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Prospective Study

Significance of Serum Carcinoembryonic antigen in metastatic breast cancer Patients - A prospective study

Role of serum Carcinoembryonic antigen in metastatic breast cancer

TM Anoop, Rona Joseph P, Saikumar S, Steffi Chacko, Mintu Mathew

Abstract

BACKGROUND

Carcinoembryonic antigen (CEA) is an important serum tumour marker with a substantial role in diagnosis and monitoring of various solid tumours. About 36%- 70% of breast cancers have elevated serum CEA. and the available studies show discrepancy in addressing the prognostic significance of CEA in advanced breast cancer.

AIM

This study to estimate the serum CEA level in our metastatic breast cancer patients and correlate it with response to treatment and clinical outcome.

METHODS

This was a prospective clinical study conducted on 50 metastatic breast cancer patients treated at Breast Clinic, with newly diagnosed metastatic breast cancer planned for palliative chemotherapy, targeted and hormonal treatment were included. We estimated the proportion of patients with elevated serum CEA level in metastatic breast cancer at baseline and after palliative treatment and also studied the association of serum CEA levels with known prognostic factors. The response to treatment were correlated with the serum CEA levels in the context of Responders and non-responders.

RESULTS

The Median pre- treatment CEA level was 7.9(1.8-40.7). Median Post- treatment CEA was 4.39(1.4-12.15); p-value (0.032) in whole study population. No statistically significant difference among responders and non-responders on their base line Serum CEA was seen. Even in luminal group pre-treatment Serum CEA was not a predictor of response, but post treatment CEA was significant predictor of tumour progression.

In patients with liver and lung metastases post treatment CEA level difference was not statistically significant in both responders and non-responders even though values were high in non-responders. Among those with bone metastases 69.5% had elevated post

treatment serum CEA and only 37.5% had elevated serum CEA in those with no bone metastases

CONCLUSION

Elevated post-treatment S.CEA levels were associated with disease progression and poor response to therapy. Persistently elevated post treatment Serum CEA levels were significantly associated with bone metastases. Elevated serum CEA and hormonal status were significant predictors of treatment response.

Key Words: Carcinoembryonic antigen; Metastatic breast cancer; Serum tumour marker; Luminal and non-luminal metastatic breast cancer; Palliative chemotherapy

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Core Tip: In breast cancer patients elevated serum CEA levels are particularly noted in advanced disease. Our study suggest that serum CEA have potential clinical value in monitoring the treatment response of metastatic breast cancer patients, especially in patients with bone metastasis.

INTRODUCTION

Breast cancer, one of the leading causes of malignancy related morbidity and mortality among women, comprises of a spectrum of clinically and histologically heterogeneous group of diseases with distinct molecular portraits.[1] In spite of increasing awareness, advanced screening and diagnostic methodologies we still witness a significant proportion of patients who present with advanced stage of disease. Deciding optimal treatment and monitoring strategies for patients with metastatic and recurrent disease remains a diagnostic challenge for physicians.

Carcinoembryonic antigen (CEA) is an important serum tumour marker with a substantial role in diagnosis and monitoring of colorectal cancers. Globally Cancer antigen 15-3 (CA15-3) and CEA are used serum tumor markers in breast cancer. [2,3,4] In breast cancer patients elevated serum CEA levels are particularly noted in metastatic and recurrent disease. Studies have reported a varying incidence of serum CEA positivity ranging from 36%- 70%.[5] Elevated levels are known to positively correlate with tumour burden, grade of tumour, site of metastasis and they also translate into poor OS and PFS.[6] The clinical utility of serial tumour marker measurements is not indicated in asymptomatic women for surveillance after treatment of breast cancer. [7,8,9]The main applications are used in metastatic disease monitoring during treatment especially CA 15-3. Among serum tumour markers in breast cancer, CA 15–3 and CEA have been the commonly used tumour markers.[10,11.12,13] Hence serum CEA estimation can be proposed as an auxiliary tool for response assessment, monitoring and gaining prognostic information. In Spite all of all, due to discordant results their clinical utility still remains unclear.[14 15 16] There are very few studies addressing the prognostic significance of CEA and the available studies show discrepancy. Hence, we conducted this study to estimate the serum CEA level in our metastatic breast cancer patients and correlate it with response to treatment and clinical outcome.

