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ORIGINAL

PROGNOSTIC SIGNIFICANCE OF CD10 PROTEIN EXPRESION IN INVASIVE BREAST CARCINOMA

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Introduction: Predicting of clinical course of primary diagnosed breast carcinoma is very difficult. Although breast cancer is an epithelial malignancy, stroma plays a key role in its development and pathogenesis. Stromal markers are now emerging as novel markers in assessing the prognosis of invasive breast cancer. CD10 is a 90-110kd cell surface zinc-dependent metalloproteinase. Since CD10 is structurally similar to matrix metalloproteinase and stromelysin, it might facilitate cancer cell invasion and/or metastasis.

Patient and Methods: The primary goal of conducted research was to determine CD10 oncoprotein expression in primary and recurrent breast carcinoma. The secondary goals included the dependence of the histologic and nuclear grade, expression of estrogen, progesteron and Her2/neu receptors and the CD expression with the recurence of the disease as well as the correlation of the CD 10 overexpression with the histologic and nuclear grade, expression of estrogen, progesteron and Her2/neu receptors and presence of breast carcinoma recurrence.

Results: The study analyzed 64 patients with primary diagnosed invasive ductal (NST) breast carcinoma, stage Ia and Ib (T1N0 and T2N0), treated at the Oncology Unit in Tuzla from 2004 to 2008. The patients had at least five years of survival. The patients were divided into two groups according to presence or absence of the diseasse progression. 29 out of 64 patients had positive CD 10 expression It has been found that age, histologic grade and absence of expression of estrogen and progesteron receptors are not in correlation with the reccurence of the disease recurrence. In contrary, nuclear grade and positive expression of Her2/neu receptors were highly correlated. CD10 showed high statisticlly significant correlation with breast carcinoma recurrence but correlation of CD 10 oncoprotein expression with the others variables has not been found.

Conclusion: This study gives substantial proof to explaining the role of stroma/CD10 in breast cancer pathogenesis. Keeping the role stroma plays in predicting prognosis and tumor response, CD10 should be included as a routine pre-chemotherapy marker in breast carcinoma. Further studies should be performed to see the role stroma plays in hormonal expression and the usefulness of CD10 to predict treatment failure in breast carcinomas receiving neoadjuvant therapy.

Key words: breast cancer recurrence, therapy resistant breast cancer, CD10 oncoprotein.

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INTRODUCTION

Breast carcinoma is malignant disease as old as the human civilisation. It most present in the developed countries and countries in development [1]. Average incidence is from 82,5 to 99,4 cases per 100.000 women; in USA 127,8; countries of Westrn Europe 78 and in Japan 18 per 100 000 women [2]. Relentless statistics analyses show also the constat increase of number of new cases. Increase of incidence in USA is by 0.6 per year, at global world level even 3,6% [3].

Though the breast carcinoma is more rare in younger age under thirty than in older one, tendence of occurance of aggresive disease in younger patients results with lower rate of five years survival [1]. Without important changes of appearing in prevention and treatment, it is expected 747.802 women to died every year from breast cancer by 2030 [2,4].

Predicting of clinical course of primary diagnosed breast carcinoma is very difficult. Behaviour and nature of breast carcinoma depends of much on interacting individual characteristics of each particular patient and characteristics of carcinoma also. Predictive and prognostic factors may be favorable or unfavorable to prediction time of overall survival and specific (disease free) survival after initial treatment. Factors negativly influencing the rate of survival first of all are: age of patient, high grade

of nuclear and histologic differentiation and positive expression of Her2/neu receptors.

Today, some prognostic factors of breast cancer have been reliably confirmed (histologic type and size of tumour, grade of histologic and nuclear differentiation, estrogen and progesteron receptors, Her2/neu expression etc), but the reliability of others is just to be confirmed. There are 65 significant immunoregulatory proteins binding to themselves about 135 antibodies, but none of them is independent and specific [5,6]. At the begining of 2015 year a group of authors with professor Douglas F. Easton in front published spectacular results of discovering 15 new gene loci connected with occurance of breast carcinoma, obtained by analysis of 120.000 cases [7]. The risk of disease progression and occurrence of distant metastases in breast carcinoma is very difficult to define as there is no valid independent biomarker to show the activity of pathogenic process.

