Original Article

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Association of CD10 and VEGF Expression with Tumour Characteristics and Treatment Response in Patients of Carcinoma Breast- A Prospective Cohort Study

Surgery Section

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ABSTRACT

Introduction: Majority of breast cancer patients receive systemic therapy. This has led to an extensive search for effective factors to predict the outcome. Two such markers for breast cancer are Cluster of Differentiation 10 (CD10) and Vascular Endothelial Growth Factor (VEGF). There is limited data available in the literature to support these parameters in breast cancer patients, especially from the Indian subcontinent.

Aim: To ascertain the association of pre-chemotherapy levels of CD10 and VEGF with tumour load in breast cancer and treatment response.

Materials and Methods: A prospective cohort study was conducted in the Department of Surgery in collaboration with the Department of Pathology at Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India, from November 2015 to February 2017. A total of 39 patients with Locally Advanced Breast Cancer (LABC) were included in the study. Preoperative levels of CD10 and VEGF were estimated in large needle core biopsy specimens. Standard anthracycline based chemotherapy was given to all patients as a 21 days cycle for three cycles. All patients underwent modified radical mastectomy after Neoadjuvant Chemotherapy (NACT). Levels of CD10 and VEGF were estimated again in the mastectomy specimen. Increase/decrease or no change in VEGF and CD10 expression percentage was ascertained for each patient after systemic therapy. Variables that were studied in the present study were Tumour, Nodes, and Metastasis (TNM) staging of patient, expression of VEGF and CD10 in large needle core biopsy specimens and its association with tumour load, response to NACT and its association with CD10 and VEGF and histopathological characteristics like presence or absence of lymphovascular invasion oestrogen, progesterone and Human Epidermal Growth factor Receptor 2 (HER2)/neu receptor status. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 22.0. Association between two ordinal variables was established using Kruskal-Wallis test. A comparison of ordinal paired data was done using Wilcoxon signed-rank sum test. The p-value <0.05 was considered significant.

Results: The mean age of study participants was 42.0±11.4 years. Increase in TNM staging lead to higher CD10 and VEGF expression (p-value <0.05 and <0.029, respectively). There was a significant reduction in CD10 and VEGF expression postchemotherapy (p-value <0.05). CD10 expression was found higher in subjects with ER-negative status (22 patients) with p-value=0.014 and HER2/neu positive status (19 patients) with p-value=0.028. Subjects with HER2/neu positive status had higher VEGF expression (20 patients) with p-value=0.032.

Conclusion: CD10 and VEGF can be used as independent markers for indicating poor prognosis and can be used as target for development of novel therapies in carcinoma breast.

Keywords: Effective factors, Markers, Novel therapies

INTRODUCTION

Carcinoma breast is one of the most common malignancy of women, both in developed and developing nations. It amounts to about 25% to 33% of all female malignancies worldwide and in urban areas of India, it is the most common cancer [1]. Moreover, over 50% breast cancer patients in India present in stage III and IV disease [2]. Early invasive breast cancer represents stage I, II a and stage II b. LABC extends beyond the breast to the skin or chest wall, but distant metastasis is absent. The term is commonly associated with stage III cancer. NACT is increasingly being used in the treatment of primary breast cancer, which is diagnosed by core biopsy prior to surgical excision. NACT has gained worldwide acceptance in treating LABC [3]. For around 25 years, LABC are first approached through systemic therapy, while in early breast cancer, it has a role in tumour load reduction. So, a patient may be converted into a breast conservation surgery rather than a radicle surgery. On the other hand, systemic therapy is the mainstay of treatment for metastatic breast cancers [3].

Considerable amount of search has undergone for new and more effective parameters which can predict the outcome in breast cancer more effectively. This can be attributed to the fact that, most of the breast cancer patients receive systemic therapy. At present, Oestrogen Receptor (ER) and Progesterone Receptor (PR) status are the most important and helpful predictive factors available [4]. Tumours with increased HER2 augmentation are linked with poor outcome and higher grade tumour [5]. New markers have been recognised which are able to predict invasive and metastatic tumour potency. These markers could be of help in making a proper treatment decision. The two such markers for breast cancer are CD10 and VEGF [6]. Myoepithelial cells of normal breast tissue have been found to harbour CD10 positivity [7]. CD10 is a zinc-dependent peptidase which comes under metalloproteinase class. Structural similarity between Matrix Metalloproteinases (MMPs) and stromalysin might play a role in facilitating cancer cell takeover and/or metastasis. It has further been found that, its expression in stroma of invasive breast cancer correlates with poor prognosis and

high grade [8,9]. Experimental data from the past also indicate that, CD10 may be a potential target of new cancer therapies [10].

