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ORIGINAL ARTICLE

Clinical importance of discordance of hormone receptors and Her2/neu status after neoadjuvant chemotherapy in breast cancer

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Summary

Purpose: *The aim of this study was to compare the hormone receptors' (HR) and HER2/neu status between core needle biopsy (CNB) and residual tumor after surgery of breast cancer treated with neoadjuvant chemotherapy (NAC), and also to evaluate the impact of discordance and other clinicopathological factors on survival.*

Methods: *Oestrogen receptor (ER), progesterone receptor (PR) and HER2/neu status were evaluated by immunohistochemistry (IHC) on 90 CNBs of primary tumors and surgical specimens after NAC (study group); 53 patients without NAC served as control group, and discordance was compared between the two groups. The association between discordance of HR status after NAC and various other clinicopathological factors was tested with Spearman's test.*

Results: *Pathological complete response (PCR) was achieved in 10 (11.1%) patients after NAC. ER and PR changed significantly more in the study than in the control group. ER and PR discordance was detected in 10 (12.5%) and 17 (21.2%) patients in the NAC group and in 1 (1.8%) and 2 (3.7%) patients in the control group (p=0.04 and p=0.005, respectively). ER discordance was related with HER2/neu change. Furthermore, PR discordance correlated with CNB, ER and treatment response, while HER2/neu discordance was associated with treatment response (p=0.05). ER discordance was found to be an independent prognostic factor for progression-free survival (PFS) (p=0.02).*

Conclusion: *NAC might cause alterations in ER, PR or HER2/neu status in breast cancer, and they should be re-tested in the residual tumor after NAC to optimize adjuvant therapy.*

Key words: *breast cancer, discordance, HER2-neu, hormone receptor, neoadjuvant chemotherapy*

Introduction

NAC has been used increasingly in breast cancer, where the primary aim is to downstage the primary tumor to enable breast conservation therapy and to eradicate distant micrometastatic disease [1]. Overall survival (OS) and DFS are not different between NAC or adjuvant chemotherapy [2]. The clinical efficacy of NAC depends on pathological tumor response detected after surgery. PCR is defined as the disappearance of invasive tumor both in the breast and axilla after NAC and is reported to range between 3-46% [3]. Complete response to NAC is correlated with survival [3]. While NAC with anthracycline-based chemotherapy (AC: doxorubicin plus cyclophosphamide) resulted in 5-14% PCR, the addition of taxane to AC preoperatively increased PCR from 13% to 26% in the NSABP-B27 trial [4].

CNB has been an important tool for diagnosis of breast cancer [5]. An assessment of CNB might provide early determination of prognostic

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and predictive markers such as ER, PR and HER2/neu. However, CNB may not accurately define these markers because of tumor heterogeneity. Concordance between CNB and excision specimen was reported to range between 61 and 99% for HR and HER2/neu status [5]. Systemic adjuvant chemotherapy is based on tumor marker expression in CNB before NAC, but there is no consensus about the influence of NAC on the expression of HR or HER2/neu status and the clinical significance of discordance of HR status. In retrospective studies, ER/PR alteration after NAC has been identified [5,6]. In the literature, HR discordance was reported as 8-33% of breast cancer patients after NAC [7].

There is no consensus about the prognostic importance of these alterations of HR status. A positive switch of HR is reported to be related with better survival with endocrine therapy compared with patients without endocrine therapy [1,8]. Herein, CNB and surgical specimens after NAC in 90 patients with breast cancer and 53 control group patients without NAC were compared in respect to discordance of HR and HER2/neu status; also it was investigated whether changes were related with tissue sampling or the chemotherapy administered. We also analysed the importance of factors and their discordance in predicting prognosis and DFS or OS.

Methods

This study consisted of 143 breast cancer patients who were treated at the Oncology Department of two different centres in Istanbul from 2004 to 2013. In total, 2650 breast cancer patients were retrospectively reviewed and 90 patients who received NAC (study group) and 53 patients without NAC (control group) were included.

