Original Research Article

Prolactin: An Emerging Prognostic Marker in Breast Cancer

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ABSTRACT

Introduction: The outcome for women with breast cancer varies widely, so it becomes increasingly important that the clinician is provided with accurate prognostic information on which to base the therapeutic decision. Some bio-chemical prognostic markers like hormones & tumor markers are use for prognostic purposes, yet need to be established as independent prognostic marker. Prolactin, a peptide hormone, has a role in carcinogenic process of the breast. Some studies have shown that there was a significant correlation between the serum concentration of prolactin before treatment and time and size of metastasis.
Aim: We undertake this study to find out levels of serum prolactin in breast cancer patients and to compare their levels in early and in locally advanced breast cancer.
Materials and Methods: The prospective study of 50 patients of proven breast cancer patients was included in this study whose TNM stage and a baseline serum levels was detected.
Results: This study found that 32% cases had raised level of Prolactin out of which 81.8% were in locally advanced stage. Baseline Prolactin levels was more raised in locally advanced breast cancer than in early breast cancer cases (39.39%, than the early one 17.65%). The Odds of finding late stages in patients with Prolactin $>=19$ ng/ml was 3.0 times higher as compared to those with lower prolactin levels.
Conclusion: Results point towards hypothesis that pre-operative prolactin levels can be used to predict tumor burden as levels could be related to poor outcome with possibility of micro-metastases thereby predicting type of surgery or adjuvant or neo-adjuvant therapy required.

Keywords: breast cancer, prolactin, early breast cancer, locally advanced breast cancer,

INTRODUCTION

Breast cancer is the commonest malignancy in female worldwide. [1] As the range of options for the treatment of patients of breast cancer widens, so it becomes increasingly important that the clinician is provided with accurate prognostic information on which to base the therapeutic decision. [2]

The breast (mammary tissue) is a modified apocrine gland. Some women experience changes to their breast tissue over their lifetime like an increase in the number of breast cells (hyperplasia) or the emergence of atypical breast cells (atypical hyperplasia). In some instances, a portion of breast tissue that exhibits abnormal characteristics can eventually develop into a cancerous tumor. [3]

Prolactin, a peptide hormone secreted by anterior pituitary, has a role in carcinogenic process of the breast, possibly due to its stimulatory effect on the breast tissue. The new evidence is that prolactin seems to be the stimulator of the movement or motility of breast cancer cells, & it can

actually trigger the invasive potential of these cells. [4] In a subset of women at risk for Familial breast cancer, basal serum prolactin levels were found to be significantly elevated, [5] and even hyperprolactinemia is seen in daughters of breast cancer patient. [6]

The role of prolactin in breast cancer has been elucidated by several epidemiological studies. For example, higher than average serum prolactin levels have been reported in premenopausal women with breast cancer, [7] and a positive correlation exists between circulating prolactin levels and the risk of breast cancer. [8,9]

The aim of our study was to evaluate the serum level of hormone prolactin in breast cancer patients and to compare the level in early breast and in locally advanced breast cancer patients, in order to investigate if its level provide with accurate prognostic information on which to base the therapeutic decision can be made for individual breast cancer patient.

MATERIALS AND METHODS

In this prospective study baseline serum level of prolactin was determined for a total of 50 breast cancer patients (diagnosis confirmed by biopsy or FNA) during a period of 18 months (september 2010 to march 2012)). With the assessment of pTNM staging, participants are grouped into Early & Locally Advanced Breast cancer (according to American Joint Committee for Cancer Staging and End Results Reporting). [10] Early breast cancer is the one that remain contained in breast tissue only and is not spread to lymph nodes: TNM Stage I, IIa. Locally advanced breast cancer (LABC) is characterized by presence of a large primary tumor (>5 cm), associated with or without skin or chest-wall involvement or with fixed axillary lymph nodes in the absence of any evidence of distant metastases: TNM Stage IIb, IIIa, IIIb, IIIc.

The quantitative determination of the prolactin in serum was determined by sandwich ELISA assay kits using commercial kit (CALBIOTECH Inc), with cut off level was taken as for Pre-menopausal women as 1.2 - 19.5 ng/ml and for Post-menopausal women as 1.5 - 18.5 ng/ml.

Statistical Analysis

The results obtained were interpreted and correlated statistically. Mean and standard deviations were calculated. Association between various variables was calculated by using ANOVA; and by categorizing these into dichotomous variable and using chi-square test (any value was significant with a p-value '<' or '=' 0.05).

All calculations are done using window Excel and SSPS software.

RESULTS

Of total 50 patients, the maximum number of participants was in the age group 40-59yrs, constituting 62% of total participants. Nearly 2/3rd of the participants were post-menstrual: the ratio between the pre-menstrual and post-menstrual females was 1: 2.

Table1 illustrate the distribution of cases according to the pTNM staging, the maximum number of cases 16 (32%) were of stage T2N0M0 (early), while next maximum 13(26%) are of T3N0M0 stage (locally advanced). Overall, two thirds of the participants (66%) were in the late stage.

Table2 shows association between menstrual status and early and late stages of breast cancer. Among the patients with post-menopausal 72.72% were found to be having late stage as compared with 52.94% in those with premenopausal.

