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Original Research Article

The study of prognostic significance of CA 15-3 in breast cancer

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ABSTRACT

Background: Cancer Antigen 15-3 (CA 15-3) is a tumour-associated antigen used as serum marker for breast cancer surveillance in patients and for monitoring the response to treatment. Aim of this study was to prospectively evaluate CA 15-3 as a prognostic factor in early detection of breast cancer relapse, recurrence and early detection of distant metastasis as well as to analyse the statistical correlation between CA 15-3 levels and clinical-pathological parameters including tumour size, lymph node, histological type, grading, hormonal receptors.
Methods: Sera of 85 women with breast carcinoma obtained pre-treatment, post-treatment and follow-up at 6 months were assayed for CA 15-3 by solid phase enzyme-linked immunosorbent assay (ELISA).
Results: Author founds that the mean serum CA 15-3 levels in patients before treatment were significantly higher (50.59U/ml) compared with those of CA 15-3 after treatment (24.07U/ml) and follow-up at 6 months (21.07U/ml). Author also found that elevated pre-treatment serum levels of CA 15-3 were significantly correlated with poor prognosis of patients. In particular, among 16/85 patients (18.8%) that displayed over cut-off (>24.95U/ml) pre-treatment levels of CA 15-3, 2 patients (2.35%) developed recurrence,2 patients (2.35%) developed residual tumour, 2 patients (2.35%) developed advanced disease (metastases to distant sites) and 10 (11.76%) patients expired during and after study. Chi-square correlation analysis revealed that the presences of increased serum levels of CA 15-3 after treatment are significant risk factors for poor prognosis in patients.
Conclusions: Elevated pre-treatment concentrations of CA 15-3 may be a useful prognostic factor for cancer progression in patients.

Keywords: Breast cancer, CA 15-3, Follow-up, Metastasis, Prognostic marker

INTRODUCTION

Breast cancer is a leading cause of cancer related morbidity and mortality among females worldwide. Breast cancer itself accounts for 25% of all cancer cases and 15% of all cancer deaths among females worldwide.[1] CA 15-3 is a mucinous carbohydrate antigen product of the MUC1 gene, the mucin protein product encoded by the MUC1 gene contains approximately 50% carbohydrate by weight with a relative molecular mass of 400 kDa.[2] This cell surface mucin trans membrane glycoprotein, is expressed at the apical surface of most epithelia (e.g. mammary gland, female reproductive tract, stomach, etc.) in normal tissue. It is comprised of three structural do-mains: a large and heavily glycosylated extracellular segment (exo-domain), a hydrophobic type 1 trans membrane region, and a short cytoplasmic tail domain involved in several signaling processes.[3] But in cancerous tissue, this MUC-1 biomarker expression can be detected on the entire cell membrane due to transformation and loss of polarity.[4,5] After transport to the cell membrane, it undergoes proteolytic cleavage in which the soluble form of the large ectodomain is released into circulation.[6] The tumour marker antigen CA 15-3, which corresponds to an immuno-dominant epitope

in the extracellular portion of the membrane bound mucin MUC1, is shed into the bloodstream. An increase in the serum CA 15-3 shed ectodomain is associated with progression of carcinoma in patients.

The high level of CA 15-3 associated with larger burden of occult disease. There are many studies showing worse prognosis in patients with high concentration of CA 15-3.[7,8] The CA 15-3 is independent predictor of recurrence and advanced breast cancer.[9] During follow-up of patients, this CA15-3 marker used in surveillance of patient with diagnosed breast cancer and monitoring of treatment.[10] It remains raised in 100% case of patient with progressive disease, decrease of value in 81% of patient to response to full treatment modality.

Aim and objectives

- Clinico-pathological study of the patients with breast cancer
- Evaluation of CA15-3 as a prognostic marker in terms of response to treatment
- Evaluation of CA15-3 in patients with residual tumour, recurrence and distant metastasis

METHODS

Patients

Author included 85 consecutive patients with breast carcinoma and analysed serum samples obtained from patients who underwent full treatment modality (neo-adjuvant chemotherapy, modified radical mastectomy or conservative surgery [quadrantectomy + axillary dissection], adjuvant chemotherapy, radiotherapy) according to patients profile at Department of Surgery, Department of Pathology and Radiotherapy, JN Medical College and Hospital, AMU, Aligarh, UP, India from February 2014 to November 2015. All breast cancer patients were staged according to AJCC staging system (7th Edition) classification: Information concerning age, diagnosis, type of surgery, therapy administered, and clinical pathology such as tumour size (T), lymph node status (N), grade and hormonal status, for each patient were collected through clinical charts (Table 1). Treatments administered to breast cancer patients are summarized in Table 2.

