HER-2/neu (c-erbB-2) Expression Assessment in Breast Cancer

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Abstract

Objective: *Our study attempts to determine the prognostic value of the qualitative measurement of the c-erbB-2 in a group of patients with breast cancer.*
Method: *In a series of 41 patients with breast cancer we analyzed clinical and pathological variables, menopausal status, tumor size, number of affected nodes, type and histology grade and molecular variables like estrogen and progesterone receptors.*
Results: *In the multivariate analysis, however, only the tumor size, number of affected ganglia, the p185 and the ER remained associated with the clinical progression of the disease.*
Conclusions: *c-erbB-2 overexpression is correlated with axillary positive nodes, less differentiated tumor phenotypes and reverse proportional correlated with hormonal receptors expression, reflecting an aggressive tumoral phenotype with reduced sensitivity to cellular control mechanisms and increasing resistance to chemotherapy or hormonotherapy.*
Keywords: *tumor markers, breast cancer, predictive factors, c-erbB-2*

Introduction

The tumor growth, as reflected by tumor size and cellular proliferation measurements, has an important prognostic value. The growing factors and their receptors represent valuable candidates to prognostic markers[1,2,3,4]. HER-2/neu showed to be of a particular interest; coding a trans-membrane glycoprotein of 185 kD, representing an extended homology with EGFR and is a GF potential receptor[5].

The amplification of c-erbB-2 gene is considered an unfavorable prognostic factor. It is associated with overexpression of p185 protein (immuno-histochemically marked out), this overexpression being correlated with decreased disease-free survival and global survival and with limited response to hormone-therapy and chemotherapy[6].

The aim of the survey was to identify the c-erbB-2 molecule expression and setting some relations between its expression and other markers.

Materials and methods

The surveyed lot was made up of 41 patients diagnosed with mammary neoplasm and surgically treated in "Cuza-Voda" Obstetrics-Gynecology Clinical Hospital of Iasi.

The aim of the immuno-histochemical survey was to identify the c-erbB-2 molecule on section at paraffin by a three-step technique.

The coloring pattern in case of c-erbB-2 is a membrane-targeted one corresponding to the trans-membrane location of p185 glycoprotein. There were considered as positive the tumors whose cells showed membrane coloring in a percentage exceeding 10%. The coloring intensity was subjectively estimated and marked by + for poor marking, ++ for moderate marking, +++ for strong marking. The results analysis considered positivity versus negativity of the c-erbB-2 expression.

The statistical analysis was based on Chi2 statistical test for comparing the results and also for revealing possible relations between HER/neu expression and histological and hormonal characteristics of corresponding tumors. Statistical tests were considered as positive beginning with the value $p<0.05$.