All of the patients were diagnosed by CNB. Patients who were diagnosed by fine needle aspiration biopsy or those without pathological specimens were excluded. All of the patients underwent operations after being diagnosed by CNB. Patients were staged clinically preoperatively: 7 (4.8%) of them had metastatic disease, 79 (55.4%) had locally advanced disease with clinically palpable fixed axillary lymph nodes, and another 57 (39.8%) had early stage disease. While 27 (18.8%) patients underwent breast conserving surgery (BCS), 110 (76.9%) underwent modified radical mastectomy (MRM), and 5 (4.3%) underwent simple mastectomy without axillary dissection. All patients were staged according to the 6th edition of AJCC of cancer staging [9].

Anthracycline-taxane combinations (TAC/TE/AC-T- docetaxel, doxorubicin, cyclophosphamide/docetaxel, epirubicin) or only anthracycline regimens [AC/EC/CEF- doxorubicin, cyclophosphamide/epirubicin, cyclophosphamide/cyclophosphamide, epirubicin-5-Fluorouracil (5-FU)], only taxane-based chemotherapy or hormonotherapy were given as NAC in 31, 46, 9 and 4 patients in order of frequency. Trastuzumab was combined with NAC in 21 patients with HER2/neu positive expression sequentially with anthracyclines.

Surgical specimens were re-examined by IHC with respect to HR and HER2/neu status by the same pathologist in Haydarpasa Numune Education and Research Hospital. The cut-off value for positivity was 1% for both 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 [10]. Any IHC change of ER, PR and HER2/neu status between CNB and residual tumor after the operation was defined as discordance. The histological tumor type, the size of the invasive component, the tumor grade, and the lymph node involvement were recorded. PCR was defined as no residual invasive tumor in the breast or axillary lymph nodes after surgery. Following surgery, adjuvant chemotherapy if not completed preoperatively, and radiotherapy if indicated, were given sequentially. In addition, patients with positive HR and HER2/neu overexpression received adjuvant hormonotherapy and trastuzumab therapy. Patients were followed-up and recurrences were recorded. Patients who received NAC were compared with the control group regarding HR and HER2/neu status discordance. The clinicopathological factors related with ER and PR discordance was analysed. In addition, the importance of these factors for OS and DFS was analysed.

Statistics

Statistical analyses were performed using the SPSS software 17.0 (SPSS Inc., Chicago, IL, USA). The relationship between NAC and control groups and the other clinicopathological factors were analyzed using the Chi-square test and Fisher's exact test. Clinicopathological factors related with ER and PR discordance were also compared with Chi-square test. Associations between discordance of HR status after NAC, and other clinicopathological factors were tested with Spearman's test for nonparametric correlations. Logistic regression analysis was performed to evaluate important factors related with treatment response. Survival analysis and curves were established according to the Kaplan-Meier method and compared using the log-rank test. DFS was defined as the time from surgery to the time of relapse. OS was defined as the time from diagnosis to the date of the patient's death or last known contact. Univariate and multivariate analysis of prognostic factors related to survival were performed by the Cox proportional hazards model. 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. All p values were two-sided

and p values less than or equal to 0.05 were considered significant.

Results

The median patient age was 48 years (range 26-94) and 54.5% were premenopausal. Tumors were localized in the right breast in 68 patients (47.5%), in the left breast in 70 patients (49%) and were bilateral in 5 patients (3.5%). Of the patients, 87.4% had invasive ductal carcinoma, and the remainder invasive lobular (7%), mixed type (3.5%) and other types.

In the control group, 53 patients underwent operation without NAC. Operations were performed in 90 patients following NAC. In the NAC group, PCR was achieved in 10 (11.1%) patients and 89.9% of the patients had partial response. We could not find any factor related with PCR by logistic regression analysis in the NAC group. Non-haematological toxicities were grade 1-2 and most common were alopecia, asthenia followed by nausea, arthromyalgia and stomatitis, which occurred in fewer than 4% of patients. The only grade 3-4 haematological toxicity was neutropenia, which was seen in 3 patients. No dose reduction was required because of myelotoxicity.