The Odds of finding late stages in patients with post-menopausal was 2.3 times higher as compared to those with pre-menopausal.

This study found that out of overall 50 cases, 32% cases had raised level of Prolactin.

Levels of prolactin were more raised in locally advanced breast cancer (39.39%), than the early one (5.88%). Prolactin was

also found to be more raised in postmenopausal cases than the premenopausal cases.

The mean Prolactin level in patients with early breast cancer was 14.44 ng/ml, while it was 18.79 ng/ml in the locally advanced cases. However, the difference was not statistically significant (P value >0.05).

Table 3 shows association between prolactin dichotomized with cut of value of < 19 ng/ml and >= 19 ng/ml and early and late stages of breast cancer. Among the patients with >=19 ng/ml, 81.25% were found to be having late stage as compared with 58.82% in those with Prolactin <19 ng/ml. The Odds of finding late stages in patients with Prolactin >=19 ng/ml was 3.0 times higher as compared to those with lower prolactin levels.

Serum prolactin levels when correlated with axillary lymph node invasion, it was found that out of 19 patients with lymph node invasion only 9 patients had elevated serum prolactin levels, in which 47.3% were locally advanced. However, it was statistically insignificant with p-value>0.050.

TABLE 1: pTNM STAGE:

pTNM stage	Count	EA/LABC
T1N0M0	1	E
T2N0M0	16	E
T2N1M0	7	LA
T2N2M0	3	LA
T2N3M0	1	LA
T3N0M0	13	LA
T3N1M0	6	LA
T3N2M0	2	LA
T3N3aM0	1	LA
Grand Total	**50**	

TABLE 2: Association between Menstrual Status and Early/ LABC Presentation

MENSTRUAL STATUS	LABC	Early	Total
Post-Menstrual	24	9	33
	72.73	27.27	
Pre- Menstrual	9	8	17
	52.94	47.06	
Total	33	17	50

TABLE 3: Association between Prolactin and Early/ LABC Presentation

PROLACTIN	LABC	Early	Total
HIGH	13	3	16
	81.25	18.75	
NORMAL	20	14	34
	58.82	41.18	
Total	33	17	50

DISCUSSION

Prognostic markers help to stratify cancer patients for treatment by identifying patients with different risks of outcome (e.g. recurrence of disease), and may be used as decision aids in determining whether a patient should receive adjuvant chemotherapy or how aggressive that therapy should be. [11] Axillary lymph node status has been the most important prognostic factor for primary breast cancer; tumor size, histologic grade, and hormone receptors status are also traditional prognostic factors. [2,3,12]

Breast being a dynamic tissue, is influenced by many hormones and changes in the breast are most dynamic and profound in the reproductive years. [12] Prolactin, hormone of anterior pituitary which promote breast development during pregnancy and lactation, can promote cell proliferation, alter cell motility, and increase tumor vascularization. Both in vitro and animal studies have suggested that prolactin can influence breast carcinogenesis. [13,14]

The mitogenic and anti-apoptotic properties of local prolactin were demonstrated by a faster growth of tumors derived from prolactin-overexpressing breast cancer cells in nude mice[14], which was further supported by the development of intraepithelial neoplasia in transgenic mice with targeted prolactin over-expression in the mammary epithelium. [15]

Human breast tumors are found to express higher levels of the prolactin receptors (PRLR) than adjacent healthy tissue, [16-18] even in an aggressive form of carcinomas. [19]

Our study found that elevated prolactin levels were found in 32% of participants, out of which 81.8% were in locally advanced stage conceding with findings of other authors like Zlata and Hamza et al who founds that the baseline serum level of Prolactin is higher in breast cancer patients, [20] suggestive that high prolactin levels can indicate late stage of the primary breast cancer.

Of participants with normal serum level of Prolactin, 58.82% were in advanced group and 41.18% were in early group, showing that the normal level does not predict the stage of the disease.

Of total 33 participants in locally advanced breast cancer stage, 13 (39.4%) participants were associated with elevated Prolactin levels.

The odds ratio for Prolactin was found to be 3.03, showing that finding an advanced stage in a patient with high serum prolactin level is 3 times higher as compared to the one with lower serum Prolactin level.

This result is comparable to that found by Bhatavdekar et al who showed excellent correlation between serial plasma prolactin changes and the progression of disease in patients with advanced breast carcinoma. They found that increased prolactin levels serve as an independent predictor of short term (2yrs) prognosis in patients with advanced breast cancer. [21]

Despite the statistically insignificant association of Prolactin (p value=0.079), with early and locally advanced breast cancer stage, the study observed the superior sensitivity of Prolactin in both for primary diagnosis and in patients with advanced disease.

As the measurement of the tumor markers is an easy, simple, reproducible, quantitative and cost-effective, serum level of prolactin can serve as a tumor marker which could provide prognostic information to be taken together with conventional markers measured in breast cancer patient, to predict the prognosis and thereby plan of management needed for the individual patient.

However, because of lack of significant sample size, nothing could be conclusively said but results point towards hypothesis that serum levels of prolactin can be used as a prognostic marker and can help the clinician to predict stage of breast cancer thereby help in the individual management plan (type of surgery or adjuvant or neo-adjuvant therapy required).

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