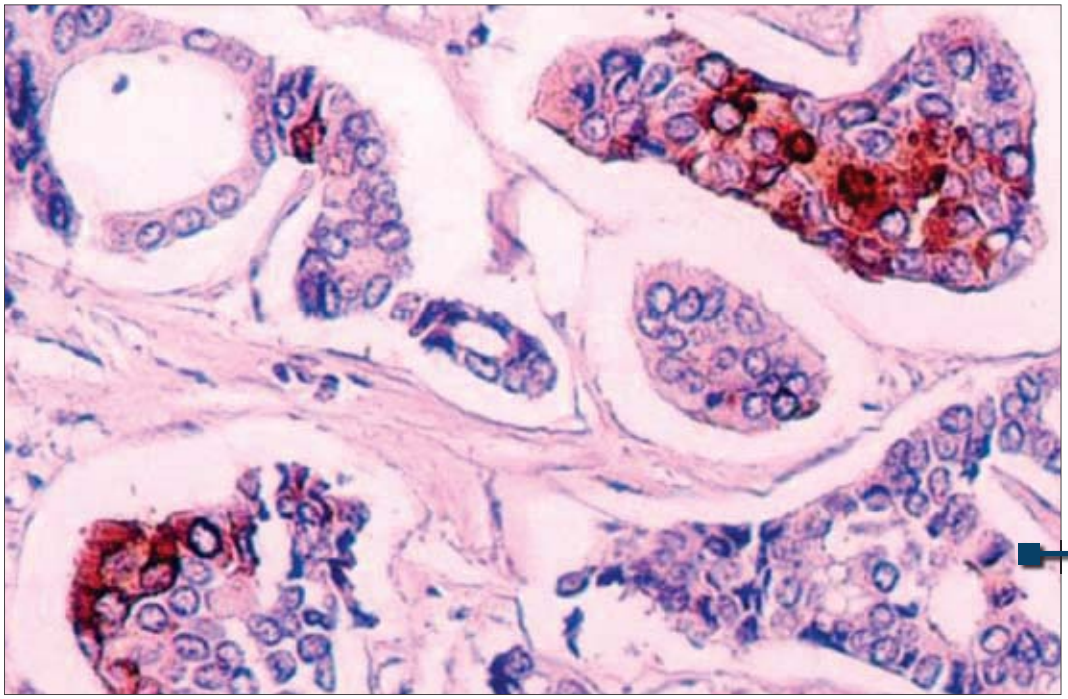

Image A. c-erbB-2+ invasive ductal carcinoma. (Tumor Immunology Laboratory Collection of Iasi)

Results

38 of the investigated tumors were positive for c-erbB-2.

The carried out survey shows that the c-erbB-2 oncogene expression does not seem to correlate with patient age, although a coloring positivity for HER was suggested, lower for pre-menopause patients as compared to post-menopause ones.

It seems that the tumor volume influences the oncogene expression, the molecule positivity being distributed as follows: all tumors sized less than 2 cm expressed c-erbB-2; for tumors sized 2 to 5 cm the difference between the number of those expressing c-erbB-2 and the number of those not expressing this gene was significant.

The oncogene overexpression is present in 23 cases with positive axillary ganglions, while for the cases with negative ganglions the oncogene overexpression was only present in 15 cases. The association between c-erbB-2 overexpression and positive axillary ganglions, statistical significant ($p<0.05$) represents a feature suggesting a relation between HER2/neu overexpression and the presence of ganglia metastasis.

Table 1

Correlation coefficient between surveyed parameters

M/m	T	N	Elston-Ellis	Fisher	ISVL	ER	PR	c-erbB-2
1								
0.010235	1							
-0.16236	0.198992	1						
-0.21484	0.442392	0.270659	1					
-0.07776	-0.00926	0.20581	0.197287	1				
-0.14791	0.092334	0.466854	0.258095	0.662889	1			
-0.16585	0.214936	0.771443	0.267568	0.358279	0.421935	1		
0.021627	0.289464	0.315842	-0.15962	-0.16158	0.04236	0.01529	1	
0.13478	0.070128	-0.1273	-0.0358	-0.22366	-0.18308	-0.1785	0.049367	1

The number of invaded ganglions was larger in cases with c-erbB-2 overexpression than in those with negative immuno-histochemical tests. The latter were ER+ and PgR+ more frequent than the cases with c-erbB-2 expression.

The histological type correlates with oncogene expression. The relation between invasive ductal carcinoma and the expression gene was significant. Out of a total of 32, 30 have expressed c-erbB-2. In other histological types, the presence or absence of c-erbB-2 expression is quite similar.

All ER- and PR- tumors expressed c-erbB-2. This shows that HER2/neu is a marker reflecting decreased cellular differentiation, an aggressive tumor phenotype with reduced sensitivity to cellular control mechanisms. Knowing the c-erbB-2 status can be useful in selecting the therapy as there is clear evidence that c-erbB-2 positive tumors have lower response rates to hormone therapy[8,9].

Discussion

C-erbB-2 oncogene amplification appears in both in situ and invasive lesions, which translates its importance in various stages of tumor development[10,11].