After the patients with PCR were excluded from the NAC group, the control and NAC groups were compared in respect to ER, PR, HER2/neu and various factors (Table 1). Both CNB and postoperative ER and PR were more positive in the control group than in the NAC group. ER and PR discordance was detected in 10 (12.5%) and 17 (21.2%) patients in the NAC group and in 1 (1.8%) and 2 (3.7%) patients in the control group (p=0.04 and p=0.005, respectively). HER2/neu discordance was seen in 6 patients (11.3%) in the control group and in 17 (21.2%) in the NAC group (p=0.009). ER and PR changed from positive to negative in 9 (90%) and 10 (58.8%) patients respectively, and from negative to positive in 1 (10%) and 7 (41.2%) patients. While HER2/neu changed from positive to negative in 6 patients, in 2 patients it changed from negative to positive. In 5 patients, HER2/neu changed from positive (+++) to ++, and in 3 patients from negative to ++ by IHC. On the other find discordance of HR and HER2/neu status between 30 control and NAC group or between pre- and post-NAC in 25 breast cancer patients. They used Wilcoxon test for comparison, which was different from our study. They also categorized HR as none, weak, moderate and strong staining [15]. Neubauer et al. detected PCR in 1 of 87 patients that received NAC [13]. ER discordance was detected in 7 (8%) patients, PR

Table 1. The relationship between clinicopathological factors in the control and NAC group

Characteristics	*Control group N (%)*	*Neoadjuvant group with N (%)*	*p value*
Menopause			0.03
Pre	22 (41.5)	50 (62.5)	
Post	31 (58.5)	30 (37.5)	
Tumor location			0.30
Right	23 (43.3)	40 (50)	
Left	27 (50.9)	39 (48.7)	
Bilateral	3 (5.8)	1 (1.3)	
CNB ER			0.003
Positive	48 (90.5)	54 (67.5)	
Negative	5 (9.5)	26 (32.5)	
Postop ER			<0.001
Positive	49 (92.4)	46 (57.5)	
Negative	4 (7.6)	34 (42.5)	
ER discordance			0.004
Present	1 (1.8)	10 (12.5)	
Absent	52 (98.2)	70 (87.5)	
CNB PR			0.003
Positive	46 (86.7)	50 (62.5)	
Negative	7 (13.3)	30 (37.5)	
Postop PR			<0.001
Positive	48 (90.5)	48 (60)	
Negative	5 (9.5)	32 (40)	
PR discordance			0.005
Present	2 (3.7)	48 (60)	
Absent	51 (96.3)	32 (40)	
CNB HER2/neu			0.006
+++	5 (9.4)	28 (35)	
–	43 (81.2)	47 (58.4)	
++	5 (9.4)	4 (5)	
Unknown	0	1 (3.6)	
Postop HER2/neu			0.03
+++	5 (9.4)	21 (26.2)	
–	44 (83)	50 (62.5)	
++	4 (7.6)	9 (21.7)	
HER2/neu discordance			0.2
Present	6 (11.3)	17 (21.2)	
Absent	47 (88.7)	62 (77.5)	
Uknown	0	1 (1.3)	
Pathology			0.3
Invasive ductal	43 (81.1)	73 (91.2)	
Invasive lobular	6 (11.3)	3 (3.8)	
Mixed	3 (5.6)	2 (2.5)	
Other	1 (2)	2 (2.5)	
Grade			0.7
Good	8 (15)	16 (20)	
Poor	29 (54.7)	41 (51.2)	
Intermediate	16 (30.3)	23 (29.8)	
Multicentricity			0.1
Present	9 (16.9)	23 (28.7)	
Absent	44 (83.1)	57 (81.3)	
LVI			0.02
Present	19 (35.8)	45 (56.2)	
Absent	33 (62.2)	31 (38.7)	
Unknown	1 (2)	4 (5.1)	
PNI			0.05
Present	22 (41.5)	25 (31.2)	
Absent	30 (56.6)	44 (55)	
Unknown	1 (1.9)	11 (13.8)	
Recurrence			0.001
Present	2 (3.7)	20 (25)	
Absent	51 (96.3)	60 (75)	

