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ORIGINAL ARTICLE

Receptor discordances in locally advanced breast cancer after neoadjuvant chemotherapy and their effects on survival

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Summary

Purpose: *To determine estrogen, progesterone and HER2 receptors' discordances after neoadjuvant chemotherapy in patients with locally advanced breast cancer and their effects on survival.*

Methods: *Data of 186 patients who were admitted to our oncology departments between 2000 and 2014, were retrospectively evaluated. Patients'status of hormone and HER2 receptors were assessed before and after neoadjuvant chemotherapy. Univariate and multivariate Cox regression analyses, Kaplan-Meier and Log-rank tests were used, as appropriate. P<0.05 was considered as statistically significant.*

Results: *Median follow-up was 35 months. Of the patients, 20% had stage II disease and 80% stage III disease. Also, 74% showed hormone receptor positivity and 42% had HER2 overexpression. Hormone receptor discordance was detected in 63 (34%), HER2 discordance was detected in 33 (18%), and any receptor discordance was detected in 74 (40%) patients. There was a statistically significant difference regarding 5-year disease-free survival (DFS) between groups with loss of HER2 overexpression and without loss of HER2 overexpression (p=0.003). Five-year DFS was 60% with loss of any positive receptor status after chemotherapy and 72% with no change in any receptor status (p=0.023). In multivariate analysis, clinical stage (HR: 3.3, 95% CI: 1.18-9.3, p=0.022), changing HER2 status from positive to negative (HR: 2.6, 95% CI: 1.3-5.1, p=0.005), and triple-negative receptor status (HR: 2.64, 95% CI: 1.3-5.6, p=0.001) had significant impact on DFS.*

Conclusion: *In patients with locally advanced breast cancer, loss of HER2 overexpression is an independent risk factor for DFS. Further studies are needed to determine the impact of receptor discordances.*

Key words: *discordance, HER-2 overexpression, neoadjuvant chemotherapy, receptor status*

Introduction

Neoadjuvant chemotherapy is used to improve operability and increase breast conservation in locally advanced breast cancer [1]. Also, this approach provides information about the disease's sensitivity to chemotherapy and outcome of patients [2,3]. Before the initiation of neoadjuvant chemotherapy, a biopsy specimen is often required to clarify the histopathological diagnosis and to determine prognostic factors of treatment outcome. Pathologically complete response to neoadjuvant chemotherapy with or without anti-HER2 treatment is correlated with long-term outcome [4,5], but residual disease after neoadjuvant chemotherapy has been shown to correlate with poor outcome. After neoadjuvant chemotherapy, receptor status can change. Systematic reviews demonstrated that discordance of estrogen receptor (ER) and/or progesterone receptor (PR) status ranges from 2.5 to 51.7% and switch to

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a negative HER2 receptor in up to 43% of patients in the case of neoadjuvant chemotherapy combined with trastuzumab [6-10]. Few studies have evaluated the association between receptor concordance and long-term outcome of breast cancer [8].

The objective of this study was to determine ER, PR and HER2 receptors' discordances after neoadjuvant chemotherapy in patients with locally advanced breast cancer and their effects on outcome.

Methods

We retrospectively evaluated patients from four different centers, with locally advanced breast cancer,who received neoadjuvant chemotherapy in oncology departments between 2005 and 2014. We reviewed the results of the pathology reports that contained ER, PR and HER2 status of pretreatment core needle biopsy and residual post-therapy tumor specimens from the patients' charts and electronic management system database. Thirty five patients (18.8%) were identified with pathological complete remission (pCR), while 151 (81.1%) patients had residual disease in the breast or lymph nodes or both after receiving neoadjuvant chemotherapy. Those patients' medical records were reviewed for clinicopathological data. After core need biopsy, patients received neoadjuvant anthracycline-taxane based chemotherapy. Patients with HER2 positive breast cancer received trastuzumab-containing neoadjuvant chemotherapy. Patients received adjuvant radiation therapy if indicated. Hormone receptor-positive patients received adjuvant endocrine therapy with tamoxifen or an aromatase inhibitor. Any immunohistochemical change of hormone receptors and/or HER2 overexpression between pre-treatment core needle biopsy and residual tumor after the neoadjuvant chemotherapy was defined as discordance. The patient characteristics, clinical stage, histological tumor type, tumor size, tumor grade and lymph node involvement were recorded. pCR was defined as no residual tumor after the operation on breast and axillary specimens. Patients were followed-up, and any local or distant recurrences were recorded.