The reverse-proportional relation of oncogene amplification and hormone receptors expression in multiple lesions suggests that losing hormone receptor expression is part of the phenomena occurring early in the malignant transformation period, as well as oncogenes amplification[12].

The survey showed a significant correlation between the c-erbB-2 amplification and the presence of the ganglion metastases, suggesting a possible implication of p185 protein in the invasion process and in the metastasing process.

The gene amplification was identified in 20-30% of invasive carcinomas[5].

Although not consistent, a correlation was noted between gene amplification, aggressive elements and reserved prognostic.

C-erbB-2 overexpression is deemed by most authors as an independent predictor for shortening the disease-free and overall survival times[13], although some authors never mentioned this

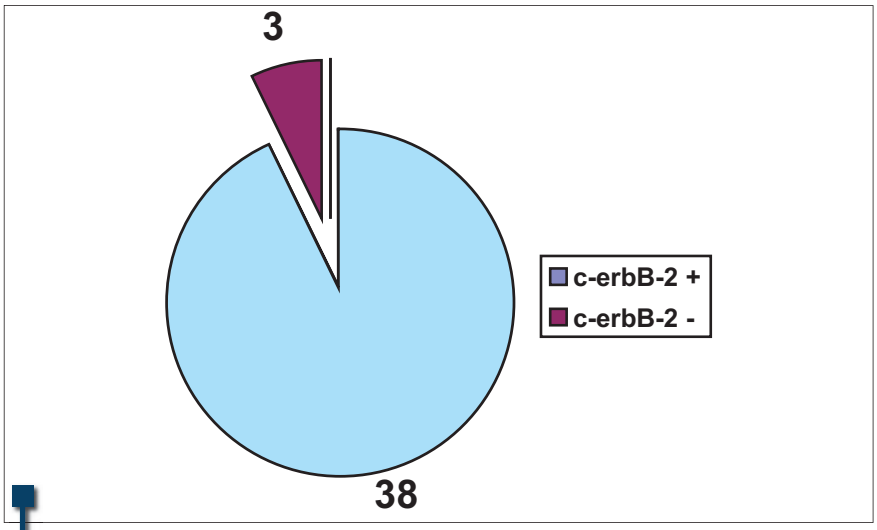

Figure 1. c-erbB-2 expression diagram

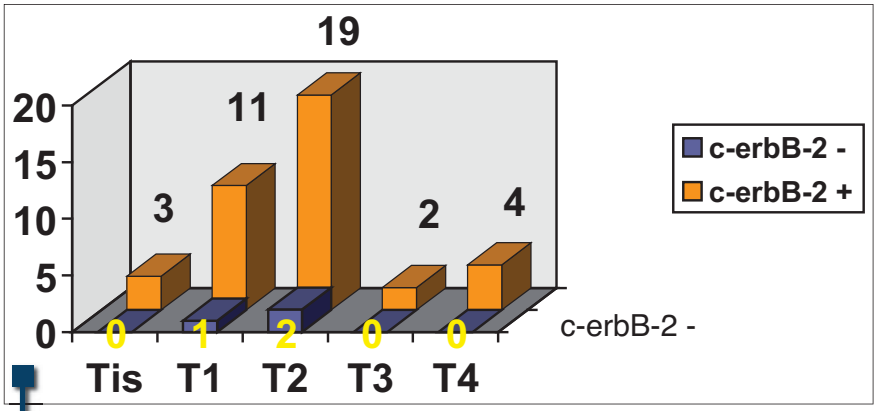

Figure 2. Relation between c-erbB-2 amplification and tumor volume

