IAAOJ
INTERNATIONAL ANATOLIA ACADEMIC ONLINE JOURNAL

ÖZGÜN ARAŞTIRMA/ORIGINAL İNVESTIGATION

IAAOJ, Health Sciences, 2013,1(1),3-10

THE COMPARISON OF TRIPLE NEGATIVE AND HER 2 POSITIVE BREAST CANCER

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Abstract:

Objectives:

The aim of this study is to investigate the results of clinicopathological characterics of patients with Her 2 positive (Any ER, any PR status with Her2 +) and triple negative (ER-, PR-, Her2-) subgroups of breast cancer.

Patients and Methods:

From prospective database of 1822 patients, 133 triple negative patients and 160 Her 2 receptor positive patients' data collected retrospectively. Clinical, histopathological characteristics (tumor size, tumor receptor status, axillary node involvement, histological grade, lymphovascular invasion, necrosis, tumor type), treatment modalities and survival rates were recorded. One way ANOVA, chi square and Kaplan Meier tests were used for statistical analysis. P value of <0.05 was accepted as a significant.

Results:

When we compared the characteristics of both groups, lymphovascular invasion (p<0.001), higher grade (grade 3) (p=0.003), adjuvant chemotherapy (p<0.001) rates were significantly more in Her 2 positive subgroup. Micrometastasis at sentinel lymph node (p=0.009), local recurrence rate (p=0.032) were more significant in triple negative subgroup. Her 2 + patients tend to have more non sentinel lymph node metastasis (p<0.001). 5 years survival of Her 2 positive patients was 95.6%, triple negative patients was 92.0% (p=0.731). 5 years disease free survival rate of Her 2 patients was 85.5% and triple negative patients was 82.6% (p=0.689). Breast conserving surgery rate was more in triple negative group (p=0.008). Triple

negative group had much local recurrence than Her2 positive group, but this was not statistically significant.

Conclusion:

Tumors with TN subgroup had poorer prognosis than counterparts of Her 2 + group in this study, but this is not significant statistically. Both subgroups have poorer survival than ER+, PR+ and Her2- subgroup of breast cancer patients according to international literature.

Key Words: Breast cancer, triple negative, Her2 positive, survival, local recurrence.

TRİPLE NEGATİF VE HER2 POZİTİF MEME KANSERİNİN KARŞILAŞTIRILMASI

Özet:

Amaç:

Bu çalışmanın amacı triple negatif meme kanseri (ER-, PR-, Her2-) ile Her2 pozitif meme kanserinin (ER+/-, PR+/-, Her2+) klinkopatolojik özelliklerini karşılaştırmaktır.

Hastalar ve Yöntem:

Merkezimizde kayıtlı 1822 meme kanseri hastası içerisinden 133 triple negatif ve 160 Her 2 pozitif hastanın dosyaları incelenerek, bu hastaların histopatolojik (tümör boyutu, reseptör durumu, aksilla pozitifliği, histolojik grad, lenfovasküler invazyon varlığı, nekroz ve tümör tipi) ve klinik özellikleri, tedavi modaliteleri ve sağkalım süreleri retrospektif olarak kayıt altına alındı. One way ANOVA, ki-kare, Kaplan Meier testleri kullanılarak istatistiksel analizler yapıldı. P değeri <0.05 anlamlı olarak kabul edildi.

Sonuçlar:

Her iki grup karşılaştırıldığında Her 2 pozitif grupta lenfovasküler invazyon varlığı (p<0.001), yüksek grad (grad 3) (p=0.003), ve adjuvant kemoterapi oranı (p<0.001), triple negatif grupta ise, lokal yineleme oranı (p=0.032) ve sentinel lenf nodunda mikrometastaz oranı (p=0.009) anlamlı derecede yüksek bulundu. Her 2 pozitif hastalar da non sentinel lenf nodu pozitifliği daha yüksek idi (p<0.001). Her 2 pozitif hastaların 5 yıllık sağkalım oranları %95.6, üçlü negatif alt grubun %92.0 olarak tespit edildi. 5 yıllık hastalıksız sağkalım oranları ise, Her 2 pozitif grupta %85.5, üçlü negatif grupta %82.6 idi. Meme koruyucu cerrahi oranı triple negatif grupta daha fazla idi (p=0.008). Triple negatif grupta lokal yineleme oranı daha fazla olmakla beraber bu durum istatistiksel olarak anlamlı bulunmadı.

Tartışma:
Triple negatif grupta olan hastaların sağ kalım oranlarının Her 2 pozitif gruba göre daha kötü olduğu görüldü, ancak bu durum istatistiksel olarak anlamlı değildi. Her iki grupta uluslararası literatürdeki ER+, PR+ ve Her2- alt grup ile karşılaştırıldığında daha kötü prognoza sahip idi.

