosterone ($P < 0.001$) levels after 8, 20 and 28 days of initiation of chemotherapy. Inspite of some variations, levels of these hormones were higher in corresponding controls on various days of sampling regimen (Tables 1 and II).

TABLE I. Mean values of circulating 17-β oestradiol in patients and controls.

Sampling reginen (days)	Patients (pg/ml) Mean ± SEM	Control (pg/ml) Mean ± SEM
0*	156.2 ± 10.98	164.84 ± 10.31
8	58.68 ± 10.16	192.1 ± 12.9
20	6.58 ± 1.15	210.59 ± 0.23
28	0.145 ± 0.005	141.68 ± 0.41

*Day 0 is the sample taken from both the groups prior to the initiation of chemotherapy to the patients group.

TABLE II. Mean testosterone values in patients and controls.

Sampling regimen (days)	Patients (nmol/L) Mean ± SEM	Control (nmol/L) Mean ± SEM
0*	2.5 ± 0.5	3.84 ± 0.21
8	1.12 ± 0.2	2.23 ± 0.41
20	1.15 ± 0.5	1.40 ± 0.21
28	0.96 ± 0.01	2.68 ± 0.11

*Day 0 is the sample from both the groups prior to the initiation of chemotherapy to the patients group.

Mean progesterone values in patients and control at 0 day differed significantly. The progesterone values increased markedly in the patients after 20 and 28 days of the initiation of chemotherapy, while in controls there was fluctuation, but with a downward trend compared to day0 (Table III).

TABLE III. Mean values for circulating progesterone in patients and controls.

Sampling regimen (days)	Patients (ng/ml) Mean ± SEM	Control (ng/ml) Mean ± SEM
0*	3.36±0.12	6.68 ± 3.21
8	3.1±1.10	6.92 ± 3.95
20	4.95 ±0.02	3.15 ± 3.32
28	8.80 ±1.08	4.89 ± 0.21

*Day 0 is the sample taken from both the groups prior to the initiation of chemotherapy to the patients group.

A comparison was made for the P-values calculated for various intervals in case of all the three hormones studied (Table IV).

TABLE IV. Comparison of P values between patient and control group.

Groups*	Estradiol	Progesterone	Testosterone
Between 0 and 8 day of patients group	<0.001	<0.05	<0.01
Between 0 and 20 days of patients group	<0.01	N.S.	N.S.
Between 0 and 28 days of patients group	< 0.01	N.S.	<0.001
Between 0 day of patients and control groups	<0.05	<0.01	<0.05
Between 8 days of patients and control groups	<0.001	<0.01	<0.05
Between 20 days of patients and control groups	<0.001	N.S.	<0.01

*The comparisons were made between the values obtained at various time intervals during the drug administration regimen.

These values were significantly different for oestradiol at all the intervals of the sampling regimen in patients and corresponding controls. In case of testosterone among the patients group itself the decrease in circulating levels was significant compared to day 0. For progesterone significant differences were observed between day 0 and day 8 of the patients and between 0 and 8 day samples of patients and controls respectively.

DISCUSSION

The results presented in this report showed significantly high levels of 17-B oestradiol in the breast cancer patients compared to normal values. During the sampling regimen employed, the oestradiol values did not differ significantly in the control group. However, in patients there was a marked decline in the cit culating levels of oestradiol (Table I), after 8, 20 and 28 days of treatment. This was accompanied with regression in tumour size and spread of micrometastasis as monitored by liver and brain scanning. Taken together the decline in oestradiol concentration in blood and regression in disease showed a positive correlation between the drugs administered and the etiology of the disease. Various epidemiological studies suggest an endocrine role in breast cancer[6]. It has also been reported that some breast tumours need specific favourable hormonal environment for their active metabolism[4]. This favourable environment can be changed by surgical ablation or radio/chemotherapy. The drugs used for chemotherapy in the present study exhibited the ablation effect possibly by suppression of the ovarian function (lowering of plasma oestradiol 17-fl levels). These observations also highlight the significance of monitoring circulating oestradiol levels after chemotherapy as a clinical tool in determining the regression of the tumour and management of the disease. The decrease in testosterone mean values in patients receiving drug therapy may be explained by the fact that testosterone is an intermediate in the biosynthesis of estrogen. The overall suppression of gonadal function as a result of chemotherapy possibly resulted in reduction in the levels of this steroid in the patients group. However, there can be a possible clinical use for testosterone levels in monitoring the progress of chemotherapy

in controlling the tumour[5,7]. Progesterone levels in patients group increased following chemotherapy. This increase was not mediated through hypothalmo- hypophysial-gonadal axis, since the plasma levels of gonadotrophins (FSH and LH) remained high during chemotherapy[5]. However a local effect of the drugs on the ovaries appear to be the most likely cause of increased level of progesterone in the patients group. Hormone sensitive tumours are either estrogen or progesterone dependent[7]. In estrogen dependent tumours the growth is favoured by a high estrogen/progesterone ratio. The chemotherapy employed in the present study possibly had ablation effect on tumour by reducing the estrogen and increasing progesterone thus altering the ratio of these steroids required for growth/maintenance of the tumour.

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