Changes in Hormone Receptor and Her2 Status After Neoadjuvant Chemotherapy in Breast Cancer

Meme Kanserinde Neoadjuvan Kemoterapi Sonrası Hormon Reseptörü ve Her2/neu Değişiklikleri

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ABSTRACT Objective: Hormone receptor (HR) and Her2/neu expressions may change following neoadjuvant chemotherapy. The clinical significance of this receptor alteration is unclear. We retrospectively investigated the frequency of HR and Her2/neu status change in response to neoadjuvant chemotherapy. **Material and Methods:** Medical records of 49 patients with locally advanced breast cancer treated with anthracycline- and/or taxane-based neoadjuvant chemotherapy were retrospectively evaluated. The median age at diagnosis was 53 years (range, 27-79). All patients were operated within 3-4 weeks of the last cycle of chemotherapy. We also analyzed the relation of tumor marker alterations with patient outcome. **Results:** Alterations in hormonal receptor and Her2/neu protein expression were observed in 16 (32.6%) of the 49 patients. There was no statistically significant difference in HR expressions before and after neoadjuvant chemotherapy (p=NS). In addition, two (4%) patients with positive Her2/neu became Her2/neu negative after neoadjuvant chemotherapy. Twelve (24%) patients with negative estrogen and progesteron receptor expressions were converted to positive after neoadjuvant chemotherapy. There was no effect of HR alterations on patient outcome. **Conclusion:** HR and Her2/neu expression alterations are not infrequent in response to neoadjuvant chemotherapy. Tumor marker status determination in the final surgical specimen is recommended.

Key Words: Breast neoplasms; drug therapy; receptors, estrogen; receptors, progesterone

ÖZET Amaç: Neoadjuvan kemoterapi ile tedavi edilen lokal ileri evre meme kanserli hastalarda tedavi sonrası hormon reseptör (HR) ve Her2/neu değişiklikleri bildirilmiştir. Ancak bu değişikliklerin klinik önemi bilinmemektedir. Biz de kliniğimizde neoadjuvan kemoterapi alan meme kanserli hastalarda HR ve Her2/neu değişimini inceledik. **Gereç ve Yöntemler:** Taksan ve/veya antrasiklin içeren neoadjuvant kemoterapi ile tedavi edilen lokal ileri evre 49 meme kanserli hastanın dosyaları retrospektif olarak değerlendirildi. Ortanca yaş 53 yıl (aralık, 27-79) idi. Tüm hastalar kemoterapi bitiminden itibaren 3-4 hafta içinde opere oldular. Tümör marker değişiminin hastaların klinik prognozu ile ilşkilerini de değerlendirdik. **Bulgular:** HR ve Her2/neu ekspresyonundaki değişiklikler 49 hastanın 16'sında (%32.6) gözlendi. HR ekspresyon düzeyleri neoadjuvant kemoterapi öncesi ve sonrası karşılaştırıldığında istatistiksel anlamlı farklılık bulunamadı (p=NS). Ayrıca, neoadjuvant kemoterapi sonrası Her2/neu pozitif iki (%4) hasta negatif olmuştu. HR negatif olan 12 hasta cerrahi sonrası pozitif yönde değişiklik gösterdi. Ancak bu değişikliklerin hastaların sağkalımı üzerine etkisi olmadı. **Sonuç:** Lokal ileri evre meme kanserli hastalarda neoadjuvant kemoterapi sonrası ER, PR ve Her2/neu ekspresyon değişiklikleri görülebilir. Bu reseptör durumları son cerrahi sonrası materyalde de yeniden değerlendirilmelidir.

Anahtar Kelimeler: Meme kanseri; ilaç tedavisi; östrojen reseptörü; progesteron reseptörü

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Neoadjuvant chemotherapy offers several benefits including breast conservation in patients with locally advanced breast cancer (LABC).[1,2] Moreover it provides the opportunity of early recognition of chemotherapy failure or therapy success.[3] Therefore, biological factors

that may predict response to treatment may be identified. Hormonal receptors (HR) and Her2/neu protein expression are available primary prognostic markers for treatment planning.[4,5] Patients with estrogen receptor (ER) and progesterone receptor (PR) positive but Her2/neu negative tumors were associated with improved overall survival.[6,7] NSABP B27 and NSABP B18 studies have shown higher pathologic complete response (CR) rates in HR negative patients when compared to HR positive patients.[8,9] Preoperative chemotherapy may change HR and Her2/neu expressions in the final surgical specimen.[10,11] The significance of this change is unclear. We retrospectively investigated the frequency of HR and Her2/neu status change in response to neoadjuvant chemotherapy.