Anahtar kelimeler: Meme kanseri, triple negatif, Her2 pozitif, sağ kalım, lokal nüks

Background:
Breast cancer is the most common malignancy in women worldwide and is one of the leading causes of cancer related mortality (1). Breast cancer comprises a heterogeneous group of diseases that vary in morphology, biology, behaviour and response to therapy. Tumors apparently homogenous morphological character still vary in response to therapy and have distinct outcomes (2). Traditional pathological parameters such as tumor size, axillary lymph node involvement, histologic grade have been shown to correlate with prognosis (3,4). Therefore, molecular biology has greatly enhanced our understanding of the heterogeneity of the disease (5), but only a few molecular tumor features (hormone receptor and Her 2 status) are used in clinic to guide the choice of a systemic treatment strategy (6). Currently, breast cancer patients are managed according to algorithms based on a constellation of clinical and histopathological parameters in conjunction with estrogen receptor, progesterone receptor and Her 2 overexpression. For estrogen receptor positive patients, allocation of 5 year adjuvant endocrine treatment reduces annual breast cancer death rate approximately by 30% (7). The addition of trastuzumab to adjuvant chemotherapy has improved outcome of Her 2 positive breast cancer patients (8-10). However, for estrogen receptor (ER) negative, progesteron receptor (PR) negative and Her 2 receptor negative patients (Triple negative), only conventional chemotherapy can be used and these patients continue to carry a poor overall prognosis. Hormone receptor positive tumors account 75-80% of all cases. In contrast, Her 2 positive tumors are identified in approximately 15-20%, with around half of these coexpressing hormone receptors (11). The remaining 10-15% of breast cancer are triple negative. In this study, we aim to investigate the clinicopathological characterics and survival of Her 2 positive and triple negative subgroups of breast cancer patients.

Methods:

Between January 2000 and December 2008, at Istanbul University, Istanbul Medical Faculty, General Surgery Department, from prospective database of 1822 breast cancer patients, 133 triple negative and 160 Her 2 receptor positive subgroups were selected for this study. Patients were divided into two groups. One was triple negative group (ER-, PR- and Her2- subgroup) and the other was Her2 positive group (with either ER and PR status, Her2 positive subgroup). Patients' data collected retrospectively. Clinical, histopathological characteristics (tumor size, tumor receptor status, axillary node involvement, histological grade, lymphovascular invasion, necrosis, tumor type), treatment modalities and survival rates were recorded.

Hormone receptor status was determined by immunohistochemistry (IHC) method. Her 2 status determined by IHC, if IHC (–) the result was negative, if IHC was (+) the result was negative, if IHC was (+++) the result was positive and if IHC was (++), then FISH technique was performed and the result was determined according to FISH result.

The difference in clinicopathological characteristics of both subgroups, survival rates, local and systemic recurrences were examined. Statistical analysis was performed by using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) software. One way ANOVA, chi square were used for statistical analysis and Kaplan Meier test was used for survival analysis. P value of <0.05 was accepted as a significant.

Results:

133 ER-, PR-, Her 2 – (triple negative) (TN) and 160 Her 2 positive patients with either hormone receptor status were included in the study. The clinicopathological characteristics of both subgroups were shown at table 1.

When we compared the characteristics of both groups, lymphovascular invasion rate ($p<0.001$), higher grade (grade 3) ($p=0.003$), adjuvant chemotherapy rate ($p<0.001$) were significantly more in Her 2 positive subgroup. Micrometastsis at sentinel lymph node ($p=0.009$), local recurrence rate ($p=0.032$) were more significant in triple negative subgroup. Her 2 + patients tend to have more non sentinel lymph node metastasis ($p<0.001$). Breast conserving surgery rate was more in TN group than Her2 positive group ($p=0.008$).

Twelve patients (9.0%) at triple negative group and 5 patients (3.1%) at Her 2 positive group developed local recurrence. Mean time to develop local recurrence in TN group was 42.3 (9-23) months and in Her 2 positive group was 45.8 (2-70) months (Statistically non significant). In TN group 9 patients had tumor side recurrence, one had axillary recurrence and 2 had regional lymph node recurences. In Her 2+ group, 5 patients had tumor side recurences.

Eleven patients (8.3%) at triple negative group and 18 patients (11.3%) at Her 2 positive group had systemic recurrences. Mean time to develop systemic metastasis in TN group was 47.3 (12-108) months and in Her 2 positive group was 39.2 (14-22) months (Statistically non significant). In TN group, 2 brain, 3 lung, 4 bone metastasis detected and in Her 2 + group, 5 brain, 3 lung, 3 liver and 4 bone metastasis detected, others were developed multiple site tumor metastasis in both groups. There is no significant difference detected between local or systemic recurrence time of TN group and Her 2 positive group. Mean follow up was 33 months. At this period 4 patients at triple negative group and 2 patients at Her 2 positive group were died due to disease recurrence. 99 patients (89.2%) at triple negative group and 140 patients (90.0%) at Her 2 positive group were disease free at the end of follow up period.
5 years survival of Her 2 positive patients was 95.6%, triple negative patients was 92.0% (p=0.731). 5 years disease free survival rate of Her 2 patients was 85.5% and triple negative patients was 82.6% (p=0.689) (Table 2).

