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ORIGINAL ARTICLE

Neoadjuvant human epidermal growth factor receptor-2 targeted therapy in patients with locally advanced breast cancer

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Purpose: We analyzed the responses of patients with locally advanced breast cancer to neoadjuvant chemotherapy (NAC) and NAC combined with neoadjuvant human epidermal growth factor receptor-2 (HER2) targeted therapy (NCHTT). **Methods:** We retrospectively reviewed 59 patients with HER2 amplified locally advanced breast cancer among patients who were treated surgically after neoadjuvant therapy at Samsung Medical Center between 2005 and 2009. Thirty-one patients received conventional NAC and 28 patients received NCHTT. Pathologic responses were assessed according to response evaluation criteria in solid tumors (RECIST) guidelines. **Results:** Pathologic complete response (pCR) was achieved in 13 out of 28 patients treated with NCHTT and in 6 out of 31 patients treated with NAC alone (46.4% vs. 19.4%, respectively, P = 0.049). Breast conserving surgery (BCS) was more frequently performed in the NCHTT group than in the NAC only group (71.4% vs. 19.4%, P < 0.001). The 3-year recurrence-free survival (RFS) rate was 100% in the NCHTT group and 76.4% in the NAC group (P = 0.014). Together, NCHTT, type of operation (BCS vs. mastectomy) and pathologic nodal status were significant prognostic factors for RFS in univariate analysis. **Conclusion:** We found that NCHTT produced higher pCR rates than NAC alone in locally advanced breast cancer.

Key Words: Breast neoplasms, Neoadjuvant therapy, ErbB-2, Response

INTRODUCTION

Breast cancer is the second most common cancer and the sixth leading cause of cancer deaths in women in Korea. Neoadjuvant therapy, surgery, and adjuvant therapy are standard treatments for locally advanced breast cancer. Typically, neoadjuvant therapy plays an important role in patients with locally advanced breast cancers and in treating distant micrometastasis, downstaging tumors, improving operability, and sometimes in allowing breast

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conserving surgery (BCS). The multidisciplinary management approach combined with neoadjuvant chemotherapy (NAC) and the incorporation of anthracyclines and taxanes has resulted in a significant reduction in the risk of death and a subsequent reduction in the 5-year recurrence rate for patients with early and advanced stage breast cancers [1,2].

NAC was first introduced in the 1970s [3] and several clinical studies since then have corroborated the efficacy of NAC [4,5]. A majority of studies report that after NAC, the partial response rate was 60% to 80% and the complete response (CR) rate was 10% to 20% [5,6]. The primary goals of NAC are to increase the rate of BCS and to predict prognosis through the response of tumors to treatment [7,8].

On the other hand, studies have estimated that approximately 20% to 25% of invasive breast cancers exhibit overexpression and gene amplification of human epidermal growth factor receptor-2 (HER2, also known as ERBB2) [9,10]. This represents an adverse prognostic indicator associated with aggressive histopathologic parameters and is correlated with decreased recurrence-free survival (RFS), overall survival (OS), and poor prognosis and outcome.

Trastuzumab, a monoclonal antibody directed against HER2, has become a standard treatment in HER2 positive breast cancer patients and has resulted in increased remission rates after neoadjuvant therapy [11]. Given the improvement in outcomes with the neoadjuvant use of trastuzumab with HER2 positive breast cancer patients, the optimal use of these compounds is still unclear. A number of new treatment approaches directed against HER2 are currently being examined in clinical trials. The purpose of this retrospective study was to assess pathologic CR (pCR), RFS, and OS rates in patients treated with NAC combined with neoadjuvant HER2 targeted therapy (NCHTT) compared to patients treated with NAC only.

METHODS

From January 2005 to December 2009, 60 patients who were histologically confirmed to be HER2 positive (defined as either immunohistochemical 3+ or 2+ and gene amplification determined by fluorescence *in situ* hybridization [FISH]) underwent NAC or NCHTT followed by surgery to treat breast cancer at Samsung Medical Center, Seoul, Korea. Histologic confirmation of invasive tumors was performed by fine needle aspiration biopsy or core needle biopsy. We excluded one patient because she had a remnant skin tumor that was detected 38 days postoperatively after modified radical mastectomy. We reviewed clinicopathologic factors and treatment modalities (type of operation, use of hormonal therapy, and radiation therapy) in 59 patients. Before initiation of therapy, all patients underwent staging evaluations that included complete histories, physical examinations, complete blood counts, chemical profiles, chest radiographs, ultrasounds or computed tomography scans of the liver, and bone scans. Mammography of both breasts was performed and additional breast and axillary assessment was conducted by ultrasound.