MATERIALS AND METHODS

This was a prospective experimental study conducted on 50 metastatic breast cancer patients treated at Breast Clinic, Department of Medical Oncology during the period December 2019 to November 2020. Patients with newly diagnosed metastatic breast cancer planned for palliative chemotherapy, targeted and hormonal treatment were included. Routine protocol for metastatic breast cancer work-up included biopsy from breast lump or metastatic lesion, histopathology and immunohistochemistry for oestrogen, progesterone and her 2 receptors, computer tomography of chest abdomen pelvis, bone scan and serum biochemistry. Patients with inflammatory breast cancers and active inflammatory conditions were excluded in this study due to the fact that it

could cause elevation of serum CEA levels. A 5 mL of venous blood was drawn from metastatic breast cancer patients consented for study participation and serum was isolated after centrifugation at 3000 run per minute for 10 minutes and transported into new disposable tubes and stored at -20^{o}c. In patients with hormone positive MBC with visceral crisis and TNBC patients, sample for serum CEA levels was collected before initiation of first cycle of palliative chemotherapy and after completion of six cycles of chemotherapy. In patients with hormone positive MBC without visceral crisis, serum CEA sample collected before initiation of endocrine agents and at 6 mo after initiation. In patients with Her 2 positive MBC, blood sample was collected before initiation of first cycle of palliative chemotherapy plus trastuzumab and after completion of six cycles of chemotherapy plus trastuzumab.

Concentrations of the serum tumour marker CEA was measured by an automated sandwich ELISA test system using the manufacturer's recommended kits, ELISA 2010 from Roche Company. CEA concentrations were recorded in nanogram per millilitre. CEA value more than 3.8 ng/mL was considered positive. Patient treatment and response evaluation were as per the institutional protocol. Treatment and follow up details of the patient were noted from the medical case records. We estimated the proportion of patients with elevated serum CEA level in metastatic breast cancer and also studied the association of serum CEA levels with known prognostic factors. The radiological response was assessed using Response Evaluation Criteria in Solid tumours (RECIST1.1). The response to treatment were correlated with the serum CEA levels in the context of Responders and non-responders.

Statistical analysis

Statistical calculations were performed using the SPSS for Windows, version 15.0. (SPSS, Inc., Chicago, USA), software packages. The categorical variables were expressed using frequencies and percentages. The continuous variables were presented in terms of mean and standard deviation. The Association between two categorical variables was done using Chi square or fisher's exact test. Non parametric tests were used for finding the statistical significance. Wilcoxon Signed rank test was used for comparing pre and

post treatment serum CEA in different categories. Comparison of serum CEA in different clinical categories were carried out using Mann-Whitney test and Kruskal Wallis test.

The optimal cut-off values of the CEA were determined using receiver operator characteristic (ROC) curve. A p value of <0.05 were considered significant.

RESULTS

The median age of diagnosis was 57.5(48.7-63.2). Median duration of symptoms was 4 mo (1.75-6.0). About 24% (12) were premenopausal and 76% (38) were post-menopausal. The main comorbidities were Diabetes Mellitus 24% (12), Hypertension28% (14), CAD 4% (2). About 64% (32) had distant nodal mets ,50% (25) had bone mets, 72% (36) had lung mets, 36% (18) had liver mets and 6% (3) had oligometastatic diseases. About 96 % (48) were IDC and 4% (2) were other histology. 72% (36) were hormone positive and 38% (19) were her2 neu positive. Grade 2 IDC were 24% (12) and grade 3 IDC in 76% (38%). Among study population, luminal type was seen in 70% (35%), Her 2 enriched in 8% (4%), TNBC in 22% (11) patients. The Pre chemotherapy CEA levels were more than 3.8 in 72% (36) patients. About 82% (41) were treated with chemotherapy and 18% (9) treated with hormonal agents. Anti Her2 Neu treatment was received by 16% (8) patients. The median number of cycles of chemotherapy was 6 (4-6) cycles. The main palliative chemotherapy agents were docetaxel 68% (34), Paclitaxel 4% (2), capecitabine 2% (1), doxorubicin plus cyclophosphamide2% (1), carboplatin 2% (1), Paclitaxel plus carboplatin 4% (2). About 6% (3) patients received palliative radiation to their painful bone mets.