VEGF, is a multifunctional cytokine that acts as a highly specific mitogen on endothelial cells. It is recognised as one of the most important regulators of physiological and pathological angiogenesis [11]. Tumour angiogenesis is associated with invasiveness and the metastatic potential of various malignancies. Furthermore, the increased expression of VEGF has been associated with increased risk of metastasis, recurrence, and poor prognosis in many cancers [12].

However, there is a limited data available in the literature to support these parameters in breast cancer patients especially from Indian subcontinent [13,14]. The present study was aimed to firstly, ascertain the association of pre-chemotherapy levels of CD10 and VEGF with tumour load in breast cancer which included TNM staging of tumour, grade of tumour, lymphovascular invasion, and receptor status and to secondly, find the association of pre-chemotherapy levels of CD10 and VEGF with post-chemotherapy levels and treatment response.

MATERIALS AND METHODS

A prospective cohort study was conducted in the Department of Surgery in collaboration with Department of Pathology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India, from November 2015 to February 2017. Ethical clearance T.P(MD/MS)(39/2015)/IEC/PGIMER/RML/4914 was obtained. All subjects gave written informed consent before being enrolled in the study.

Inclusion criteria: Patients in the age range of 15-70 years with LABC and who gave written consent were included in the study.

Exclusion criteria: Patients with LABC who received prior NACT, those unfit for chemotherapy, and patients with any other synchronous malignancy were excluded from the study.

Sample size calculation: Sample size was calculated and considered according to the previous study with p=5% and d=absolute error of 5% [15].

Study Procedure

Patients were investigated with routine blood investigation, chest X-ray, Electrocardiogram (ECG), ultrasound breast and/or bilateral mammography, large needle core biopsy and ultrasound abdomen. Clinically, TNM staging was done and cases were selected after confirmation from histologically proven biopsy reports. The American Joint Committee on Cancer (AJCC) version 8 TNM staging system was used for staging of patients [16]. Preoperative levels of CD10 and VEGF were estimated in large needle core biopsy specimen. Estimation of VEGF and CD10 was done in the following way:

Vascular Endothelial Growth Factor (VEGF): Tumour tissue was fixed in formalin and then was fixed in paraffin. Detection was performed using super sensitive Polymer-Horseradish Peroxidase (HRP) Immunohistochemistry (IHC) Detection System. Semi-quantitative scoring of staining intensity of cytoplasm of tumour cells was scored according to the table below [Table/Fig-1].

VEGF score	Staining	Quantitative information
1	Weak/no	<10% of tumour with strong intensity
2	Moderate	10 %<=strong intensity <1/3rd of tumour
3	Strong	1/3rd < strong intensity <2/3rd of tumour
4	Strong	strong intensity >2/3rd of tumour

[Table/Fig-1]: VEGF scoring.

A homogenous staining in tumour cells lead to a score of 4 when, there was a doubt between two scores, the highest score was chosen.

Cluster of Differentiation 10 (CD10): CD10 expression in tumour stroma was assessed by IHC [Table/Fig-2].

CD10 interpretation		Tumour stromal cell staining with CD10
Negative		<10%
Positive		>=10%
	Weakly positive	10%-30%
	Strongly positive	>30%

[Table/Fig-2]: CD10 scoring.

The percentage of tumour cell expressing VEGF and CD10 antigens were estimated and documented before chemotherapy. Standard anthracycline-based chemotherapy (cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, 5-fluorouracil 500 mg/m^2 was given to all patients as a 21 days cycle for three cycles. All patients underwent modified radical mastectomy after NACT. Levels of CD10 and VEGF were estimated again in the mastectomy specimen. Increase/decrease or no change in VEGF and CD10 expression percentage was ascertained for each patient after systemic therapy.