Serum CA 15-3 concentration was determined by Enzyme Immunoassay Kit based on the principle of a solid phase enzyme-linked immunosorbent assay (ELISA), purchased from Calbiotech, Inc, USA, CA 94404.

The lower limit of sensitivity was 1.2 U/ml and the established cut-off was 24.95U/ml determined by 95 percentile of 25 benign breast disease and mastitis patients and upper normal limit of CA 15-3 was calculated (24.95U/ml).

Table 1: Main clinical-pathological characteristics of 85 breast cancer patients selected from 127 cases.

Characteristic	N	%
Total patients	85	
Mean age= 46.28 (range 24-75 years)		
Surgery	85	
Modified radical mastectomy	83	97.65
Conservative surgery (quadranctectomy±axillary dissection)	2	2.35
Neo-adjuvant chemotherapy	71	83.5
Adjuvant chemotherapy	83	97.65
Radiotherapy	1	1.2
Histological diagnosis	85	
Infiltrating ductal carcinoma(IFDC)	81	95.3
Infiltrating lobular carcinoma(IFLC)	4	4.7
Hormone receptor status (luminal type)	85	
Luminal A	33	38.8
Luminal B	9	10.6
Nonlum her-2neu type	14	16.5
Triple negative	29	34.1
Grade	85	
I	8	9.4
II	56	65.9
III	21	24.7
Tumour size(cm)	85	
<2	23	27.1
2-5	47	55.3
>5	15	17.6
Clinical lymph node status(n)	85	
N0	29	34.1
N1	41	48.2
N2	13	15.3
N3	2	2.4
Pathological lymph node status(pN)	85	
0-3	50	58.8
4-9	19	22.4
>9	16	18.8
Pre-treatment serum ca15-3 level	85	
>24.95U/ml	74	87.05
<24.95U/ml	11	12.95
Post-treatment (after 7 days of full treatment modality) serum ca15-3 level	85	
>24.95U/ml	21	24.7
<24.95U/ml	64	75.3
Follow-up at 6 months serum ca15-3 level	80	
>24.95U/ml	11	13
<24.95U/ml	69	87
Outcome after full treatment modality		
Ca 15-3 >24.95U/ml	21	
Death	10	47.7
Recurrence	2	9.5
Residual tumour	2	9.5
Distant metastasis	2	9.5
Ca 15-3 <24.95U/ml	64	
Recurrence	0	
Residual tumour	0	
Distant metastasis	0	

Table 2: Treatments administered to 85 breast cancer patients.

Treatment	N	%
Surgery	3	3.5
Surgery + adjuvant chemotherapy	11	12.9
Neo-adjuvant chemotherapy + surgery + adjuvant chemotherapy	70	82.4
Neo-adjuvant chemotherapy + surgery + adjuvant chemotherapy + radiotherapy	1	1.2

Statistical analysis

The relation between qualitative variables was assessed by chi square test; t-test was used to compare percentage of paired data. The quantitative variables were summarized as mean and 95% Confidence Interval (CI).

RESULTS

This analysis focused on 85 patients with breast carcinoma. The mean age was 46.28 years (range 24-75 years) and 81/85 patients (95.3%) were diagnosed histologically as ductal infiltrating carcinoma. Tumour size was classified as T1 (Tumour size less than or equal to 2cm) in 23/85 (27.1%), T2 (Tumour size between 2 and 5cm) in 26/85 (30.6%) and T3 (Tumour more than 5cm) in 4/85 (4.7%), T4 (Tumour extends to chest wall) in 32/85 (37.6%) of cases of cases according to the TNM classification. The percentage of patients with negative lymph nodes was 34.1% (29/85) whereas the percentage of patients with positive nodes was 65.9% (56/85). The follow-up time was 21 months). The progression of disease was observed in 16/21 patients (76.2%) after full modality of treatment among these 10/21 deaths (47.6%) were reported. Main characteristics of 85 patients included in the present study are shown in Table 1.