Determination of hormone receptors and HER2 status

The ER, PR, HER2 status of all core needle biopsies and surgical specimens were determined using immunohistochemical analysis (IHC). The cut-off value of positivity was 1% both for ER and PR. The pathologist scored IHC staining as 0, 1+, 2+, or 3+ based on intensity and proportion of membrane staining according to criteria based on ASCO/CAP [11]. If the IHC score was determined as 2+ (equivocal), then further examination with in situ hybridization (ISH) assay was performed.

Statistics

Patient status of hormone and HER2 receptors were assessed before and after neoadjuvant chemotherapy. Clinicopathological factors related to hormone and HER2 receptors discordance were compared with x^2 test and Fisher's exact test. Survival analyses were performed according to the Kaplan-Meier and Log-rank test. DFS was defined as the time from surgery to the time of relapse or death from any cause. Univariate and multivariate analyses of prognostic factors related to DFS were performed by Cox regression analysis. Multivariate p values were used to characterize the independence of these factors. A 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. $P<0.05$ was considered statistically significant.

Results

Median duration of follow-up was 35 months (range 6-136) and the mean age of patients was 49 years. Before receiving neoadjuvant chemotherapy, 38 (20%) patients had clinical stage II cancer and 148 (80%) had clinical stage III cancer. Before receiving neoadjuvant chemotherapy, 138 patients (74%) had hormone receptor positivity with HER2 negativity and 79 (42%) had HER2 positivity with hormone receptor-positive or negative status. Thirty-five (18.8%) patients (18.8%) achieved pCR. Hormone receptor discordance was detected in 63 patients (34%), HER2 receptor discordance was detected in 33 patients (18%), and any receptor discordance was detected in 74 patients (40%). After neoadjuvant chemotherapy, 57 (31%) patients with positive hormone receptor status had negative hormone receptor status and 33 patients (18%) with positive HER2 receptor status had negative HER2 receptor status. Thirty-one percent of 19 patients with triple-negative disease had positive hormone

Table 1. Patient characteristics according to hormone receptor status

Characteristics	*Patients n*	*Patients %*
Median age, years (range)	49 (26-82)	
Clinical stage		
Stage II	38	20
Stage III	148	80
Grade		
Grade I	9	5
Grade II	65	35
Grade III	80	43
Unknown	32	17
Subtype		
Invasive ductal carcinoma	172	92
Invasive lobular carcinoma	14	8
HR status before treatment		
Positive	138	74
Negative	48	26