The following variables were studied during the study:

- TNM staging of the patient.
- Expression of VEGF and CD10 in large needle core biopsy specimen and its association with tumour load.
- Response to NACT and its association with CD10 and VEGF.
- Histopathology characteristics-

Presence or absence of lymphovascular invasion. Oestrogen, progesterone and HER2/neu receptor status.

Response to NACT was ascertained using Response Evaluation Criteria in Solid Tumours (RECIST) which includes the following [17]:

- Complete responders- Disappearance of all target lesions.
- Partial Responders- Atleast a 30% decrease in the sum of the Longest Diameters (LD) of target lesions.
- Non responders included progressive disease and stable disease.
- Progressive disease- Atleast a 20% increase in the sum of the LD of target lesions or the appearance of one or more new lesions.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for partial responder nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 22.0. Data was represented as mean±SD. Mean value of continuous variables was compared using Analysis of Variance (ANOVA). Association between two ordinal variables was established using Kruskal-Wallis test. Comparison of ordinal paired data was done using Wilcoxon signed-rank sum test. The p-value <0.05 was taken as significant.

RESULTS

A total of 39 patients were included in the present study. Their mean age was 42.0±11.4 years (range 15-70 years). Out of 39 patients, 38 (97.4%) were females and 1 (2.5%) was male.

Frequency distribution of TNM staging of the subjects: Out of 39 subjects included in the study, 13 were in TNM stage II b. 26 subjects were in TNM stage III (11 had stage III a and 12 and 3 had stage III b and III c, respectively).

Comparison of effect of TNM staging on pre-chemotherapy CD10 and VEGF expression: Kruskal-Wallis test was done to evaluate the relationship between TNM staging and CD10, VEGF expression. It was observed that, increase in TNM staging leads to higher CD10 and VEGF expression. (p-value <0.05) [Table/Fig-3]. Mean CD10 and VEGF expression was calculated using standard formula for mean calculation. The total expression of CD10 and VEGF in each subset was summed up and divided by the number

TNM stage	N	Mean rank of CD10 expression	Chi-square value	p-value	Mean rank of VEGF expression	Chi-square value	p-value
II b	13	10.27	20.442	**<0.001**	13.46	9.017	**0.029**
III a	11	23.64			25.41		
III b	12	25.46			21.42		
III c	3	27.00			22.83		
Total	39						

[Table/Fig-3]: Comparison of effect of TNM staging on pre-chemotherapy CD10 and VEGF expression.

of patients in each subset. Out of total 39 subjects in large needle core biopsy, 2 (5.1%) subjects were CD10 negative, 25 (64.1%) and 12 (30.8%) subjects were strongly positive and weakly positive respectively. In mastectomy specimen, 3 (7.7%) subjects were CD10 negative, 26 (66.7%) were weakly positive and 10 (25.6%) subjects were strongly positive [Table/Fig-4].

Status of CD10	LNBS* specimen		Mastectomy specimen	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Negative	2	5.1	3	7.7
Weakly positive	12	30.8	26	66.7
Strongly positive	25	64.1	10	25.6
Total	39	100.0	39	100.0

[Table/Fig-4]: Frequency distribution of subjects according to their CD10 expression in large needle biopsy specimen and mastectomy specimen.
*LNBS: Large needle biopsy specimen

Wilcoxon signed-rank sum test analysis suggests that, there was a significant reduction in CD10 expression after chemotherapy. (p-value=0.002). Out of total 39 subjects tested for VEGF expression in large needle core biopsy, 5 (12.8%) were weakly positive, 12 (30.8%) and 22 (56.4%) were moderately and strongly positive, respectively. In mastectomy specimen tested for VEGF, 23 (59.0%) were weakly positive, 11 (28.2%) and 5 (12.8%) were moderately and strongly positive, respectively [Table/Fig-5].

Status of VEGF	LNBS* specimen		Mastectomy specimen	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Weak positive	5	12.8	23	59.0
Moderate positive	12	30.8	11	28.2
Strongly positive	22	56.4	5	12.8
Total	39	100.0	39	100.0

[Table/Fig-5]: Descriptive statistics of subjects according to their VEGF expression in large needle biopsy specimen and mastectomy specimen.
*LNBS: Large needle biopsy specimen

Wilcoxon signed-rank sum test analysis suggests that, there was a significant reduction in VEGF expression after chemotherapy. (p-value <0.001)

Descriptive statistic of subjects according to their response to therapy: Out of total 39, 23 (59.0%) subjects were completely responded to chemotherapy, 10 (25.6%) partially responded and 6 (15.4%) did not responded at all.

