USEFULNESS OF SERUM CA 15.3 AND HISTOPATHOLOGICAL PROGNOSTIC INDICES IN BREAST CANCER

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ABSTRACT

Prognostic factors influence the modality and course of therapy in breast cancer. These include both histopathological and biochemical variables. This study was aimed to find out if any correlation exists between the biochemical tumor marker - serum CA 15.3, and the lymph node staging of Nottingham's Prognostic Index (NPI). It was observed that serum CA 15.3 showed a statistically significant correlation with lymph node staging of NPI. Therefore it is concluded that CA 15.3 can be utilized as a useful prognostic marker, particularly in cases where histopathological variables such as tumor size and grade have been altered by pre-operative chemotherapy.

KEYWORDS

Breast Cancer, CA 15.3, Nottingham's Prognostic Index, NPI

INTRODUCTION

Breast cancer is one of the commonest cancers and causes of mortality in women in India (1). With the various options available for treatment such as surgery, radiotherapy, chemotherapy and hormonal therapy, it becomes essential to consider prognostic and predictive factors, which guide the clinician to an appropriate therapeutic regimen (2). Of the various prognostic factors, the conventional ones are tumor size, status of axillary lymph nodes, metastases, histological type, histological grade, lymphatic or vascular invasion, markers of proliferation, and DNA content of tumor (3). The biological ones are hormone and growth factor receptors, oncogenes, tumor suppressor genes, proteases, second messenger systems and others (4).

Among these, histopathological variables like tumor size, lymph node status and tumor grade of differentiation, form some of the most widely used parameters in prognostic evaluation. These have been collectively included under Nottingham's Prognostic Index (NPI) (5). Patients with a low NPI have a much better prognosis than those with a high NPI. NPI is among the various prognostic indices, which are used to determine the need for adjuvant therapy in a patient (6). A study conducted by D' Eredita et al (7), where NPI categories were as: Good (NPI < 3.4), Moderate (3.4 ≤

NPI = 5.4) and Poor (NPI > 5.4), demonstrated the prognostic value of this composite index. The ten-year survival rates in these categories were 88 %, 70 % and 40 % respectively with a 'p' value less than 0.0001. In another study conducted by P. Chollet et al (8), it was concluded that patients with an NPI less than 4 had a better prognosis than others, with ten-year survival rates of 91.2 % and 84.6 % respectively.

CA 15.3 is the most widely used serum biochemical tumor marker in breast cancer (9). It is a carbohydrate antigen secreted from the mammary epithelial cells. Assay of CA 15.3 is a relatively convenient and non-invasive method for evaluating prognosis in newly diagnosed breast cancer patients (10). NPI is a parameter, which guides the clinician to an appropriate course of therapy. The prognostic index can be assessed on biopsy specimens obtained post-operatively. Further, in patients who have been given chemotherapy pre-operatively, this index is altered (11). CA 15.3 estimation, on the other hand, is relatively non-invasive and convenient to perform. Its value can be obtained pre-operatively. Gai et al (12) demonstrated the usefulness of this marker in facilitating the selection of patients who may require additional therapy, though correlation with NPI was not studied. Therefore this study was aimed to find if any correlation exists between serum CA 15.3 and the NPI nodal staging. If any correlation was found, it could provide the clinician an estimate of the prognosis pre-operatively, thus enabling appropriate surgical management and adjuvant therapy. None of the previous investigators have studied this relationship and this study is the first of its kind.

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MATERIALS & METHODS

The study was carried out at St. John's Medical College Hospital, by taking forty-five histopathologically confirmed malignant and benign female breast tumor patients in the age group of 18-70 years as cases and controls. The control & malignant groups comprised twenty and twenty-five patients respectively. Pre-operative serum samples were collected from both the groups for CA 15.3 estimation. The marker was estimated by Sandwich ELISA method using Glaxo Qualigens kit. This kit uses monoclonal antibodies against DF3 and 115D8 - two epitopes on CA 15.3. A cut-off value of 35 units per ml (13) was taken. Marker concentrations greater than the cut-off were considered as "elevated"; the rest were considered "normal".