The pathologic tumor stage was assessed according to the American Joint Committee on Cancer 7 staging system [12]. The histologic grade was determined according to the Bloom-Richardson classification. The Allred score was used for estrogen receptor and progesterone receptor positivities, and HER2 was scored as 0–3. Patients with an immunohistochemistry score of 3+ or 2+ and gene amplification determined by FISH were considered positive. Responses to neoadjuvant therapy were categorized by pCR. The pCR was defined as no detectable invasive or noninvasive residual cancer cell in the breast or axillary lymph nodes by histopathology.

NAC regimens consisted of adriamycin with cyclophosphamide, adriamycin with docetaxel, adriamycin with cyclophosphamide plus docetaxel. All patients were treated with 3–8 cycles according to their regimen protocols in 3-week intervals. In the NAC only group, 31 patients received anthracycline-based chemotherapy. In the NCHTT group, trastuzumab, pertuzumab or lapatinib were used for HER2 targeted therapy concurrently with a chemotherapeutic agent. Neoadjuvant trastuzumab was administered as a loading dose of 4 mg/kg intravenously over 90 minutes on the first day and then subsequently given weekly at a dose of 2 mg/kg over 30 minutes, concomitantly with the above chemotherapy. Statistical anal-

yses were performed using the IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). Student's t-test, Pearson's chi-square test or Fisher's exact test were used to compare the clinicopathological characteristics between the NCHTT group and the NAC only group in HER2 positive cases. The Kaplan-Meier method and Logistic regression analysis were used to determine RFS and OS rates.

RESULTS

Clinicopathological characteristics and treatment modalities were analyzed for 59 patients who underwent NAC with or without NCHTT due to invasive breast carcinoma. Twenty-four patients had estrogen and/or progesterone receptor positive disease. Fifty-three patients had invasive ductal carcinoma, five patients had micropapillary carcinoma, and one patient had invasive papillary carcinoma. The mean breast tumor size was 5.3 cm. After adjuvant therapy, 33 patients (55.9%) underwent mastectomies, whereas 26 patients (44.1%) had BCS. Nineteen patients had stage III disease. Sentinel lymph node biopsy was performed on only one patient. An average of 19 lymph nodes were dissected in patients who underwent axillary lymph node dissection. The mean follow-up period was 33.3 months (range, 5.7 to 70.0 months).

Table 1 summarizes clinicopathologic characteristics of 31 patients treated with NAC only and 28 patients treated with NCHTT. The mean age of patients treated with NCHTT was 46.6 years, and the mean age of patients treated with NAC only was 47.3 years (P = 0.434). Thirteen patients achieved pCR in the NCHTT group and 6 patients achieved pCR in the NAC only group (46.4% vs. 19.4%, P = 0.049). BCS was more frequently performed in the NCHTT group than in the NAC only group (71.4% vs. 19.4%, P < 0.001). All 28 patients treated with NCHTT showed normal cardiac function before and after chemotherapy (Table 2). There were no significant differences in tumor size, nodal status, receptor status or hormone therapy use between the two groups.

During the median follow-up of 28.7 months (range, 5.7 to 70.0 months), seven patients experienced disease re-

Table 1. Clinicopathologic characteristics of patients with neoadjuvant HER2 targeted therapy and without HER2 targeted therapy