About 36% (18) of patients progressed on treatment while 64% (32) had responded to palliative systemic treatment. Among responders (64%), 2% (1) had complete remission (CR),32% (16) had partial response (PR),30% (15) had stable disease (SD). About 36% (18) had progressive disease (PD).

Serum CEA and its correlation with other variables

Serum CEA value more than 3.8 ng/mL was considered positive. Baseline serum CEA and its correlation with other variables in metastatic breast cancer is given in Table1. None of the factors like menstrual status, grade of the tumour, number and sites of metastases, presence or absence of metastases, her 2 status, TNBC status has shown any statistical significance except luminal type with a p value of 0.016.

Serum CEA as predictor of response to treatment

The Median pre- treatment CEA level was 7.9(1.8-40.7). Median Post- treatment CEA was 4.39(1.4-12.15); p-value (0.032) in whole study population. Serum CEA and response to treatment in Responders and Non-Responders is given in Table 2. Among responder's median pre-treatment CEA was 8.87(2-49.6) and post treatment CEA was 2.07(1-8.7); p value -0.001. Among non-responder's median pre-treatment CEA was 5.4(1.7-36.01) and post treatment CEA was 11(4.65-22.5); p value 0.06. Since there was no statistically significant difference among responders and non-responders on their base line Serum CEA it cannot be taken as predictor of response but post treatment increase in CEA is associated with non-response or progression.

Pre-treatment and post treatment ROC Curve of whole study population and Luminal type breast cancer is given in Figure 1A,1B,1C and ID. We tried to find pre-treatment cut-off for Serum CEA in luminal breast cancer using ROC Curve with a sensitivity of 50% and specificity of 64% cut off can be taken as 29.7 as a predictor of tumour progression. But that cut off was not statistically significant. Receiver Operator curve (ROC) for finding the cut-off for post treatment CEA was also done. Post treatment CEA for predicting the progression was taken as 2.16, sensitivity of 94.1% and specificity of 54.8%. For hormone positive tumours post treatment cut-off can be taken as 9.46 with a sensitivity of 88.9% and specificity of 75.9% (p-value 0.02). With a cut-off of 9.41 we have analysed the statistical significance in the whole group of patients and was statistically significant with a p-value of 0.006.

Serum CEA and Luminal and non-luminal metastatic breast cancer

Table 3 shows Serum CEA and response to treatment in Responders and Non-Responders according to different classification of breast cancer types. Among

responder's median pre-treatment CEA for luminal type was 14.7(5.4-50.6) and post treatment CEA was 3.0(1-10). P value;0. 001.Even in luminal group pre-treatment Serum CEA was not a predictor of response, but post treatment CEA was significant predictor of tumour progression.

Association of Serum CEA and various sites of metastatic breast cancer

Figure 3A &3B shows Median pre-treatment and post treatment serum CEA level in Responders and non-responders according to various sites of metastasis. Among responders, median pre-treatment serum CEA of patients with bone metastases, lung metastases and liver metastases are 27.2ng/mL,8.4ng/mL and 24.5ng/mL respectively. Among non-responders' median post-treatment serum CEA of patients with bone metastases, lung metastases and liver metastases are 12ng/mL,11ng/mL and 14 ng/mL respectively.

Table 4 shows Serum CEA and response to treatment in Bone, liver and lung metastases. In patients with liver and lung metastases post treatment CEA level difference was not statistically significant in both responders and non-responders even though values are high in non-responders.

In non-responders, comparing patients with or without bone metastases, the median post treatment Serum CEA of patients with bone metastases is 12 ng/dL whereas median Post treatment S CEA in those without bone metastases, is 10ng/mL and post treatment CEA level difference was statistically significant, p value;0.063. Among those with bone metastases 69.5% had elevated post treatment serum CEA and only 37.5% had elevated serum CEA in those with no bone metastases (Figure 4).

DISCUSSION

The measurement of serum tumour marker levels could provide useful information for earlier detection of recurrence or accurate prediction of outcomes after recurrence in various cancers. They are more useful when patients have elevated level at baseline.