MATERIAL AND METHODS

Between May 1999 and November 2007, 49 patients with LABC (stage IIB, IIIA, IIIB and IIIC) treated with neoadjuvant chemotherapy were retrospectively evaluated. Median age at diagnosis was 53 years (range, 27-79). Median Eastern cooperative oncology group (ECOG) performance status of the patients was 0 (range, 0-2). Patient characteristics are shown in Table 1.

TABLE 1: Pretreatment characteristics.

Characteristics	n (%)
Median age (range)	53 (27-79)
ECOG performance status	
0-1	45 (92)
2	4 (8)
Menopausal status	
premenopausal	18 (37)
postmenopausal	31 (63)
Histology	
Invasive ductal carcinoma	49 (100)
Invasive lobular carcinoma	0
Stage of disease at diagnosis	
IIB	6 (12)
IIIA	18 (37)
IIIB	13 (27)
IIIC	12 (24)
Tumor grade	
1-2	16 (33)
3	33 (67)
Estrogen receptor status	
Positive	28 (57)
Negative	17 (35)
Unknown	4 (8)
Progesteron receptor status	
Positive	17 (35)
Negative	29 (59)
Unknown	3 (6)
Her2/neu status	
Positive	19 (39)
Negative	21 (43)
Unknown	9 (18)

ECOG: Eastern cooperative oncology group.

Pretreatment histologic confirmation of the invasive tumor was performed by core needle biopsy for all patients. After surgery, HR and Her2/neu status were identified on the mastectomy specimens. Thirty-three patients received three or four cycles of neoadjuvant chemotherapy with docetaxel 75 mg/m² and epirubicin 75 mg/m² (TE). Sixteen patients received three or four cycles of doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² plus 5-fluorouracil 600 mg/m² (CAF). Her2/neu-positive patients did not receive trastuzumab treatment. All patients underwent modified radical mastectomy or breast conserving surgery after neoadjuvant treatment. After surgery, all patients received two or three cycles adjuvant chemotherapy with the same regimens to complete six cycles. In addition, patients were given radiotherapy when appropriate. All HR-positive patients received endocrine therapy.

ER and PR were considered positive if more than 10% of the tumors cells showed nuclear immunohistochemical (IHC) staining. Her2/neu IHC 3+ or fluorescence in situ hybridization (FISH) positivity were considered as positive. Pre- and post-treatment HR and Her2/neu expressions were recorded. Changes in HR and Her2/neu status were evaluated in terms of response to neoadjuvant treatment and survival.

In statistical analysis, SPSS for Windows 11.5 was used. McNemar test was used to evaluate the paired correlation between HR and Her2/neu expressions before and after neoadjuvant chemotherapy. Objective response rates were compared using Fisher exact test. The disease-free survival

(DFS) and overall survival (OS) were analyzed by the Kaplan-Meyer test. Survival curves were compared with the log-rank test. P values less than 0.05 were accepted as significant.

RESULTS

Changes in HR and Her2/neu status after neoadjuvant chemotherapy are presented in Table 2. Neoadjuvant chemotherapy had no effect on ER or PR expression in 35 patients (71%). Positive ER expression was identified in 28 (57.1%) and 32 patients (65.3%) before and after neoadjuvant chemotherapy, respectively (p=0.375). Positive PR expression was detected in 17 (34.7%) and 25 patients (51.0%) before and after neoadjuvant chemotherapy, respectively (p= 0.109). Two PR positive patients lost their PR expressions (4%) following neoadjuvant chemotherapy. In addition, two (4%) patients with positive Her2/neu became Her2/neu negative after neoadjuvant chemotherapy.

Twelve (24%) patients with negative ER and PR expressions were converted to positive after neoadjuvant chemotherapy. These 12 patients were further analyzed for response rates, DFS and OS. Median follow up was 56 months (range, 32-98). Overall response rate (ORR) was 69%. Clinical CR was observed in three (6%), partial response (PR) in 31 (63%) and stable disease (SD) in 15 patients (31%). An objective response was observed in nine (75%) of the 12 patients who were converted to HR-positive status in contrast to the remaining 37 patients with an ORR of 67% (p=0.536). Similarly, 5-year DFS (100% vs 85%) and OS (100% vs 90%) were not statistically significantly different between these groups (p= 0.921 and p=0.772, respectively).