Characteristic	NCHTT (n = 28)	NAC (n = 31)	P-value
Mean age (yr)	46.6	47.3	0.434
Clinical tumor size (cm)			0.606
<5	13 (46.4)	17 (54.8)	
≥5	15 (53.6)	14 (45.2)	
Operation method			<0.001
MRM	8 (28.6)	25 (80.6)	
BCS	20 (71.4)	6 (19.4)	
Pathology			0.673
IDC	26 (92.9)	27 (87.1)	
Others	2 (7.1)	4 (12.9)	
Histologic grade			0.038
1	18 (64.3)	11 (35.5)	
2, 3	10 (35.7)	20 (64.5)	
Clinical nodal status			0.648
cN-	3 (10.7)	4 (12.9)	
cN+	25 (89.3)	27 (87.1)	
Pathologic CR (cm)			0.709
<5	25 (89.3)	26 (83.9)	
≥5	3 (10.7)	5 (16.1)	
Pathologic nodal status			0.196
pN-	16 (57.1)	12 (38.7)	
pN+	12 (42.9)	19 (61.3)	
Pathologic CR			0.049
Yes	13 (46.4)	6 (19.4)	
No	15 (53.6)	25 (80.6)	
Multifocal/multicentricity			0.659
Yes	15 (53.6)	17 (54.8)	
No	13 (46.4)	14 (45.2)	
Ki67			0.709
(+)	25 (89.3)	26 (83.9)	
(-)	3 (10.7)	5 (16.1)	
Hormone receptor status			0.795
ER+ and/or PR+	12 (42.9)	12 (38.7)	
ER- and PR-	16 (57.1)	19 (61.3)	
Hormone therapy			0.793
Yes	11 (39.3)	11 (35.5)	
No	17 (60.7)	20 (64.5)	
Radiation therapy			0.306
Yes	25 (89.3)	24 (77.4)	
No	3 (10.7)	7 (22.6)	

Values are presented as number (%).
HER2, human epidermal growth factor receptor-2; NCHTT, neoadjuvant chemotherapy combined with neoadjuvant HER2 targeted therapy; NAC, neoadjuvant chemotherapy; MRM, modified radical mastectomy; BCS, breast conserving surgery; IDC, invasive ductal carcinoma; CR, complete response; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Adverse events

Event	No. of patients	
	NCHTT (n = 28)	NAC (n = 31)
Neutropenic fever	8	5
LFT increase	2	1
Diarrhea	5	5
Stomatitis	12	5
Cardiac problem	0	0

NCHTT, neoadjuvant chemotherapy combined with neoadjuvant human epidermal growth factor receptor 2 targeted therapy; NAC, neoadjuvantchemotherapy; LFT, liver function test.

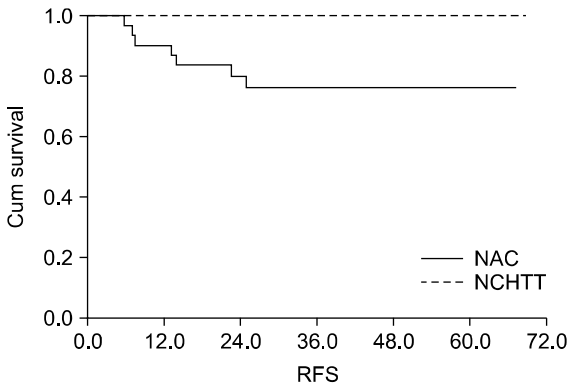

Fig. 1. Recurrence-free survival (RFS) curve for advanced breast cancer patients treated by neoadjuvant chemotherapy combined with neoadjuvant human epidermal growth factor receptor 2 targeted therapy (NCHTT) and neoadjuvant chemotherapy (NAC).

currence; interestingly, all were from the NAC only group. The 3-year RFS rate was 100% in the NCHTT group and 76.4% in the NAC only group (P = 0.014) (Fig. 1). During follow-up, only three patients died and the 3-year OS rate was 100% in the NCHTT group and 89.3% in the NAC only group (P = 0.149) (Fig. 2).

Table 3 shows the results of the RFS and OS-related univariate analysis of all patients in this study. NCHTT, type of operation (BCS vs. mastectomy), and pathologic nodal status were significant prognostic factors for RFS. For death and recurrence, multivariate analysis could not be applied to this study because of low incidence (3 deaths, 7 recurrences).

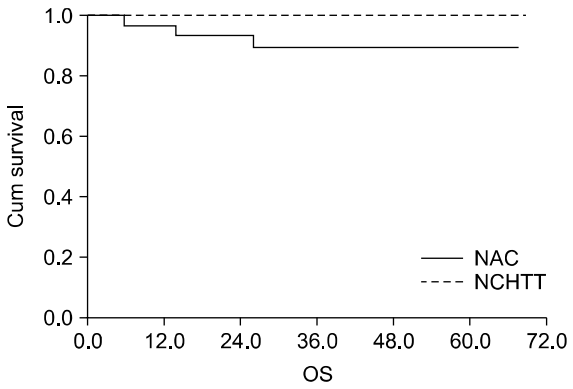

Fig. 2. Overall survival (OS) curve for advanced breast cancer patients treated by neoadjuvant chemotherapy combined with neoadjuvant human epidermal growth factor receptor 2 targeted therapy (NCHTT) and neoadjuvant chemotherapy (NAC).