The commonly studied tumour markers in breast cancer are cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA). The significance of these markers remains still unclear.[17,18] Even though , prognostic value of CA15-3 in breast cancer had been documented in some studies , Serum CEA is less widely investigated as a prognostic factor than CA15-3 because of its poor sensitivity and specificity.[18,19] Elevated serum levels of CA 15-3 and CEA preoperatively were significantly associated with tumour size, axillary node metastasis and advanced stage.[20,21,22,23] A recent meta-analysis investigated the prognostic value of these two markers serum cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) in 12,993 breast cancer patients and this study indicated that an elevated CA15-3 Level significantly corresponded with poor DFS and OS of breast cancer.[23]

In our study, it has been noted that no clinically meaningful significance was seen with factors like menstrual status, grade of the tumour, number and sites of metastases, presence or absence of metastases, her 2 status, TNBC status except luminal type. This finding was consistent with a study by Geng, Biao *et al*[23] Elevated CEA levels were significantly associated with breast cancer molecular subtypes and luminal subtypes exhibited a higher percentage of elevated CEA levels compared to non-luminal subtypes and lower CEA in the HER2-enriched and TN subtypes. The reason for this differential expression of CEA is that, expression patterns of luminal, HER2-enriched and basal-like tumours are closely associated with its maturation and differentiation. Luminal subtypes have high expression of hormone receptor related genes, whereas HER2-enriched or basal-like have low expression of HR-related genes, which explains the association between CEA elevation and luminal subtype. Our study showed that pre-treatment Serum CEA cannot be taken as predictor of response even in luminal subtype but post treatment CEA was significant predictor of tumour progression. Hence, we can conclude that monitoring CEA levels in luminal metastatic breast cancer at the end of treatment is a significant predictor of treatment response.

The correlation between tumour marker levels and various metastatic sites in metastatic breast cancer is poorly defined.[24,25] Study by Yerushalmi R *et al* identified that tumour

marker elevation was documented in the majority of patients with metastatic breast cancer and luminal subtypes expressed more frequently compared with the non-Luminal groups.[26] CEA elevation was not different between the different sites of metastasis. Whereas in our study, in patients with liver and lung metastases, post treatment CEA level difference was not statistically significant in both responders and non-responders even though values were high in non-responders.

Study by Yazdani A *et al* showed that age, menopausal status, number of axillary lymph node metastases, tumor size, and ALP were identified as prognostic factors for bone metastasis in patients with breast cancer whereas significantly persistent elevated post treatment serum CEA levels were seen with bone metastases in our study.[27] Kosaka Y *et al* proposed that in hormone receptor positive breast cancer, nodal metastasis and elevated serum CEA had poor prognosis and there was a significant rate of recurrence in those with high serum CEA levels compared with those with low levels of CEA. [28] Elevated serum levels of Serum Her2/neu, BCL2, CA15-3 and CEA in breast cancer patients are useful markers for predicting aggressive behaviour and predicting relapse.[29,30]

One major limitation of our study is that of small sample size of 50 patients and it limits the predictive power of these markers and needs larger studies to confirm the findings.

CONCLUSION

Pretreatment S.CEA was elevated in luminal subtype. With treatment, responders had significant fall in Serum CEA level but that was clinically significant in luminal breast cancer type. Elevated post-treatment S.CEA levels were associated with disease progression and poor response to therapy. Persistently elevated post treatment Serum CEA levels were associated with bone metastases. Elevated serum CEA and hormonal status were significant predictors of treatment response.

ARTICLE HIGHLIGHTS

Research background

In breast cancer patients elevated serum CEA levels are particularly noted in metastatic and recurrent disease and its significance in clinical practice is doubtful.

Research motivation

We aimed to study the estimate the serum CEA level in our metastatic breast cancer patients and correlate it with response to treatment and clinical outcome.

Research objectives

Aim to evaluate the efficacy of Serum CEA levels as a prognostic marker in metastatic breast cancer patients

Research methods

This was a prospective experimental study

Research results

Pretreatment S.CEA was elevated in luminal subtype. With treatment, responders had significant fall in Serum CEA level but it was clinically significant in luminal breast cancer type. Metastatic breast cancer patients with bone metastases had significantly elevated post treatment Serum CEA levels after treatment.

Research conclusions

Based on our results, we suggest that serum CEA have potential clinical value in monitoring the treatment response of metastatic breast cancer patients, especially in patients with bone metastasis.

Research perspectives

Serum CEA as a tumour marker warrants further studies in metastatic breast cancer especially with bone metastases.

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