Prognostic biologic molecular markers are sorted into groups such as steroid receptors (estrogen, progesterone, androgen receptors); markers of proliferation (Ki-67 antigen); regulators of cell cycle and apoptosis (Cyclin D1, Cyclin A, Cyclin E, P16, P21, P27, P53, Bax, Bak, Bcl-2, Bc1-XL, Survivin, Cmyc, Retinoblastoma(Rb) gen); proteins factors of angiogenesis (Vascular endothelial factor of growth (VEGF), Heparinasa); family of human epidermal factors of growth (HER2, HER1, HER3, HER 4); proteins of extracellular matrix (CDlO, SPARC, Cyclooxygenase-2); family micro-RNK; cellular factor of growth (Acrogranin-Progranulin (GP88); ATF3 "master-switch"stress-gene.

The objective of this study was to define the age of patients, grade of histologic and nuclear differentiation of tumour, expression of estrogen and progesterone receptors and HER2 receptors in primary and recurrent breast carcinoma, also to define CD 10 expression in primary and recurrent breast carcinoma and correlate beetwen CD10 expression the expression with breast carcinoma recurrence and to investigate relation of CD10 expression in primary and recurrent breast carcinoma to the grade of histologic and nuclear differentiation of tumour, expression of estrogen, progesterone and HER2 receptors.

PATIENTS AND METHODS

Retrospective-prospective study analyzed 64 patients with primary diagnosed invasive (ductal) breast carcinoma of no special type („NST"), stage T1/T2NO who underwent the complete therapy treatment in period from 2004 to 2008 years.

The patients had the shortest five years overall survival (OS). They were divided into two groups, experimental and control group.

All analyzed details (age of patients; TNM classification; histologic and nuclear grade; status of hormone receptors and status Her2 protein) were obtained by retrospective analysis from pathologic reports of Pathology department of Polyclinic for laboratory diagnostics in period from 2004 to 2008 year, medical documentation of daily hospital at Clinic for oncology, hematology and radiotherapy and Clinic for plastic and maxillofacial surgery of Public Health Institution University Clinical Center Tuzla.Two groups patients were separated consecutively each with 32 patients of stage T1/T2NO invasive NST breast carcinoma, with and without disease recurrence. The age was defined in all the patients at time of primary diagnosed breast carcinoma and at time of the disease recurrence, then the grade of histologic and nuclear differentiation (grade I, II, III and NG 1, 2, 3), status of hormone receptors using Quick score and value of HER2/neu receptors („0" and „+1"are negative,"+2" is limit value done by additional CISH analysis, and „+3"positive).

On formalin fixed in paraffin embedded samples of tumour tissue of all the patients immunohistochemical analysis expression of CD10 (primary antibody, clone 56C6, Dako, Glostrup, Denmark) was made by method of three-stage immunoperoxidase with streptavidin. For visualization expression CD10 diamino-benzidine hydrochloride was used. Immunohistochemical colouring CD10 was marked negative if no stromal colouring, slight if diffuse poor colouring is present or local intensive colouring less than 30% of stromal cells and/or extracellular matrix, and intensive if strong colouring is present over 30% of stromal cells and/or extracellular matrix.

In statistical data processing, numerical data are given by measure of central tendency and relevant measures of dispersion. For testing between two independent groups, T-test or Mann-Whitney-test were used if discrepancy was noticed in distribution beinning checked by Kolmogorov-Smirnov test. Characteristics of patients between two groups were compared by X-test, Fisher test, respectively Mann-Whitney test for not parametrical data.

Independent predictors of the disease course being included in model were obtained by logistic regression analysis. Model is shown graphically so that predictive value of disease outcome can be determined. Predictive precision of model was tested by analysis of area under the curve-AUC, sensitivity and specificity of model was defined. With curves ROC (Receiver Operator Characteristic), the changes in sensitivity were described and specifities for individual examination with numerous points of limit value.

For statistical significance of p value the usual level of significance was selected where $p<0.05$. All data were analyzed using SPSS statistical programme (Version 21 SPSS Inc. Chicago), NedCalc v 12 and Orange.