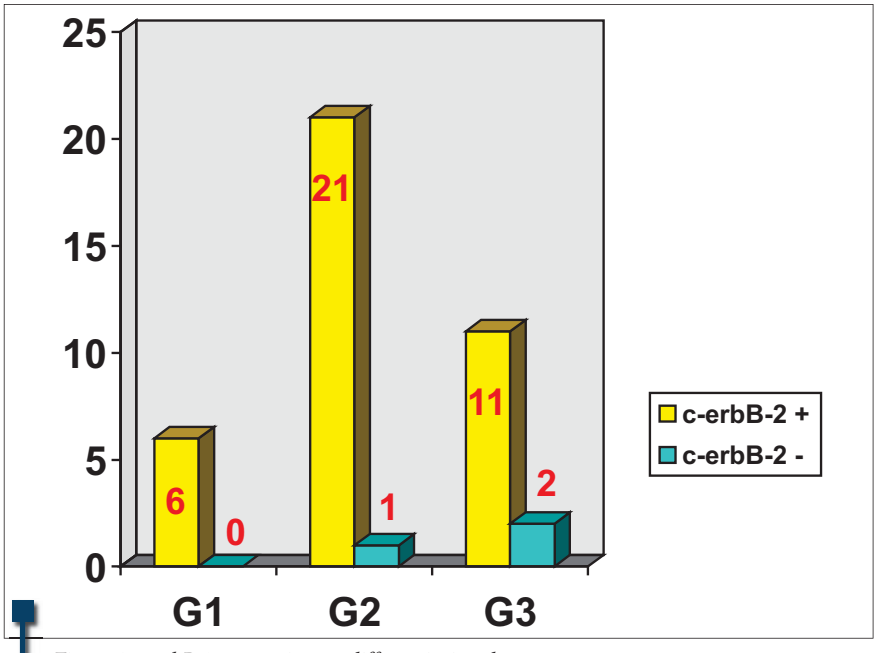

Figure 3. c-erbB-2 expression vs. differentiation degree

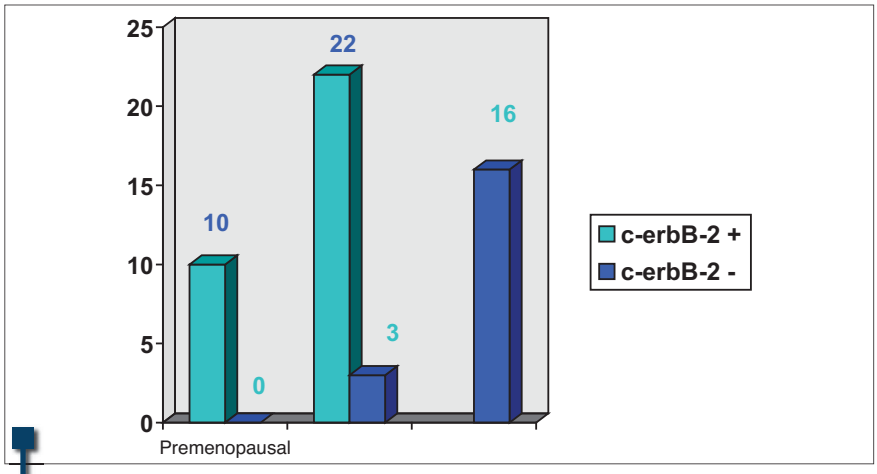

Figure 4. Relation between HER2/neu expression and menopausal status

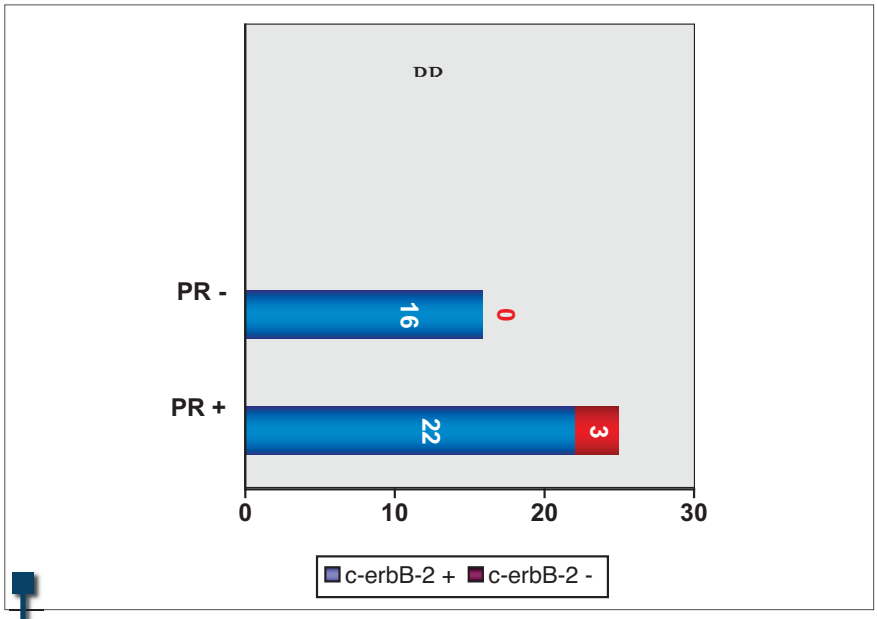

Figure 5. HER2/neu amplification in relation to PR

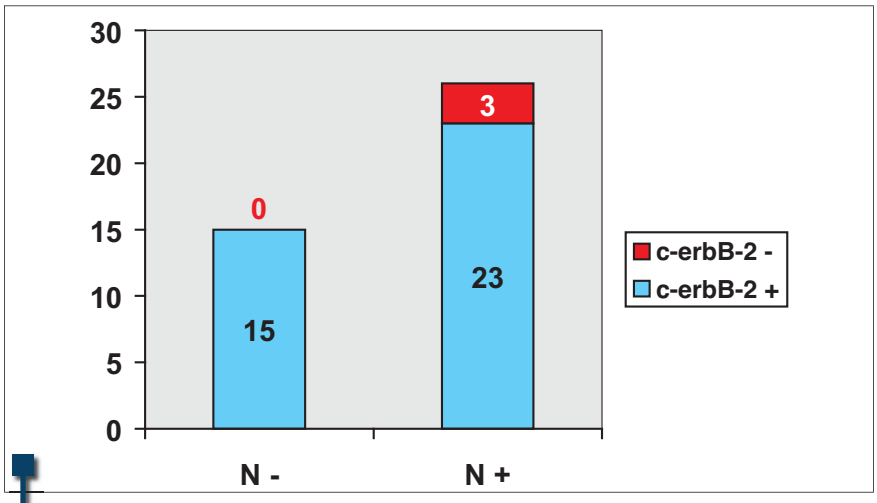

Figure 6. Relation between c-erbB-2 amplification and ganglion status

or only noted it for positive axillary ganglions.

C-erbB-2 amplification and overexpression are associated with aggressive forms of breast cancer, so surprisingly appearing detection by immune histochemistry in ductal carcinoma in situ[14].

Herceptin is a recombined monoclonal antibody related to the transmembrane receptor of HER-2/neu growth factor and is one of the successful examples of cancer therapies. However, it was noted that significant percentages of patients receiving Herceptin as first line therapy did not show a positive response, not even for highly positive tumors for HER. The explanation could be offered by the different expression of HER at tumor and metastases level[3,15,16].

Conclusions

It seems that tumor volume influences the oncogene expression, the molecule positivity being distributed as follows: all tumors sized less than 2 cm expressed c-erbB-2; for tumors sized 2 to 5 cm the difference between the numbers of those expressing c-erbB-2 and the number of those not expressing this gene was significant.

The histological type correlates to oncogene expression. The relation between invasive ductal carcinoma and its gene expression is significant, suggesting the relation between oncogene and cellular differentiation, as a measure of the invasive character of the tumor. In other histological types, the presence or absence of c-erbB-2 expression is approximately similar.

The oncogene overexpression was present in 80% of the cases with positive axillary ganglions, while for negative ganglions the oncogene expression was only present in 10%. The statistically significant ($p<0.05$) association between c-erbB-2 overexpression and positive axillary ganglions suggests a relation between HER2/neu overexpression and the presence of ganglion metastases.