TABLE 2: Hormonal receptor expressions before and after neoadjuvant chemotherapy.

Receptor	Before treatment n (%)	After treatment n (%)	P value
ER positive	28 (57.14%)	32 (65.30 %)	0.375
PR positive	17 (34.69%)	25 (51.02 %)	0.109
Her2/neu positive	19 (39 %)	17 (34.69 %)	0.500

ER= estrogen receptor, PR= progesteron receptor

DISCUSSION

We have investigated changes in the pattern of HR and Her2/neu protein expressions in patients with LABC treated with preoperative taxane and/or anthracycline-based chemotherapy. We observed changes in 16 (32.6%) of the 49 patients. Among those, 12 patients gained HR positivity and two lost PR expression. Only two patients' Her2 status changed to negative. These results are in accordance with the results reported in the literature.

The issue of change in the HR and Her2 status in pre- and postoperative specimens has been the subject of various studies. Several studies have shown changes in HR and Her2/neu protein expression after neoadjuvant chemotherapy.[10-15] Jain et al.[10] demonstrated ER and/or PR expression change in 33% of neoadjuvant chemotherapy recipients. Makris et al. described a decrease in ER expression following neoadjuvant chemotherapy.[11] Interestingly, this was correlated with tumor response. Piper et al. similarly reported 26% incidence of change in expression of HR and Her2/neu after neoadjuvant chemotherapy compared to only 6% in those who did not get any treatment in between.[12] In another study, Lee et al. reported that 61% of the study population had alterations of pre- and postchemotherapy ER and/or PR expressions.[13]

There are several studies showing that HR status may change in the final surgical specimen compared to initial core biopsy without any confounding chemotherapy or other factors. Piper et al. reported changes in 6% of the patients without neoadjuvant intervention.[12] However, Lee et al. showed a 48% difference in HR expression status between the initial core biopsy and final pathology specimen.[13] Cahill et al. claimed that initial diagnostic core biopsies significantly overscored HR expression.[16,17] Possible explanations for this variation include tissue sampling errors or technical fixation and staining variables. This issue warrants further investigation.

Her2/neu protooncogen is overexpressed in approximately 25% of patients with breast cancer.[18] Its overexpression has traditionally been correlated

with poor prognosis. Many studies have investigated the correlation between Her2 expression and tumor response to anthracycline- and/or taxane-based neoadjuvant chemotherapy in breast cancer. Most of these studies have not reported a significant correlation between tumor response and Her2/neu status.[19,20] The introduction of trastuzumab, an anti-Her2 chimeric monoclonal antibody, has changed the natural history of breast cancer with Her2 overexpression.[21] However, most of the studies investigating HR change were published in the pre-trastuzumab era. In recent a study, Tiezzi et al. reported a significant association between DFS and OS and Her2 protein overexpression in breast cancer patients.[22] Additionally, they reported no significant Her2/neu expression alteration before and after neoadjuvant chemotherapy. Similarly, Zhao et al. and Arens et al. failed to demonstrate any change in Her2 status with neoadjuvant chemotherapy.[15,23] However, there are also conflicting reports that show alterations of Her2 status.[12] In our study, there was only 4% change in Her2 status with no association with the tumor response.

Despite all these reports, clinical relevance of these alterations in HR and Her2 status has not been clearly demonstrated. Literature data are conflicting on this issue. Change in ER and/or PR status did not appear to affect response to treatment in one study,[10] but Makris et al. claimed that these alterations were correlated with response to treatment.[11] Lee et al. reported that changes in ER and PR expressions did not change overall HR status.[13] There was a change in HR status in only 5% of the patients. Similarly, Piper et al. concluded that these receptor alterations effected only two patients (6%).[12] Another study from China reported no significant difference in HR status.[15] Finally, our results showed that these alterations in HR and Her2 status did not have any effect on patient survival. Possible explanations for these results may be insufficient patient number and absence of enough events to cause a statistical significance. Taken together these data indicate that, although a minority of the patients are involved, the results of marker analysis in the final surgical specimen should be awaited for definite HR status determination to avoid adverse outcome.

In conclusion, we have investigated changes in HR and Her2/neu expression status in response to neoadjuvant chemotherapy. We found alterations in HR and Her2 status with no effect on survival. HR and Her2 status determination in the final surgical specimen is recommended. Clinical studies with greater number of patients are warranted.

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