HR: hormone receptor

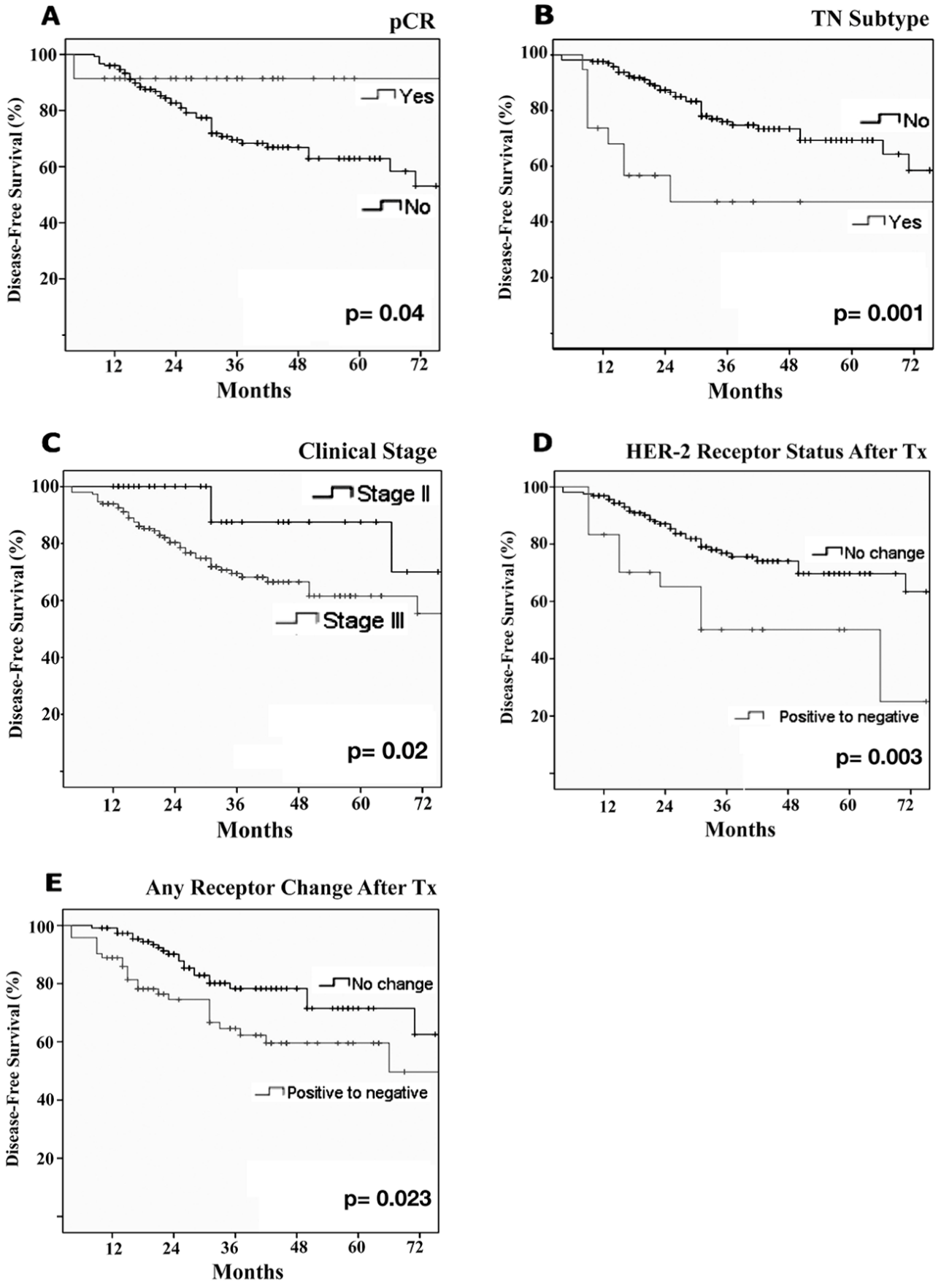

Figure 1. Kaplan-Meier disease-free survival estimates according to: **(A)** Pathologic complete response, **(B)** triple-negative breast cancer, **(C)** clinical stage, **(D)** HER2 receptor status after treatment, **(E)** any receptor change after treatment. pCR: pathological complete response, TN: triple-negative, TX: treatment.

receptor status after chemotherapy, but none of all patients had positive HER2 receptor status after chemotherapy. Patients' characteristics according to the change of their receptor status are shown in Table 1.

Five-year DFS was 67%. Five-year DFS was 64% in patients with negative hormone receptor status after chemotherapy who had positive hormone receptor before chemotherapy, whereas 5-year DFS in patients with no change in hormone receptor status after chemotherapy was 79%. However, no significant difference was observed between both groups (p=0.40).

Five-year DFS was 50% in patients with negative HER2 receptor status after chemotherapy who had positive HER2 status before, and 70% in patients with no change in HER2 receptor status after chemotherapy. The difference between groups was significant (p=0.003).

Five-year DFS was 60% in patients with any negative receptor status after chemotherapy who had positive receptor status before chemotherapy. Five-year DFS in patients with no change in any receptor status after chemotherapy was 72%. The difference between groups was significant (p=0.023).

Five-year DFS in patients who had any positive receptor status after chemotherapy while it was triple-negative before chemotherapy was 83%. Five-year DFS in patients with triple-negative disease before and after chemotherapy was 67%, without significant difference between both groups (p=0.80). Five-year DFS of patients who had pCR was higher than in patients who had pathologically incomplete response (92 vs 63%, respectively, p=0.04; Figure 1). In univariate analysis clinical stage (p=0.02) and having triple-negative tumor (p=0.001) were statistically significant, whereas lymphovascular invasion, perineural invasion, age, hormone receptor status and HER2 receptor status were not statistically significant (Table 2).