The number of invaded ganglions was higher in c-erbB-2 overexpression cases than in those with negative immune histochemical tests. The latter were ER+ and PgR+ more frequent than the cases with c-erbB-2 expression.

We can consider that the HER2/neu oncogene amplification and the p185

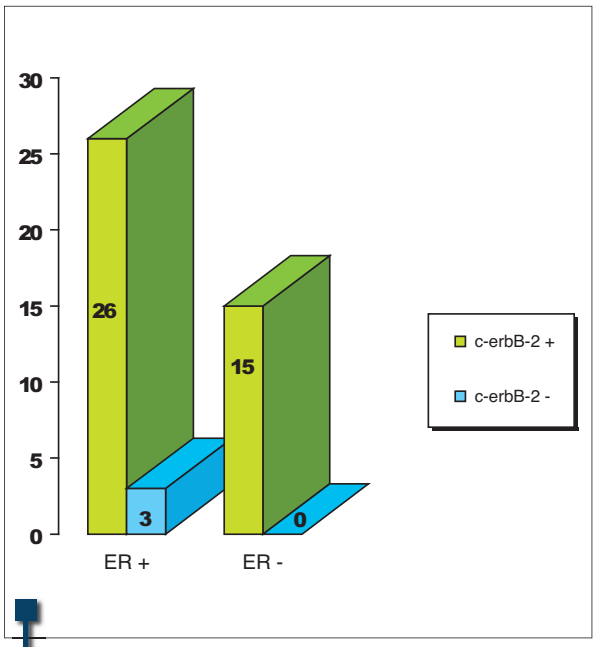

Figure 7. HER2/neu amplification in relation to ER

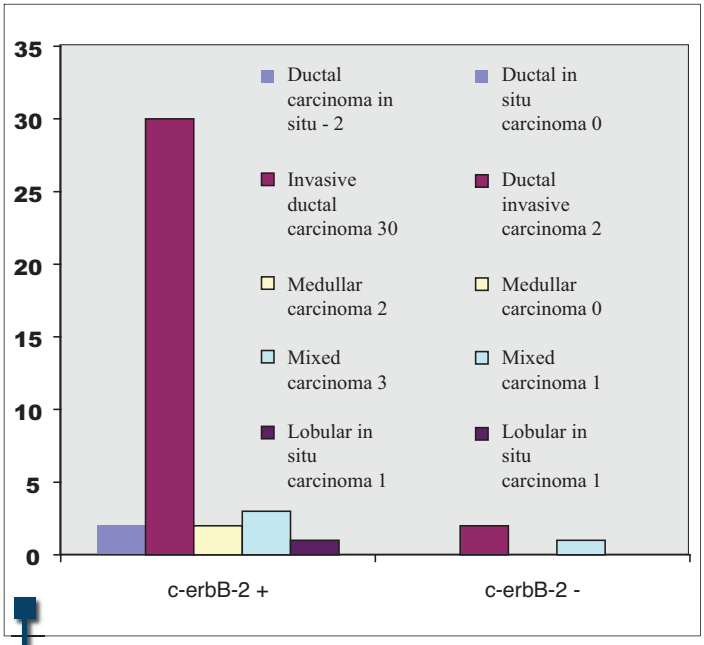

Figure 8. c-erbB-2 expression depends on tumor histological type

protein overexpression characterize the less differentiated tumor phenotype. Therefore, this marker is associated with more aggressive tumors, with a difficult to control behavior, being considered a reserved prognostic factor, associated with an increased risk of invasion and metastasing.

Another relevant feature of this survey is the reverse proportional correlation between oncogene amplification and hormonal receptors expression. This supports the conclusion that HER2/neu is a marker reflecting decreased cellular differentiation, an aggressive tumor phenotype with reduced sensitivity to cellular control mechanisms and an increased resistance to chemotherapy or hormone therapy.

Knowing the c-erbB-2 status can be useful in selecting the therapy as there is clear evidence that positive c-erbB-2 tumors have lower response rates to hormone therapy[8,9]. ■

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