CA 15-3 serum levels were evaluated pre-treatment, Post-treatment (at 7 days after full treatment modality) and at 6 months follow-up in each patients. Mean serum value of CA 15-3 prior to treatment was significantly higher 50.6 U/ml as compared to mean value of CA 15-3 after 7 days of Full treatment modality 24.07 U/ml. 74/85 of patients (%) had higher serum levels of CA 15-3 before treatment (consisting in surgery, radio- or chemo- therapy) whereas only 21/85 of cases (%) displayed values over cut-off after full treatment. Author found that decreased serum levels of CA 15-3 in these patients were statistically significant (Test t-test. $p < 0.0001$).

In addition, author also found a significant direct correlation between CA 15-3 serum levels before treatment and follow-up at 6 months ($p < 0.0001$). Statistically significant difference in prognosis (outcome) was found in correlation chi square analysis by following factors: 1) tumour size 2) histological types.

No statistically significant difference in prognosis (outcome) was found in correlation chi square analysis by following factors: 1) lymph node 2) grade 3) hormonal receptor.

DISCUSSION

The problem of breast cancer has always existed and increasing in most countries. Breast cancer mortality can only be reduced by detecting the tumour at the earlier stage. Serum marker in breast cancer are helpful for clinicians in providing more effective management of the disease. Main use of CA 15-3 is to monitor the breast cancer patient response to treatment and for early breast cancer recurrence or metastasis. In this study 85 cases of breast cancer, change in the value of serum CA15-3 after full modality of treatment and follow-up were assessed and its relate to outcome of patient (prognostic significance). CA15-3 levels were also compared with tumour size, histological type, grade and Luminal type and its role in prognostic significance. 25 patients with benign breast disease and mastitis included in control group. Upper normal value was calculated 24.95U/ml by 95 percentiles.

The main use of CA 15-3 is to monitor the breast cancer patient response to treatment and for early breast cancer recurrence, residual tumour or distant metastasis. CA 15-3 can be used as a marker only if cancer is producing elevate amounts of it. However, it may be useful as a prognostic marker even in a small percentage of patients with localized breast cancer showing increased levels of CA 15-3. If CA 15-3 is initially elevated may be used to monitor treatment and when repeated on a regular basis, to detect early recurrence and residual tumour; CA 15-3 is not useful when breast cancer is detected early by other examinations. In general, higher levels of CA 15-3 are correlated with a larger tumour burden and a more advanced disease. The serum levels of CA 15-3 increase as cancer develops.

An initial elevation of CA 15-3 that does not return to the normal range, is an indicator of lack of response to treatment and represents an adverse prognostic factor. Present study shows a significant correlation between CA 15-3 and the response to treatment. In fact, author demonstrated a continuous increase of the marker in patients with metastatic disease that had subsequently developed relapse, recurrence, distant metastasis and even death by analyzing CA 15-3 serum concentrations in breast cancer patients during follow-up. Similar observations were reported by different authors.

For example, FG Ebeling et al showed that following successful treatment serum CA 15-3 value fell significantly below pre-treatment level($p=0.000$).[2] Su-jiezhang et al, showed elevated serum marker CA15-3, CEA, VGEF, CA125 in recurrence group during follow-up of patients.[11]

In line with the findings, Hiba Qassem Ali and co-workers showed that high preoperative levels of CA 15-3 can predict adverse outcome in patients with larger tumour size of breast cancer. In particular, present study showed that patients presenting CA15-3 levels over 24.95U/ml (cut-off) have poor prognostic significance with concentrations <24.95U/ml in larger tumour size of breast cancer patients. The aim of this prospective study was to determine the applicability of serum CA 15-3 assay in the detection of prognostic significance in term of outcome (residual tumour, recurrence, distant metastasis and death) after full treatment modality and during the follow up.

present results demonstrated that CA 15-3 levels are frequently higher before treatment than after treatment of primary tumour. In addition, author found that higher levels of CA 15-3 in patients prior to treatment are more frequently associated with disease progression and worse prognostic significance (outcome) compared to patients with lower levels of CA 15-3. The most likely explanation can be that patients with elevated levels of CA 15-3 may harbor micro metastatic disease undetectable with the standard diagnostic procedures. Using chi-square test and t-test analysis, author show that the only independent variables are increased levels of CA 15-3 and poor prognostic significance. Finally, pesent study demonstrated the important role of this marker in monitoring the efficacy of post-treatment therapies (i.e. Surgery, chemo or radiotherapy).

CONCLUSION

In conclusion, the present study suggests serum CA 15-3 as an independent prognostic factor as well as having additive effect with other poor prognostic factors.

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