PR: partial response, ER: estrogen receptor, PR: progesterone receptor, CNB: core needle biopsy, LVI: lymphovascular invasion, PNI: perineural invasion

discordance was 18%, and Her2/neu discordance 15%. Kasamiet et al. indicated that only PR, but not ER or HER2/neu discordance was detected in 173 patients after NAC [16]. In another study that included 56 breast cancer patients treated with NAC and 56 controls, HR alteration was detected in 18% of the NAC group of patients [17] but they defined alteration of both ER and PR and they could not find any significant difference between the NAC and control groups.

After we excluded patients with PCR, we analysed the alteration of HR and HER2/neu in residual tumor tissue after operation following NAC. ER and PR and HER2/neu discordances were detected in 12.5%, 21.2% and 21.2% of the patients post-NAC, respectively. These changes were significantly higher in the NAC group compared to the control group. The cut-off value for positive HR was changed in the literature from 5% to 10% [7]. We used 1% for HR positivity according to ASCO guidelines, which are different from the literature [18]. In light of these results, we believe that alteration of HR and HER2/neu status likely depends on a direct effect of chemotherapy. The reason of discordance might be the re-expression of the HR in the tumor cell after chemotherapy. Only insensitive tumors with different biology might remain after chemotherapy in residual tumors. With chemotherapy lower levels of circulating oestrogen may cause downregulation of HR of the remaining tumor [7].

Taucher et al. did not show alteration of HER2/neu in 92 breast cancer patients post-NAC [19]. In another study performed by Li et al., there was 11.6% PCR in 131 breast cancer patients after NAC [14]. They compared HER2/neu in 37 controls and 131 patients who received NAC. Although discordance of HER2/neu was detected more frequently in the NAC group than in the control group (p=0.01), the rate of increased HER2/neu by IHC was not different between the two groups (p=0.8), and only a decrease of HER2/neu in the NAC group was significant (p=0.02). They concluded that the therapeutic agents may lead to downregulation of the tumor's HER2/neu expression and a decrease of expression might be related to secondary resistance to chemotherapy or trastuzumab therapy, given preoperatively. We detected HER2/neu discordance in 17 (21.2%) patients with 6 patients from positive to negative and 2 patients from negative to positive, although another 12 patients were accepted as having discordance if expression changed from ++ to +++ or negative or *vice-versa*, and we accepted discordance without FISH analysis. In contrast to our study, van de Ven et al. performed FISH for ++ and +++ specimens and found no significant changes of HER2/neu gene amplification. Good concordance of the HER2/neu amplification tested with FISH was reported [7]. If we had analysed tissue samples with 2- or 3-positive HER2/neu by IHC with FISH, we might get different results.

Tacca et al. found HR discordance in 23% of their 420 breast cancer patients. Switch from HR negative to positive was 42% and switch from positive to negative was 13%, and positive switch was related with better prognosis [1]. They detected 3% discordance of HR in 100 controls who were not treated with NAC. Hirata et al. reported 91 PCR after NAC in 459 patients and 16% of HR discordance (from positive to negative 8.2%, and from negative to positive 7.9%). The group of patients with HR conversion had poor prognosis without endocrine therapy [8]. Although discordance of HR status was reported in the literature, the relationship of discordance with response was not definite [17]. We found PCR in 10 patients after NAC but there was no factor related with PCR. On the other hand, PR discordance, HER2/neu discordance and grade were associated with treat-

Table 2. Hormone receptor changes after NAC

Hormone receptors	*Negative→ negative* *N*	*Positive→ positive* *N*	*Negative→ positive* *N*	*Positive→ negative* *N*	*Change* *N (%)*
ER					
Control	4	48	1	0	1 (1.8)
NAC	25	45	1	9	10 (12.5)
PR					
Control	5	46	2	0	2 (3.7)
NAC	22	41	7	10	17 (21.2)
HER2/neu					
Control	41	4	0	1	1 (1.8)
NAC	42	18	2	6	8 (10)

