

Interaction between HER-2 and Hormone Receptors in Breast Cancer

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Abstract

Introduction: Breast cancer is the most common malignancy with more than one million new cases diagnosed annually all around the world. Its growth is mostly regulated by steroid hormones such as estrogen and peptide growth factors in interaction with epidermal growth factor 1 and 2.

Methods and materials: In this study, 237 patients who had consulted the Oncology Clinic of Tabriz University of Medical Sciences with pathologic diagnosis of breast cancer (from 2003 to 2010) were involved. Data was extracted from medical record.

Results: From the total of 237 patients, 50.6% were ER⁺, 48.9% were PR⁺ and 37.1% were HER-2⁺. The greatest percentage of HER-2 positivity (51.6%) was detected in the age group of patients over 60 and the least in the group aged 31 to 40 yrs. The greatest percentage of HR⁺ (71%) patients were also over 60 and the least (50%) were less than 30. 35.5% of patients in pre- menstrual period were HER-2⁺. HR was positive in 64% of LN⁺ patients; HER- 2 and HR were positive in 35.4% and 65.4% while in LN⁻ patients they were positive in 39% and 61.9% of cases, respectively.

Conclusion: Acquired data showed reverse relation between the expression of epidermal growth factor II and hormone receptors in breast cancer. 40-55% of cases with epidermal growth factor expression lacked hormone receptors. Co-existence of hormone receptors and HER-2 expression in breast cancer are considered as important prognostic factors.

Keywords: Breast Cancer, HER-2, Hormone Receptors

Introduction

Being the most common malignancy in women, breast cancer is the definite diagnosis in more than a million new cases every year. Its progression is mostly regulated by steroid hormones including estrogen and peptide growth factors showing an interaction with epidermal growth factor I and II.(1) Hormone receptors are barely detectable in normal breast tissue while high levels have been reported in two thirds of cancer cases. Documents state that there is a reverse relation between epidermal growth factor II and hormone receptors detected in sample tissue.(2)

Considering steroids as leading regulators of disease progression, ER and PR concentrations are measured to predict prognosis and benefits of anti-

hormone therapy.(3) PR expression is depended on estrogen so that most PR positive carcinomas are also ER positive.(4, 5)

Postmenopausal cases of breast cancer show higher levels of ER and PR in comparison with premenopausal ones, while the latter show lower ER concentrations.(6) Breast cancer seems to be more malignant in young women compared to older ones; this might be due to fewer ER positive tumors reported in the youth.(7)

Paper and research work on HER-2 and breast cancer hormone receptors have been conducted worldwide, while the present study tries to evaluate the precise association between HER-2 and hormone receptors as prognostic factors to determine its dependent or independent role. As an

innovative study in our local area, we planned to conduct the study evaluating patients in Tabriz Medical University, Oncology Clinic.

Material and methods

261 patients were included in the study, 24 being omitted due to incomplete lab profile. 237 patients were evaluated considering age, sex, menopausal state, ER and PR concentrations, HER-2 status, disease stage, and grade and tumor microscopy. Involved patients were diagnosed through pathologic studies performed by experts.

ER, PR and HER-2 status measured by IHC method for 237 patients were extracted from their medical recordings. For 198 cases measurements were performed in Imam Khomeini Hospital IHC center, where positive cut-off point for ER and PR concentration was considered 10% (more than 10% of cells being stained). The other 39 cases were evaluated by total scoring system (PS+IS). $TS > 2$ was considered positive while $TS \leq 2$ was negative. HER-2 level was put into a grading scale in which 2+ and 3+ scores were considered positive while 1+ and 0 scores were negative.

Acquired data is showed in the face of Mean \pm SD, frequency and percentage. SPSS 16 was the software used to analyze the data. Quantitative and qualitative variables were analyzed in Student t-test and Qi-square test (the Exact Fischer test as needed), respectively. Results were considered significant if $P < 0.05$.

Results

Age and gender description: From 237 cases, 1(0.4%) was male and 236(99.6%) were female. Minimum and maximum ages were 26 and 78 years. The mean age was 47.2 and the median was 46 years.

Lymph node involvement: From 237 cases, 105(44.3%) had no LN involvement while 132(55.7%) were LN positive from which 49(20.7%) had < 4 and 83 (35%) had ≥ 4 involved lymph nodes.

Metastasis: Staging was performed in all cases; 59 (24.4%) patients were in stage I, 142 (60%) in stage II, 11 (4.6%) in stage III a, 11 (4.6%) in stage III b and 14 (5.9%) were in stage IV. Highest frequency seen in stage II and lowest in stages III a and III b. From the sample group, 14 patients were in stage IV; metastatic locations are described in order of frequency:

8 (51%) cases of bone metastasis, 1 (7.2%) pleural metastasis, 3 (21.6%) lung besides bone involvement. The other 2 (14.2%) presented with liver metastasis only.