Effect of chemotherapy response on CD10 and VEGF expression: Wilcoxon signed-rank sum analysis suggests that, subjects who had complete and partial chemotherapy response had statistically significant reduction in CD10 and VEGF expression in Modified Radical Mastectomy (MRM) as compared to large needle core biopsy sample. In chemotherapy, non responder subject there was no reduction in CD10 and VEGF expression was observed. Decrease in CD10 and VEGF expression was more in complete responder than in partial responder [Table/Fig-6].

Association between lymphovascular invasion and CD10 expression: Kruskal-Wallis test was done to evaluate the relationship between lymphovascular invasion and CD10 expression. No relation was observed between CD10 expression and lymphovascular invasion. Chi-square value was 0.072 and p-value=0.788.

Variables			Number (n)	Mean rank	Sum of rank	z-score	p-value
Complete responder	CD10	MRM**<LNBS*	15	0.50	142.50	-2.828	**0.005**
		MRM>LNBS*	3	9.50	28.50		
		MRM=LNBS*	5				
		Total	**23**				
	VEGF	MRM<LNBS*	19	10.0	190.00	-3.938	**<0.001**
		MRM>LNBS*	0	0	0		
		MRM=LNBS*	4				
		Total	**23**				
Partial responder	CD10	MRM<LNBS*	4	2.50	10.00	-1.890	**0.049**
		MRM>LNBS*	0	0	0		
		MRM=LNBS*	6				
		Total	**10**				
	VEGF	MRM<LNBS*	5	3.00	15.00	-2.070	**0.038**
		MRM>LNBS*	0	5.60	56.00		
		MRM=LNBS*	5				
		Total	**10**				
Non responder	CD10	MRM<LNBS*	1	2.0	5.0	-0.577	0.564
		MRM>LNBS*	2	0	4.0		
		MRM=LNBS*	3				
		Total	**6**				
	VEGF	MRM<LNBS*	3	2.33	7.0	-0.138	0.890
		MRM>LNBS*	2	4.00	8.0		
		MRM=LNBS*	1				
		Total	**6**				

[Table/Fig-6]: Effect of chemotherapy response on CD10 and VEGF expression.
*LNBS: Large needle biopsy specimen
**MRM: Modified radicle mastectomy; Bold p-value: Statistically significant

Association between lymphovascular invasion and VEGF expression: Kruskal-Wallis analysis suggested no association between lymphovascular and VEGF expression. Chi-square value was 0.996 and p-value=0.318.

Descriptive statistic of subjects based on their hormone receptor profile: The IHC profiling of study subjects, was done using ER/PR and HER2/neu detection. 17 (43.6%) subjects were ER positive and 16 (41%) and 20 (51.3%) subjects were PR and HER2/neu positive respectively.

Association between hormone receptor and CD10 expression: The Kruskal-Wallis analysis suggests that CD10 expression was higher in subjects with ER negative status and HER2/neu positive status. PR receptor status had no association with CD10 expression. Kruskal-Wallis statistical analysis suggests that, subjects with HER2/neu positive status had higher VEGF expression. The ER and PR receptor status had no association with VEGF expression [Table/Fig-7].

ER	N	CD10			VEGF		
		Mean rank	Chi-square value	p-value	Mean rank	Chi-square value	p-value
0	22	23.32	6.039	**0.014**	22.32	2.642	0.104
1	17	15.71			17.00		
Total	39						
PR	N						
0	23	19.46	0.180	0.671	20.74	0.298	0.585
1	16	20.78			18.94		
Total	39						

HER2/ neu	N						
0	19	16.53	4.859	**0.028**	16.42	4.622	**0.032**
1	20	23.30			23.40		
Total	39						

[Table/Fig-7]: Association between hormone receptor and CD10, VEGF expression. Bold p-value: Statistically significant; ER: Oestrogen receptor