RESULTS

Total 64 patients were processed. Average age in whole sample was 53.31±0.1. The youngest patient was 35 years old and the oldest one 78 years. In group without recurrence the youngest patient was 40 years old, the oldest one 78 years, but in group with recurrence of carcinoma disease the youngest patient was 35 years old and the oldest one 69 years. Descriptive value of all analyzed parameters is given in Table 1.

Table 1. Descriptive value of analyzed parameters in total sample

Parameter	Value			
	Total sample	Without recurrence	With recurrence	P
Age	53,3±10.1	55.2±10.7	51.4±9.3	p=0.136
T (mm)	22,7±10	21.3±9.1	24.1±10.9	p=0.260
N0 (number)	9,7±3.9	9.1±4	10.4±3.8	p-=0.208
gr I/II	45	24	21	p=0.341
gr III	19	8	11	p=0.339
NG 1/2	48	29	19	p=0.000
NG 3	16	3	13	p=0.0037
gr III/NG 3	10	2	8	p=0.120
Er+ (pos)	55	30	25	p-=0.00
Er– (neg)	9	2	7	p=0.150
Pr+ (pos)	52	29	23	p=0.000
Pr – (neg)	12	3	9	p=0,109
HER2/neu– (neg)	54	31	23	p=0.000
HER2/neu+ (pos)	10	1	9	p=0.0468
CD 10 + (pos)	29	9	20	p-0.012
CD10 – (neg)	35	23	12	p=0.00

(mm-milimeter; N–number lymph nodes; gr-grade of histologic diferentiation; NG= nuclear grade; Er= estrogen receptor; Pr= progesteron receptor; pos.= positve; neg.= negative)

First it was done the analysis of basic parameters essential for diagnostic-prognostic-predictive estimation of the status of analyzed breast carcinoma.

Average age in group without disease recurrence was 55.2±10.7 years and in group with disease recurrence was 51.4±9.3 years (p=0.136) (Figure 1).

According to obtained results there is no statistically important difference in age of patients without and with disease recurrence. Tumour size in total sample was within the range of 3 to 50 mm, in experimental group 10-50 mm and control 3-45 mm. Average tumor size of total sample was 22.7±10. In experimental group is 24.1±10.9, and control group is 21.3±9.1. Important difference was not observed in size of primary node in examined groups (21.3±9.1 vs 24.1±10.9; p=0.6) (Figure 2).

Though the removed lymph nodes were not affected with tumour deposits, numerical participation of removed lymph nodes was analyzed in both groups and compared. There was no significant difference in number of removed lymph nodes of patients in both groups (9.1±4 vs 10.4±3.8; p=0.208) (Figure 3).

In both groups it was analyzed the incidence of high grade of histologic and nuclear differentiation and their importance in disease recurrence.

Table 2. Comparative value of grade and nuclear grade of examined groups

Parameter	Without recurrence	With recurrence	p
Grade*	2(2:2)	2(2:3)	0,339
Nuclear grade*	2(2:2)	2(2:3)	0,0037

Legend: *Median (95% CI)

With this statistical method it was not observed significant difference of histological grade between examined groups (p=0.339) but there is significant difference in nuclear grade that statistically is more present in group with carcinoma recurrence (p=0.0037) (Table 2).In total sample, the positive expression of estrogen receptors was found in 55/64 patients. In experimental group, 30 tumors of 32 patients were positive to estrogen, but in control group tumors, in 25/32 patients. Obtained results show that there is no statistically significant difference (Chi2=2,07; p=0.15). Positive expression of progesterone receptors is quite high in total sample and in both groups of patients. There were found 52/64 tumors with positive expression in total sample. In experimental group tumors of 29/32 patients, but in control group tumors of 23/32 patients were positive to progesterone receptors, without statistically significant difference (Chi2=2.56; p=0.109).

Positive expression of HER-2 receptors in total sample was found in of 10 patients, respectively 18.5% tumours. Positivity to HER-2 receptors is much bigger in group with recurrence in relation to group without recurrence (9/32 vs. 1/32; Chi2=3.95; p=0.0468). Though near to limit value, there is significant difference of positive expression in group with carcinoma recurrence.