Hormone receptors and HER-2 status in association with lymph node involvement: From HR+ patients, 65.4% (87 cases) were LN+ (axillary nodes) and 61.9% (65 cases) were LN-. The HR status was not significantly different in the two LN+ and LN- patients ($P = 0.06$).

In the HER-2+ group, 35.4 % (47 cases) had axillary node involvement and 39 % (41 cases) were LN-. There was a significant difference ($P = 0.04$) in the HER-2 status between the LN+ and LN- groups; pointing out the fact that LN+ cases are HER-2- in most cases and vice versa; LN-patients are mostly HER-2+.

Hormone receptor status in association with HER-2 status:

HER 2 was positive in 25 % (30 cases) of ER+ patients and 49.6 % (58 cases) of ER- patients, with significant difference ($P = 0.03$). HER-2 was positive in 27.6 % (42) of HR+ and 54.1 % (46) of HR- patients, being significantly different too ($P = 0.04$).

Hormone receptors and HER-2 status in different disease stages:

From HR+ patients, 35 (59.4%) cases were in stage I, 97 (65.1%) were in stage II, 9 (81.1%) were in stage III a, 5 (45.5%) in stage III b and 6(85.7%) in stage IV. The highest and lowest frequencies are associated with stage IV and III b respectively.

In HER-2+ patients 24 (40.7%) were in stage I, 56 (37.6%) in stage II, 2 (18.2%) in stage III a, 4 (36.4%) in stage III b, and 2 (28.6%) in stage IV; Showing highest and lowest frequencies in stage I and stage IIIa.

Discussion and conclusion

Results have illustrated a reverse association between epidermal growth factor 2 and hormone receptors expression in cancerous breast tissue. Hormone receptor existence and HER-2 gene expression both are known as important prognostic factors.(2)

As mentioned before, research in western populations has shown high levels of hormone receptor in 65% of breast cancer cases (HR+). (2, 4) In our study we had 120 (50.6%) ER+ cases, 116 (48.9%) PR+ and 152 (64.1%) HR+ patients; almost close to other research work. A 55% PR

positivity has been reported in a study in Pakistan in year 2005. (5)

Considering hormone receptor etiologic prominence, it seems that breast cancer etiologic factors in our area are more like western populations and different from neighbors, though this can be the result of different measuring methodologies.

HER-2 positivity reported in a research conducted in the US is 36.5% almost close to the 88 cases (37.1%) reported HER-2+ in our study.

A significant relationship has been reported between hormone receptor positivity and HER-2 negativity in several studies. (3)

HER-2 status was also significantly different in ER+ and ER- groups ($P=0.03$) showing 25% positivity in ER+ patients (30 cases) and 49.6% positivity in ER- cases while there was no significant association between PR and HER-2 ($P=0.79$); HER-2 was positive in 27.6% of PR+ cases and 46.3% of PR- cases in contrast with the results of Pakistan research. (5)

We could find a significant relationship between HER-2 status and lymph node involvement; aforementioned, LN+ patients are mostly HER-2+ while LN- patients are mostly HER-2- similar to several other studies. (5, 6) There was no relationship between LN+ and LN- groups considering HER-2 status in contrast with Richards' study. (6)

Playing a key role in predicting prognosis and treatment plans, we suggest defining hormone receptor status in any patient diagnosed with breast cancer. We also propose further research being held

comparing prognosis between hormone receptor positive and HER-2 negative patients and vice versa.

References:

1. Lippman M, Kasper DL, Braunwald E, et al. 2005, Breast cancer In: Harrison's Principles of Internal Medicine, McGraw-Hill, New York., Vol. 1, 16th ed., PP. 516-523.
2. Vincent T, Devita J, Hellman S, et al. 2005, Cancer, Lippincott Williams and Wilkins, Philadelphia, 7th ed., PP. 1399-1478.
3. Rosai J. 2004, Rosai and Ackerman's surgical pathology, Mosby, Edinburg, Vol. 1 and 2, 9th ed., PP. 1786-1820.
4. Sahin A, Singletary SE, Valero V. 1999, Prognostic factors for invasive breast cancer, 1st ed., Springer, New York, PP. 104-105.
5. Fatima S, Faridi N, Gill S. 2005, Breast Cancer, Steroid Receptors and other prognostic indicators, J Coll phy surg pak, No. 15, PP. 230-233.
6. Richard J. 2003, Interaction between estrogen and growth factor receptors in human breast cancer, The Breast J, No. 9, PP. 361-373.
7. Li C, Daling JR, Malane KE. 2003, Incidence of invasive breast cancer by hormone receptors status from 1992 to 1998, J Clin Oncol, No. 21, PP. 28-34.