Conclusion:

In breast cancer, the three predictive markers ER, PR and Her 2 have an independent prognostic value (12). Her 2 is overexpressed 15-20% of cases (11,13-15). Its prognostic significance has been obscured by an association with other poor prognostic markers like tumor grade, S phase fraction and a negative steroid receptor status (14-17).

Triple negative breast cancer represent a subset of breast cancers with a particularly aggressive phenotype and poor clinical outcome. TN breast cancer is more likely to affect younger premenopausal women and despite being responsive to traditional chemotherapy. TN patients were thought to have much distant metastasis and less locoregional recurrence than Her2 positive subgroups. However, in this study TN subgroup had higher local recurrence rate (9.0%) than Her2 positive subgroup (3.1%). This result may be related to higher BCS rate in TN subgroup than Her2 positive group in this study. According to these results, in TN patients, we should think about more agressive local surgery.

Estrogen receptor, progesterone receptor and Her 2 receptor is of central importance in the therapeutic decision making process for patients with breast cancer. Although predicting the response to therapy, these factors may also determine the patern of relapse. The most recent Early Breast Cancer Trialist Group overview revealed that breast cancer mortality among women of similar nodal status was twice as high in the ER- as the ER+ group during the first 5-6 years. In this study, the mortality rates of TN and Her2 positive subgroups were similar,

3.0% vs 1.2% respectively. This can be explained by the spesific adjuvant treatment of Her2 positive subgroup with trastuzumab therapy and much aggressive chmeotherapy regimens in TN subgroup.

Although patients with TN tumors are supposed to have survival advantages due to lack of Her 2 overexpression, these patients lack the benefit of any routinely available targeted therapy (18). Recent studies suggest that patients with TN breast cancer have a high incidence of visceral metastasis, including brain metastasis. Because TN breast cancers have more aggressive feature and lack a therapeutic target, they have become a key topic of clinical and research interest within the oncology community. Unlike the other subtypes targeted agents specifically aimed at TN are not yet available. In our study, 5 year OS of TN patients was 92.0% and DFS was 82.6%. 11 patients (8.3%) in this group developed systemic metastasis, 2 of them had brain metastasis. This rate is not significantly more than Her 2 + group which had 18 (11.3%) systemic metastasis with 5 brain metastasis. However, tumors with TN had poorer prognosis than counterparts of Her 2 + groups in this study.

Both TN and Her2 positive subgroups had lesser survival rates and higher recurrence rates in the current study than other subgroups of breast cancer according to international English literature.

Conflict of interest: Authors have no conflict of interest.

Table 1. TN and Her2 positive patients' clinicopathological characteristics.

Factors	**Triple negative group N= 133 (%)**	**Her 2 positive group N= 160 (%)**	**p**
Mean age±SD (range) (years)	51.3±11.8 (28-90)	50.6±12.5 (23-84)	0.309
Mean tumor size±SD (range) (mm)	27.1±15.9 (0.2-80)	26.1±18.2 (0.1-110)	0.932
Lymphovascular invasion Present Absent	 57 (35) 76 (58)	 104 (65) 56 (42)	**<0.001**
Tumor type IDC Others	 98 (41) 35 (67)	 143 (59) 17 (33)	**0.001**
Surgery BCS Mastectomy	 77 (53) 56 (38)	 67 (47) 93 (62)	**0.008**
Grade 1 2 3	 8 (73) 26 (49) 99 (49)	 3 (27) 27 (51) 130 (57)	**0.003**

SLNB			**0.009**
Macrometastasis	21 (48)	23 (52)	
Micrometastasis	7 (88)	1 (12)	
Negative	55 (58)	40 (42)	
NSLNM			**<0.001**
Present	35 (30)	80 (70)	
Absent	98 (55)	80 (45)	
Adjuvant CT			**<0.001**
Yes	66 (35)	125 (65)	
No	67 (65)	35 (35)	
Mean follow up time±SD (range) (months)	35.4±23.9 (6-108)	30.3±24.7 (6-100)	0.861

Table 2. Patients' local and systemic recurrence rates and survival rates in TN and Her2 positive subgroups.

Groups	**Local recurrence (%)**	**Systemic recurrence (%)**	**Dead rate (%)**	**5 year OS**	**5 year DFS**
TN group	12 (9)	11 (8.3)	4 (3.0)	92.0	82.6
Her2 positive group	5 (3.1)	18 (11.3)	2 (1.2)	95.6	85.5
p	**0.032**	NS	NS	NS	NS

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