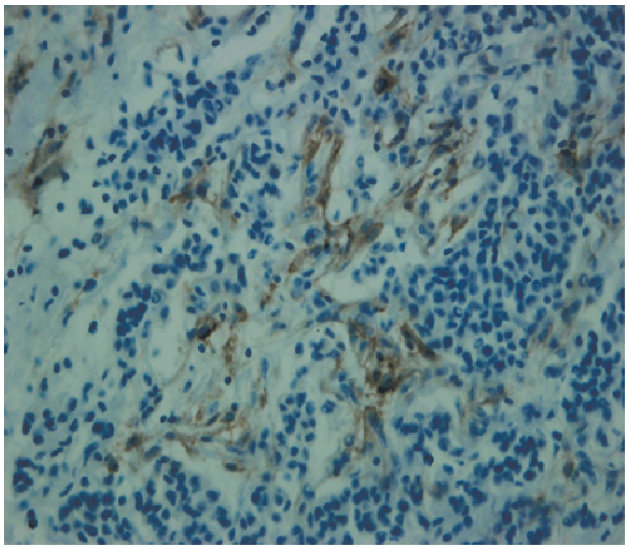

Figure 1. Slight positivness of tumor stroma and fibroblast, CD10 (IHH, 400x)

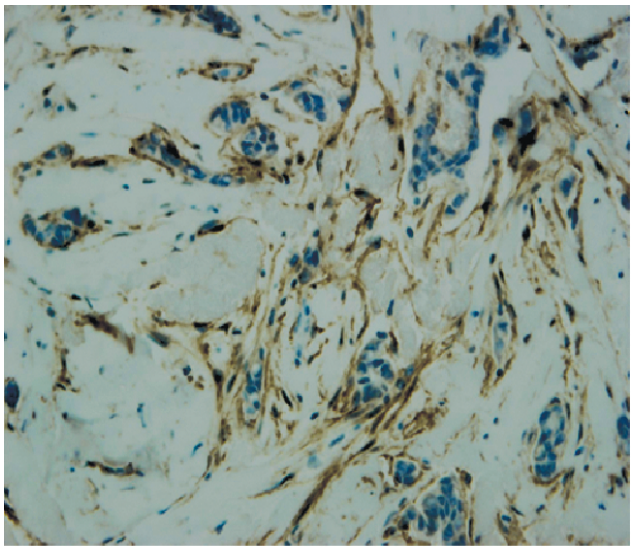

Figure 1. Distinct positivity of fibroblast and tumour stroma, CD10 (IHH, 400x)

The results of CD10 protein expression are given in Table 3., and statistically processed and compared in both groups of patients. It was found considerably more frequent positiveness in group with recurrence in relation with group without breast carcinoma recurrence (20/32 vs. 12/32; Chi2=6.305; p=0.012).

Table 3. Breakdown of frequency of CD 10 expression in tumours of both groups of patients

			Group		
			Without recurrence	With recurrence	Ukupno
CD10	Negative	N	23	12	35
		%	71,87%	37,5 %	54,68 %
	Positive	N	9	20	29
		%	28,13%	62,5%	45,32%

Table 4. Correlation of positive CD10 protein expression with other morphologic and immunohistochemical parameters of patients tumours in both groups

		Without recurrence (n=9)	With recurrence (n=20)	p
	I/II N (%)	6 (66.66)	12 (60.0)	
Gr				
	III N (%)	3 (33.33)	8 (40.0)	p=0.943
	1/2 N (%)	7 (77.77)	12 (60.0)	
NG				
	3N (%)	2 (22.22)	8 (40.0)	p=0.411
	Pos.N (%)	7 (77.77)	16 (80.0)	
Er				
	Neg.N (%)	2 (22.22)	4 (20.0)	p=0.719
	Pos.N (%)	7 (77.77)	15 (75.0)	
Pr				
	Neg.N (%)	2 (22.22)	5 (25.0)	p=0.758
	Neg.N (%)	9 (100.0)	16 (80.0)	
HER2				
	Pos. N (%)	0 (00,00)	4 (20.0)	p=0.28

Within the investigation we analyzed the possibility of existing the correlation of CD10 protein expression with other immunohistochemical parameters. Obtained results and correlation are given in Table 4.As seen in this table the correlation of CD 10 oncoprotein expression has not been found with any other variable.