ER: estrogen receptor, PR: progesterone receptor, NAC: neoadjuvant chemotherapy

Table 3. The relationship between clinicopathological factors and discordance of hormone receptors

	ER discordance			*PR discordance*		
	Present	*Absent*	*p value*	*Present*	*Absent*	*p value*
Menopause			0.50			0.10
Present	5 (50)	45 (64.2)		9 (52.9)	41 (65)	
Absent	5 (50)	25 (36.8)		8 (47.1)	22 (35)	
Tumor location			0.30			0.50
Right	7 (70)	33 (47.1)		7 (41.1)	33 (52.3)	
Left	3 (30)	36 (51.4)		10 (38.9)	29 (46)	
Bilateral	0	1 (1.5)		0	1 (1.7)	
CNB PR			0.05			
Positive	9 (90)	41 (58.5)				
Negative	1 (10)	29 (41.5)				
Postop PR			0.50			
Present	5 (50)	43 (61.4)				
Absent	5 (50)	27 (38.6)				
PR discordance			0.20			
Present	4 (40)	13 (18.5)				
Absent	6 (60)	57 (81.5)				
CNB HER2/neu			0.01			0.10
Positive	8 (80)	20 (28.5)		8 (47)	20 (31.7)	
Negative	2 (20)	45(64.2)		8 (47)	39 (61.9)	
2+	0	4 (5.7)		0	4 (6.4)	
Unknown	0	1 (1.6)		1 (6)	0	
Postop PR			0.10			0.60
HER2/neu	3 (30)	18 (25.7)		4 (23.5)	17 (26.9)	
Present	4 (40)	46 (65.7)		10 (58.8)	40 (63.4)	
Absent	3 (30)	6 (8.6)		3 (17.3)	6 (9.7)	
HER2/neu discordance			0.05			0.03
Present	5 (50)	12 (16)		6 (35.2)	11 (17.4)	
Absent	5 (50)	57 (81.4)		10 (58.8)	52 (82.6)	
Unknown	0	1 (2.6)		1 (6)	0	
Grade			0.70			0.10
Good	2 (20)	14 (20)		5 (29.4)	11 (17.4)	
Intermediate	6 (60)	35 (50)		10 (58.8)	31 (49)	
Poor	2 (20)	21 (30)		2 (11.8)	21 (43.6)	
Multicentricity			0.70			0.50
Present	2(20)	21 (30)		4(23.5)	19(30.1)	
Absent	8(80)	49 (70)		13(76.5)	4(69.9)	
LVI			0.20			0.30
Present	8 (80)	37 (52.8)		12 (70.5)	33 (52.3)	
Absent	2 (20)	29 (41.4)		5 (29.5)	26 (41.2)	
Unknown	0	4 (5.8)		0	4 (6.5)	
PNI			0.50			0.50
Present	2 (20)	23 (32.8)		6 (35.2)	19 (30.3)	
Absent	7 (70)	37 (52.8)		10 (58.8)	34 (53.9)	
Unknown	1 (10)	10 (14.4)		1 (6)	10 (15.8)	
Response to NAC			0.50			0.001
CR	0	3 (4.2		3 (17.6)	0	
PR	10 (100)	67 (95.8)		14 (82.6)	63 (100)	
Recurrence			0.20			0.80
Present	4 (40)	16 (22.8)		4 (23.5)	16 (25.3)	
Absent	6 (60)	54 (77.2)		13 (76.5)	47 (74.7)	

ER:estrogen receptor, PR:progesterone receptor, CNB:core needle biopsy, LVI: lymphovascular invasion, PNI:perineural invasion, NAC: neoadjuvant chemotherapy, CR: complete response, PR: partial response