The nodal status was obtained from the histopathological examination of the biopsy specimens of cases after staining with haematoxylin and eosin. The nodal status was given values according to Nottingham's Prognostic Index as follows: 1- no nodal involvement, 2 - involvement of less than three axillary nodes or an internal mammary node, 3 - involvement of three or more axillary nodes or involvement of both axillary and internal mammary nodes (6).

STATISTICAL ANALYSIS

CA 15.3 values thus estimated in benign and malignant cases were statistically analyzed by using student 't' test of equal variance (14). Then CA 15.3 values in the malignant lesions were compared with Nottingham's lymph node status to assess correlation.

RESULTS

When serum CA 15.3 values were compared between the benign and malignant cases, it was found that the malignant tumors had significantly higher values compared to the benign ones (refer Table 1.) Analysis of the marker values revealed a positive correlation ($r = 0.41$) between serum CA 15.3 of malignant tumors and Nottingham's lymph node staging (refer Figure 1). The trend line in the figure indicates the increase in CA 15.3 with increasing nodal stage. Figure 2 shows the correlation between elevated (> 35 units per ml) serum CA 15.3 levels in malignant tumors and lymph node staging. It may be observed that there is a better correlation ($r=0.67$) than in Figure 1, where both elevated and normal values have been considered. Further, Table 2 shows average values of serum CA 15.3 (considering only elevated values) according to nodal stages. It reveals that the average value of serum

Table 1 Serum CA 15.3 in benign and malignant tumors - a comparison

Biochemical tumor marker CA 15.3	Malignant tumors	Benign tumors
Number of samples	25	20
Minimum concentration (units per ml.)	9	6
Maximum concentration (units per ml.)	231	48
Mean value (units per ml.)	72.06	16.80
Student t value	t=3.326	
Probability	p=0.002

Figure 1. Correlation between serum CA 15.3 and Nottingham's lymph node staging

Figure 2. Relationship between elevated serum CA 15.3 and lymph node staging

Table 2 Mean value of Serum CA 15.3 in each nodal stage

Nodal Stage	Mean Value of Serum CA 15.3 (units per ml)
Stage1	51
Stage2	87.2
Stage3	176.8

CA 15.3 increases significantly with increasing nodal stage.

DISCUSSION

In the present study, when serum CA 15.3 values were compared between benign and malignant cases, it was found that the malignant tumors had significantly higher values compared to the benign ones ($p=0.002$, see Table 1). However, though the values were significantly different in the two groups taken as a whole, it was found that values < 35 units per ml. were found in 45% of malignant cases. Only one benign case showed a value higher than the cut-off level. Therefore, while a low value of CA 15.3 did not rule out a carcinoma, an elevated value (> 35 units per ml.) suggested malignancy.

Analysis of the marker values with respect to Nottingham's nodal staging revealed a positive correlation ($r=0.41$, see Figure 1) between the two parameters. This indicates that the values of serum CA 15.3 increase as the lymph nodal stages progress. Figure 2 shows that there is an improved correlation ($r=0.67$) when only elevated CA 15.3 values are considered. This observation is reinforced by Table 2, which shows that the average serum CA 15.3 value increases with increasing nodal stage. Therefore, under the sample size condition of the study, serum CA 15.3 values were found to correlate with Nottingham's lymph node staging, which is an established prognostic marker. This finding enables the clinician to assess prognosis pre-operatively with the use of CA 15.3, which is a relatively non-invasive tumor marker. In addition, serum CA 15.3 could be useful for prognosis in cases where NPI cannot be assessed, for instance, in patients who have received pre-operative chemotherapy, which is known to alter the index.

In conclusion, this study suggests the use of serum CA 15.3 (particularly when elevated) as an effective prognostic marker to guide the clinician to an appropriate therapeutic regimen.

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