DISCUSSION

Every or almost every study available in literature, indicates the age structure of women with verified breast carcinoma and impact of age to course and outcome of disease and existing the correlation with morphologic characteristics of carcinoma [8,9]. The younger population under 35 years of age and the older one over 75 years is the most jeopardized by these authors.

According to obtained results the factor of significance is (p=0.136), in our stady is no statistically significant difference in age of patients without and with recurrence of breast carcinoma.

According to reports of WHO and available studies similar to this one, carcinoma recurrences occur within the first several years. The disease recurrence was registered in 26% in early period (to 3 years). Rate of local recurrences was from 9.6% to 13.2%. Rate of five years and ten years survival is also connected with the age of patients. For the younger than 50 it was 92.3% respectively 83.9%, in older 94.4% respectively 87.6% [2, 10, 11,, 12, 13, 14].

In our patients-median time up to the recurrence was 4 years. The shortest time without disease was 0 (0.5) years and the longest time were 9 years. Average period without recurrence is 4.53 years. The shortest total survival was 3 years, the longest 12 years, average total survival 8.71 years. Death due to breast carcinoma resulted in 4 patients. Period without disease was 0 to 3 years (average 1.5 years), and total survival 3 to 11 years (average 5.25 years).

Searching out the early non-invasive carcinoma till the eighties in last century was unusual; today such carcinomas in developed countries are presented with 25-26% [12, 15]. Even among these non-invasive carcinomas the recurrence was registered in 5.3% from which 50% in invasive form [6]. Tumour size of the patients in total sample was 22.7±10 mm (3-50mm), in group with recurrence 21.3±9.1 mm and without recurrence 24.1±10.9 mm having no statistically significant difference.

Histologic and nuclear differentiation is the indicators of tumor cell maturity and their ability to produce tumour again. Most authors of the noted studies indicate the data that cancers with good differentiated histologic status is recurrent in 18-23% cases, and with good differentiated nuclear status only in 3-9% cases. Moderate and low differentiated cell status

is recurrent in 28-33%, and nuclear 20-28% of the cases [16, 17, 18]. In our study, only one patient had tumour with good differentiated histologic and nucleus status. In our total sample, 19/64 tumours were the low differentiated histologic grade, in group without recurrence were 8, with recurrence 11 (p=0.339). In total sample there were 16 tumours with cells of low differentiated nuclear grade, in patients without recurrence 3, with recurrence 13 (p=0.0037). By statistic method the significant difference of histologic grade was not observed in examined groups (p=0.339), but there is considerable difference in presence of low differentiated nuclear grade, that statistically is more presented in group with carcinoma recurrence (p=0.0037).

Estrogen receptors (Er) and progesterone receptors (Pr) are considered independent prognostic factors. Positive hormone receptors are the sign of favorable course of disease and higher rate of survival in relation to the patients with negative hormone receptors. Total survival Er+/Pr+ cases are to 83%, but with double negative receptors about 69% of cases [14, 19]. It was observed that during antihormone therapy (tamoxifen or aromatase inhibitors) the recurrence is during the first 2.5 to 5 years from 28.5% cases even to 40% cases [20, 21]. Occurrence of carcinoma is frequent in contralateral breast while taking tamoxifen in premenopause patients. Such recurrent tumours may change positive status of expression of hormone receptors to negative [14, 22]. In our study the positive expression Er was found in 30/32 in control and 25/32 in examined group (Chi2=2.07; p=0.15). For Pr 29/32 in control and 23/32 in examined group (Chi2=2.56; p=0.109). The results did not show statistical significance for any parameter.

Since 1981 when discovered, HER-2/neu receptors have very important role in diagnostic, therapeutic, predictive and prognostic meaning. Particularly in the last decade many efforts have been made to enlighten the role of HER2 receptors. Carcinomas with positive HER2 receptors are more aggressive in relation to carcinomas with negative HER2 receptors. HER2 positivity is predictors of poor prognosis, increased risk of recurrence, and it means the reduced free interval without disease and total survival. These receptors are target to monoclonal antibodies trastuzumab and double (EGFR1 and HER2) tyrosin-kinase inhibitor lapatinib [23, 24]. The results of analyses of many authors show that the positive expression of this oncoprotein occurs in 7.5% to 25% [14, 25, 26, 27]. From total 64 patients, positive expression of HER2/neu was found in tumours of 10 patients (18.5% cases). Positiveness to HER-2/neu receptors is considerably bigger in group with recurrence in relation to the group without recurrence (9/32 vs. 1/32; Chi2=3.95; p=0.0468). It is evident that the obtained results are near the limit value, there is statistically important difference of positive expression in group with carcinoma recurrence.