Table 4. Results of the univariate analysis

Characteristics	*N (%)*	*3-year DFS (%)*	*p value*	*3-year OS (%)*	*p value*
Menopause			na		na
Pre	50 (62.5)	55.7		82.5	
Post	30 (37.5)	44.3		90.3	
Breast location			0.01		0.6
Right	40 (50.0)	27.6		83.0	
Left	39 (48.7)	56.8		87.5	
Bilateral	1 (1.30)	na		na	
Clinical stage			0.01		na
2	13 (16.2)	75		75.0	
3	60 (75.0)	46.7		88.5	
4	7 (8.8)	33.3		na	
CNB ER			0.90		0.10
Positive	54 (67.5)	41		80.0	
Negative	26 (32.5)	73		na	
Postop ER					
Positive	46 (57.5)	45.4	0.70	78.6	0.10
Negative	34 (42.5)	62.7		na	
ER discordance			0.02		0.60
Present	10 (12.5)	62.5		na	
Absent	70 (87.5)	56		85.2	
CNB PR			0.70		0.80
Positive	50 (62.5)	49.8		86.2	
Negative	30 (37.5)	47.7		85.7	
Postop PR			0.20		0.04
Positive	48 (60.0)	43.3		73.3	
Negative	32 (40.0)	59.7		na	
PR discordance			0.60		0.70
Present	17 (21.2)	50		85.7	
Absent	63 (78.8)	51.2		86.2	
CNB HER2/neu			0.30		0.005
+++	28 (35.0)	37.1		80.0	
–	47 (58.7)	62		92.3	
++	4 (5.00)	50		50.0	
Unknown	1 (1.30)	0			
Postop HER2/neu			0.01		0.05
+++	21 (26.2)	46.4		80.0	
–	50 (62.5)	61.5		92.3	
++	9 (11.3)	17		66.7	
HER2/neu discordance			0.1		0.7
Present	17 (21.2)	60.6		na	
Absent	62 (77.5)	59		84.4	
Unknown	1 (1.3)	0		na	
Grade			0.1		0.003
Good	16 (20)	50		na	
Poor	41 (51.2)	67.6		na	
Intermediate	23 (28.8)	23.2		57.1	
Multicentricity			0.04		0.2
Present	23 (28.7)	33.3		83.3	
Absent	57 (71.3)	56.6		86.7	
LVI			0.4		0.2
Present	45 (56.2)	51		82.4	
Absent	31 (38.7)	51.6		na	
Unknown	4 (5,1)	na		na	
PNI			0.08		0.1
Present	25 (31.2)	32.5		na	
Absent	44 (55	48.2		85.7	
Unknown	11 (13,8)	71.7		71.4	
Recurrence					0.06
Present	20 (25			75.5	
Absent	60 (75)			na	

ER:estrogen receptor, PR: progesterone receptor, CNB: core needle biopsy, LVI: lymphovascular invasion, PNI: perineural invasion, OS: overall survival, PFS: progression free survival, na: not available

ment but not with PCR. Alteration of HER2/neu was not correlated with tumor type, pathologic response or adjuvant chemotherapy [14]. In the present study we found correlation between ER discordance with HER2/neu alteration (p=0.01). Furthermore, PR discordance was correlated with CNB ER (p=0.04).

Age, clinical stage, grade, HER2/neu status, clinical response and number of metastatic lymph nodes were important for DFS in the Hirata's study [8]. We also found that breast location, clinical stage, ER discordance and postoperative HER2/neu status were associated with 3-year DFS, while postoperative PR, CNB HER2/neu, postoperative HER2/neu and grade were important for 3-year OS. On the other hand, there were no independent prognostic factors for both OS and DFS by multivariate analysis. Our results were noteworthy because they indicated not only the discordance of HR and HER2/neu status after NAC, but also the clinical importance of ER discordance on DFS. Patients with ER discordance had better DFS compared with those without ER discordance (p=0.02). This may be the result of endocrine therapy that was given for a positive switch of ER.

Conclusions

Patients were treated with adjuvant hormonotherapy and trastuzumab, based on hormone receptor and HER2/neu status, if these tumor markers changed after NAC. Expression of ER, PR and HER2/neu should be re-evaluated in tumor specimens before the adjuvant treatment decision. New prospective trials are needed to show the clinical utility of the discordance of these markers.

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