In multivariate analysis, the impact of pCR on survival was nearly significant (HR: 0.32, 95% CI:

Table 2. Disease-free survival according to patients' characteristics and receptor changes

Characteristics	*Patients (n)*	*Recurrences (n)*	*5-y DFS (%)*	*p value*
Age, years				0.40
<50	97	28	66	
≥50	87	20	69	
Clinical stage				0.02
II	38	4	85	
III	148	44	60	
HR status before treatment				0.10
Positive	138	74	72	
Negative	48	26	62	
HER2 receptor status before treatment				0.30
Positive	79	18	68	
Negative	107	30	67	
Triple negative subtype				0.001
Yes	19	9	48	
No	167	39	70	
HR Discordance after treatment				0.40
No change	123	31	79	
Positive to negative	57	16	64	
HER2 receptor status after treatment				0.003
No change	153	36	70	
Positive to negative	33	12	50	
Any receptor change (HR/HER2 or both)				0.023
No change	112	23	72	
Positive to negative	68	25	60	
Clinical response				0.04
Pathologic CR	35	3	92	
PR/Stable disease	151	45	63	

HR: hormone receptor, CR: complete response, PR: partial response

Table 3. Multivariate analysis according to patients' characteristics and receptor changes

Characteristics	*HR (95% CI)*	*p value*
Clinical stage		0.022
Stage II	1	
Stage III	3 (1.18-9.3)	
Triple-negative subtype		0.001
No	1	
Yes	2.64 (1.3-5.6)	
HER2 receptors status after treatment		0.005
No change	1	
Positive to negative	2.6 (1.3-5.1)	
Clinical response		0.061
Pathologic CR	0.32 (0.1-1.05)	
PR/Stable Disease	1	

CR: Complete response, PR: Partial response

0.1-1.05, p=0.061). Clinical stage (HR: 3.3, 95% CI: 1.18-9.3, p=0.022), changing HER2 status from positive to negative (HR: 2.6, 95% CI: 1.3-5.1, p=0.005), and triple- negative disease (HR: 2.64, 95% CI: 1.3-5.6, p=0.001) had significant impact on DFS (Table 3).

Discussion

More recent trials have demonstrated the discordance of HER2 receptor between primary and metastatic site [12-15]. Also,increasingly more trials have reported hormone receptor discordance between primary and metastatic site [12,15]. However, there were only a few trials in the literature evaluating the discordance between primary and residual tumors after neoadjuvant chemotherapy in patients with locally advanced breast cancer.

In the present study, we evaluated ER, PR and HER2 receptor discordances after neoadjuvant chemotherapy in patients with locally advanced breast cancer and their effects on DFS.

What was found was that 40% of the 186 patients included in the study had residual tumors with one change in receptor status after neoadjuvant chemotherapy and our results are similar to the findings of previous studies [6,16]. We found that 5-year DFS for at least one receptor's discordance appeared to be correlated with significantly worse outcome than that for patients without any receptor change.

When we looked at subgroup analyses, no significant differences were observed in DFS between the groups with any hormone receptor discordance and the groups without any receptor change. However, patients with HER2 discordance had statistically significantly worse outcomes than the patients without change. And also, 5-year DFS was numerically higher in patients with any positive receptor status after chemotherapy who had triple-negative disease before chemotherapy (83 vs 67%) but the difference did not reach statistical significance (p=0.80). This result may be due to the small number of patients (6 patients) included in the analysis.

The outcomes of previous studies that have investigated the correlation between the changes in hormone receptor status are inconsistent.Tacca et al. and Parinyanitikul et al. found better outcomes in patients whose tumors changed to positive compared to the patients with tumors hormone status that remained negative after neoadjuvant chemotherapy [16,17].

Hirata et al. reported findings similar to those of our study [18]. In patients receiving endocrine therapy, they demonstrated that DFS for patients whose tumors remained with hormone positive status and whose tumors changed from hormone positive to negative did not differ significantly [18]. However, Chen et al. demonstrated that in patients who received endocrine therapy, the outcomes of tumors that changed from hormone positive to negative were significantly worse than for patients remaining hormone positive [19]. Several factors might cause these different results, including intratumor heterogeneity and accuracy of hormone receptor discordance [20-22]. Previous studies have demonstrated that HER2 receptor changed in 7.6-45.7% of the patients [6,8,16,23-25]. In the present study, we found loss of HER2 receptor in 18% of the cases after neoadjuvant chemotherapy. Multivariate analyses demonstrated that loss of HER2 receptor was associated with poor outcome (Figure 1). Likewise, Guarneri et al. demonstrated that patients with loss of HER2 overexpression tend to have greater risk of relapse compared to patients with HER2 remaining positive [8].

In conclusion, patients with locally advanced breast cancer had considerable hormone and HER2 receptor discordance after neoadjuvant chemotherapy. Loss of HER2 receptor is associated with poor outcome and is an independent risk factor for DFS. Further studies are needed to determine the influence of this receptor discordance on treatment algorithms.

Conflict of interests

The authors declare no conflict of interests.

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