As the resistance to tamoxifen of hormone dependent carcinomas was observed, the results also were given pointing at disease recurrence after or during the therapy with monoclonal blockators of HER2 receptors that is characterized with resistance to trastuzumab. This is explained by existence of more varieties of branching HER2 receptors to cell membrane. We know the branching p95HER2/neu, sensitive to tyrosin-kinase. This receptor instead to trastuzumab to which it has developed resistance or has been constantly resistant, reacts good to therapy with lapatinib or other related medicament [19,27,28].

Because of this resistance to specific therapy, there is a need for further research the expression of other proteins and possible correlation with the occurrence of relapse disease. In tissue of healthy breast, expression CD10 is present in all period of growing and development of breast in puberty, secreted by myoepithelial cells that are an external sheath of luminal epithelial cells. It can also be found during the proliferation or apocrine metaplasia of epithelial cells as well as in the content of some cystic formations coated with apocrine epithelium. To such epithelium it is usually given higher risk of the breast carcinoma. Iwaya et al. [29] mentioned that sometimes was observed CD10 expression in cases with invasive ductal breast carcinoma, but there was not any analysis done of clinical importance and his analysis is the first one of that kind. Ten years later some authors stated that in previous period no attention was paid to the importance of CD10 expression in breast carcinoma [30, 31, 32], therefore there were no so much studies presented in available literature. In several studies the statement was given that strong CD10 expression is connected with the poor prognosis and reduced rate of specific survival [33]. Therefore the results of their studies are contradictory. By some authors, the decline of CD10 expression in non-invasive intraductal carcinoma is associated with the progression of disease, inversion of non-invasive into invasive form and poor prognosis [34]. By other authors, positive CD10 expression is connected with negative prognostic and predictive factors, shortening the time without recurrence and total time of survival in general. According to the first results published by Iwaya et al. [29], positive CD10 expression was found in 18% connected with high histologic grade, absence of hormone receptors and shortened disease free survival (DFS). Similar results were published by other authors but 5 and 10 years after Iwaya. In our study we found positive CD10 expression in tumours of 29 patients. In patients from the group without carcinoma recurrence 9 had positive CD10 expression, and from group with recurrence even 20 patients. By comparative analysis of CD10 expression, more frequently positivity was found in group with recurrence in relation to the group without breast carcinoma recurrence (20/32 vs. 12/32; Chi2=6,305; p=0.012). We correlated then CD10 expression with other parameters and did not find correlation with any parameter that is usually determined.

Such result initiated the requirement of doing univariant and multivariant model of analysis of all the variables as predictors in order to define their prognostic security. In univariant model, nuclear grade and CD10 only demonstrate the significance with

percentage of precise classification from 62.5 to 64.1% while the other predictors are unreliable prognostic factors. In multivariant analysis, in logistic regression model, HER2/neu, CD10, age and T stage are important predictors with level of precise classification from 71.87% and level of significance in total model of (p=0.0001). With this analysis 4 variables were determined on base of which with high sensitivity can be determined the percentage possibility of disease recurrence. These results can be helpful for planning the adequate therapy. So it would be prevented the mistake of administrating an insufficient doses or the ways of treatment and causing the disease recurrence, or giving higher doses that would needlessly be more toxic for the patients.

CONCLUSION

Based on the results obtained it is evident that from the analyzed parameters the high nuclear grade, positive expression of HER2/neu receptors and positive CD 10 protein expression have statistically significant correlation with breast carcinoma recurrence. CD 10 is predictor of clinical course and outcome of breast carcinoma independently on the grade of histologic and nuclear differentiation, status of hormone receptors and expression of HER2/neu receptors, though being in correlation with high grade of nuclear differentiation and expression of HER2/neu receptors.

CD 10 is an independent prognostic and possibly predictive factor for the course and outcome of breast carcinoma, being also the possible target of specific therapy for the purpose of improving the results and outcome of the disease.

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