DISCUSSION

Breast cancer is the principal cause of death from cancer among women globally. In Indian women after cervical cancer, the breast is the second most common site of cancer [1]. The survival rates have improved over the years, with a five-year survival rate of 63% in the 1960s, 75% in the 1970s, 79% in the 1980s and 90% from 1995 to 2005. The greatest improvement is seen to be in women younger than 50 years of age, where, death rates have decreased by 3.2% per year [2]. In women, over 50 years, the death rates have reduced by 2% per year. The reduction in mortality is attributed to early detection via mammographic screening and improvements in therapy [3]. Newer markers that have a better predictive value for tumour invasiveness and metastatic potency can alter the course of treatment. The two such markers for breast cancer are CD10 and VEGF [6].

In the present study, it was observed that, in patients with higher TNM staging, there was statistically significant higher expression of CD10 and VEGF (p-value <0.001 and p-value <0.001 respectively). There was a statistically significant positive correlation between the expression of tumour load and CD10 and VEGF expression (p-value <0.047 and p-value <0.014 respectively). Similar results were obtained by Dhande AN et al., in their study [18]. They also found a positive association between tumour stage and CD10 expression. Wang Q et al., in their study found that there was a significant positive association between TNM stage and VEGF expression [19]. There was no statistically significant association observed between CD10 and VEGF expression and PR status (p-value=0.671 and 0.585, respectively). Increased CD10 and VEGF expression was observed in HER2/neu positive subjects (p-value= 0.028 and 0.032, respectively). This association was found to be statistically significant. ER receptor status positivity was found to have a statistically significant association with CD10 expression (p-value=0.014) while no such relationship could be established with VEGF expression (p-value=0.104). Agarwal K et al., in their study on 29 patients found that, strong CD10 expression was associated with hormone receptor negativity and HER2/neu overexpression [13]. Kamarudin NA et al., also found a similar result in their study. In their study, CD10 positivity was found more in ER-negative cases. However, there was no association between stromal CD10 expression with tumour grade, stage, PR, and HER2 status [20]. Similar results were obtained by Jana SH et al., in their study on 70 patients. They also found a positive significant association between CD10 expression and HER2/neu positivity [21].

In the present study, no statistically significant relation was observed between CD10 and VEGF expression and lymphovascular invasion (p-value=0.788 and 0.318, respectively). Shen S et al., in their study on 392 patients found similar results that, there was no association between VEGF expression and lymphovascular invasion [22]. However, Chen Z et al., in their 44 patients found a positive significant association between VEGF expression and lymphovascular invasion [23]. Ali HD et al., in their study on 91 patients found a positive association between CD10 expression and lymphovascular invasion [24]. Neo-adjuvant anthracyclin-based chemotherapy changes the expression of CD10 and VEGF expression in breast cancer and is, therefore, non static. Wilcoxon signed-rank sum test analysis suggests that, there is a significant reduction in CD10 and VEGF expression after chemotherapy (p-value <0.001 and <0.05, respectively). Ruihua T et al., in their study found a similar result. They concluded that, VEGF expression significantly reduces after NACT [25]. Thomas S et al., in their study found that, there was a decrease in CD10 expression after NACT [15]. In the present study, subjects who had a complete and partial response to chemotherapy had a statistically significant reduction in VEGF and CD10 expression, while patients who were non responders had no reduction in VEGF and CD10 expression. Similar results were found by Thomas S et al., who concluded that, partial and complete responders had a significant reduction in CD10 expression [15]. Inspite of authors best efforts no study comparing tumour response and VEGF expression could be found.

Limitation(s)

The small sample size was one of the limitation.

CONCLUSION(S)

The CD10 and VEGF expression was strongly associated with a well-established negative prognostic marker that is, HER2/neu overexpression, ER/PR negativity, higher tumour grade, and a higher tumour load thus, indicating CD10 and VEGF can be used as an independent marker indicating poor prognosis and can be used as target for the development of novel therapies. A steady or decrease in VEGF and CD10 expression associates with complete or partial clinical response, while an increase in CD10 and VEGF expression appears to be associated with poor clinical response to NACT (anthracycline-based therapy). Therefore, CD10 and VEGF have prognostic significance.

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