DISCUSSION

The results of this study indicate that NCHTT induced higher pCR rates than NAC only in patients with locally advanced breast cancer. BCS was more frequently performed in the NCHTT group than in the NCT only group and 3-year RFS rate was significantly higher in the NCHTT group. In comparison with the results from western countries, we could observe a similar benefit from NCHTT.

NAC has become a standard therapy to treat patients with locally advanced breast cancer [8,13]. The primary goals of NAC are to increase the rate of BCS and to predict prognosis through the response of the tumor to the treatment [8,14]. NAC can reduce tumor size, which increases the rate of BCS and in some cases has the effect of prolonging OS. In addition, it improves the rates of operability in previously inoperable patients, can treat early stages of micrometastasis before the presence of chemo-resistant cell lines, reduces the risk of recurrence by preventing seeding during surgery and can predict further therapeutic efficacy of chemotherapeutic agents. Conversely, due to its downstaging effects, it can lead to therapeutic confusion due to the diminishment of traditional prognostic factors such as tumor size, axillary metastatic lymph node numbers, and histologic grading which are needed to assess patients for systemic treatment and overtreatment who may benefit by surgical intervention alone. Although there are no clinical practice guidelines for

Table 3. Univariate analysis of the recurrence-free survivals (RFS) and overall survival (OS)

Variable	3-Year RFS (%)	P-value	3-Year OS (%)	P-value
Age (yr)		NS		NS
<50	88.6		94.3	
≥50	87.5		95.8	
Clinical tumor size (cm)		NS		NS
<5	90.0		96.7	
≥5	86.2		93.1	
NCHTT		0.014		NS
Yes	100		100	
No	77.4		90.3	
Operation method		0.018		NS
BCS	100		100	
MRM	78.8		90.9	
Pathology		NS		NS
IDC	83.8		100	
Others	88.7		94.3	
Histologic grade		NS		NS
1, 2	93.1		96.6	
3	83.3		93.3	
Clinical nodal status		NS		NS
cN-	92.7		96.7	
cN+	84.0		92.3	
Pathologic tumor size (cm)		NS		NS
<5	88.2		94.1	
≥5	87.5		100	
Pathologic nodal status		0.009		NS
pN (-)	100		100	
pN (+)	77.4		90.3	
Response after NT		NS		NS
CR	94.7		94.7	
Non-CR	85.0		95	
Response after NT		NS		NS
CR+PR	88.7		94.3	
SD+PD	83.3		100	
p53		NS		NS
(+)	95.3		96.8	
(-)	85.2		92.6	
Ki67		NS		NS
(+)	87.5		94.6	
(-)	100		100	
Hormone receptor status		NS		NS
ER+ and/or PR+	95.8		100	
ER- and PR-	82.9		91.4	
Hormone therapy		NS		NS
Yes	95.5		100	
No	83.8		91.9	
Radiation therapy		NS		NS
Yes	89.8		98.0	
No	80.0		80.0	

NS, not significant; NCHTT, neoadjuvant chemotherapy combined with neoadjuvant human epidermal growth factor receptor 2 targeted therapy; NAC, neoadjuvant chemotherapy; BCS, breast conserving surgery; MRM, modified radical mastectomy; IDC, invasive ductal carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, persistent disease; ER, estrogen receptor; PR, progesterone receptor.

NAC, it is more frequently used as a preliminary treatment for patients undergoing surgery than as pretreatment for locally advanced breast cancer.

The HER is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands and a potent mediator of normal cell growth and development [15]. This family of receptors consists of four closely related type 1 transmembrane tyrosine kinase (TK) receptors: HER1 (epidermal growth factor receptor; EGFR), HER2, HER3 and HER4. Each receptor comprises an extracellular domain where ligand binding occurs, an α-helical transmembrane segment and an intracellular protein TK domain. Receptor dimerization is essential for HER function and for the signaling activity of all HER receptors. Dimerization can occur between two different HER receptors (heterodimerization) or between two molecules of the same receptor (homodimerization). However, HER receptors normally exist as inactive monomers with the molecules folded to prevent dimerization [16]. The HER2: HER3 heterodimer is considered the most potent HER receptor pair with respect to strength of interaction, ligand-induced tyrosine phosphorylation and downstream signaling, and functions as an oncogenic unit.

The humanized monoclonal antibody trastuzumab (Herceptin) was developed as a therapy targeted against HER2, which is over expressed in roughly one fourth of patients with invasive breast cancer. Readily available markers of overexpression and/or gene amplification of HER2 in tumor tissue predict the activity of this agent, and exclude those who will not benefit from this therapy. Trastzumab binds to the extracellular domain of HER2. Several mechanisms of action underlie the antitumor effects of trastuzumab. Trastuzumab blocks HER2-activated cell signaling, thereby reducing cell proliferation and restoring a capacity for apoptosis by inhibiting the PI3K/Akt pathway [17,18], which increases cellular sensitivity to chemotherapy and radiotherapy [19]. It has also been shown to prevent the formation of $p95^{HER2}$ (a truncated, active form of HER2), which may lead to inhibition of tumor development [17]. Finally, trastuzumab has been shown to inhibit HER2 regulated angiogenesis and leads to antibody-dependent cell-mediated cytotoxicity and triggers the activation of natural killer cell-mediated apoptosis [17,20]. Trastuzumab is now the standard therapy used in the adjuvant setting.

Pertuzumab is a humanized monoclonal antibody that binds to an epitope in domain II, the dimerization domain of the HER2 receptor extracellular domain, which is a region of HER2 distinct from the domain IV binding site of trastuzumab [21]. Pertuzumab inhibits HER2 dimerization by preventing HER2 from pairing with other HER receptors, including HER3 [22]. Lapatinib is a dual inhibitor of HER1 and HER2 TKs to be used in clinical practice. It has been shown to inhibit the intracellular domain phosphorylation of both HER1 and HER2 in a reversible manner with a long dissociation time of receptor-drug complex estimated as ≥300 minutes [23].

The role of trastuzumab in combination with chemotherapy has been tested in the neoadjuvant setting. A phase III trial conducted at the M.D. Anderson Cancer Center evaluated the addition of trastuzumab to an anthracycline based regimen. In this study, HER2 positive stage II–II_A patients were randomly assigned to receive chemotherapy with paclitaxel followed by FEC (5-fluorouracil, epirubicin and cyclophosphamide) or the same chemotherapy regimen plus weekly trastuzumab. The addition of trastuzumab to chemotherapy resulted in more than a doubling in pCR rates compared to chemotherapy alone (65.2% vs. 26%, P = 0.016) [11]. The phase III NeOAdjuvant Herceptin (NOAH) trial evaluated the addition of trastuzumab to an anthracycline- and taxane-based chemotherapy for HER2- positive patients with locally advanced or inflammatory breast cancer. The event-free survival rate at three years was significantly better in the chemotherapy plus trastuzumab group compared to chemotherapy alone: 71% versus 56%, respectively (HR, 0.59; P = 0.013); the pCR rate was also significantly higher in the chemotherapy plus trastuzumab group than the chemotherapy only group: (38% vs. 19%, respectively P = 0.001) [24]. In the phase III GeparQuattro trial, 1,509 patients with operable or locally advanced tumors were randomized to receive NAC with four cycles of epirubicin/cyclophosphamide followed by four cycles of docetaxel, with or without capecitabine [25]. The 445 HER2 positive patients enrolled also received trastuzu-

mab 6 mg/kg (with a loading dose of 8 mg/kg) every 3 weeks during all chemotherapy cycles. The pCR rate in the HER2 positive subset was 31.7% with no relevant early toxicity observed.

In conclusion, we found that patients treated with NCHTT experienced higher pCR rates, more breast conserving rates and lower RFS rates compared to patients treated with NAC only. Unfortunately, we have few cases with HER2 amplified locally advanced breast cancer who were treated surgically after NAC. For various survival benefits, additional studies with a larger patient enrollment are required to identify survival differences between NCHTT and NAC alone with the same chemotherapy regimen.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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