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Relationship between the signal ratios of HER-2/CEP17 and c-MYC/CEP17 and the pathological response of neoadjuvant therapy using docetaxel and trastuzumab in breast cancer

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Abstract. The purpose of this study was to assess the efficacy and predictive biomarkers of combination docetaxel-trastuzumab in a neoadjuvant setting by means of a phase II trial. Women with histologically-confirmed advanced invasive breast cancer whose tumours overexpressed HER-2 received 4 cycles of docetaxel (70 mg/m^2 every 3 weeks) and trastuzumab (4 mg/kg loading dose, 2 mg/kg weekly thereafter). Twenty-one patients were enrolled, and all completed 4 cycles of treatment. Two patients were later found to be inoperable, and neither pathological nor clinical response was assessed. The pathological complete response rate was 21% (4/19; 95% CI, 6-46%) and the overall clinical response rate 89% (17/19; 95% CI, 67-99%). The relationship between the expression of biomarkers (HER-2, c-MYC, BRCA1 and Ki-67) and pathological response was assessed. The results suggested the possibility that tumours showing a high signal ratio of HER-2/CEP17 or c-MYC/CEP17 might be more sensitive to this combination therapy. Based on these results, it can be speculated that approximately 30% pCR might be obtained in cases with a high signal ratio of HER2/CEP17 or c-MYC/CEP17. Further trials are needed.

Introduction

Neoadjuvant (also known as primary or pre-operative) therapy is a major development in the management of breast cancer. It increases the possibilities for breast-conserving surgery by downstaging the primary tumour and lymph node metastases (1). It also offers early systemic treatment for micrometastasis (2). Following the reports of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial (3,4), interest in neoadjuvant chemotherapy has rapidly developed and its use has become widespread in the treatment of patients with locally-advanced breast cancer.

Docetaxel is a semi-synthetic taxoid derived from the European yew tree, *Taxus baccata* (5). It is one of the most active chemotherapeutic agents in the treatment of patients with breast cancer. Docetaxel is active in the neoadjuvant setting, both as a single agent and in combination with anthracycline-containing regimens (6-8). There is a growing amount of information on neoadjuvant docetaxel therapy, but its activity combined with a molecular target agent has not been fully clarified. Trastuzumab is a humanised monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER-2) protein. HER-2 gene amplification, which leads to protein overexpression, is associated with short survival in breast cancer (9,10); consequently, trastuzumab is used to treat such patients. Several clinical trials show that trastuzumab-containing regimens yield high rates of clinical and pathological complete response (pCR) in women with locally-advanced HER2-overexpressing breast cancer (11). Based on these findings, the incorporation of the docetaxel-trastuzumab combination into neoadjuvant therapy would appear to be promising. In the neoadjuvant setting, pCR rate is considered to be correlated with disease-free and overall survival (4,12).

Some studies, investigating the relationship between the signal ratio of HER-2/chromosome 17 centromere (CEP17) and response rate to trastuzumab monotherapy in breast cancer, reported a higher response rate in tumours with high signal ratio. c-MYC is a proto-oncogene that has been implicated in the control of cellular growth, proliferation and cell survival, and plays pivotal roles in proliferation, differentiation and apoptosis. Results from reports on the prognostic value of the overexpression of c-MYC mRNA or protein are conflicting (13), and should be interpreted with caution. Kim *et al* (14) demonstrated that high c-MYC gene copy number tumours are more responsive to chemotherapy using trastuzumab and taxanes. However, the relationship between HER-2 or c-MYC gene copy number and the pathological response to neo-

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Table I. Classification of pathological responses according to the Japanese Breast Cancer Society.

Response	Description of pathological findings
Grade 3 (Complete response)	Necrosis or disappearance of all tumour cells. Replacement of all cancer cells by granuloma-like and/or fibrous tissue. In the case of complete disappearance of cancer cells, pretreatment pathological evidence of the presence of cancer is necessary
Grade 2 (Marked response)	Marked changes in ≥2/3 of tumour cells
Grade 1 (Slight response)	1a) Mild response: mild change in cancer cells regardless of the area, or marked changes in <1/3 of cancer cells 1b) Moderate response: marked changes in ≥1/3 but <2/3 of tumour cells
Grade 0 (No response)	Almost no change in cancer cells

adjuvant therapy with a docetaxel/trastuzumab-containing regimen has not been reported. In addition, the major role of the gene BRCA1 is to respond to DNA damage by participating in the cellular pathways for DNA repair, mRNA transcription, cell cycle regulation and protein ubiquitination (15). The Ki-67 protein is a proliferation marker expressed only in cycling cells, and correlates with S-phase fraction (16). Several *in vitro* and *in vivo* studies have demonstrated that the immunohistochemical expression of BRCA1 and Ki-67 in breast cancer cells might be a useful predictive factor for chemotherapy using taxanes.

In this study, we conducted an open-label multicentre phase II trial in patients with operable HER-2-overexpressing breast cancer, and reported the efficacy and safety of triweekly (i.e., once every 3 weeks) docetaxel combined with weekly trastuzumab as neoadjuvant chemotherapy (17). We then investigated the relationship between the signal ratios of HER-2/CEP17 and c-MYC/CEP17 estimated by FISH, the immunohistochemical expression of BRCA1 and Ki-67, and the pathological complete response rate of cancer cells undergoing neoadjuvant chemotherapy using docetaxel and trastuzumab. We further evaluated the usefulness of investigating these factors.

Materials and methods

Study design and ethics. This was a multicentre open-label single-arm phase II trial, conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the institutional review board of each participating centre. All patients gave their written informed consent.

Patients. Women with histologically-confirmed locally-advanced breast cancer whose tumours overexpressed HER-2 were eligible for the study. HER-2 status was confirmed by immunohistochemistry (IHC), and patients with tumours graded with an IHC score of 3+ were enrolled. Other inclusion criteria were a tumour diameter ≥3 cm, a node-positive tumour or both, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, age of 20-75 years, measurable disease, haemoglobin >9 g/dl, a white blood cell count between 4000/mm^3 and 12000/mm^3, neutrophils >2000/mm^3, platelets >100000/mm^3, serum bilirubin within normal range, aspartate aminotransferase and alanine aminotransferase <100 IU/l and serum creatinine ≤1.5 times the upper normal limit. Prior chemo-, radio-, or immunotherapy, or prior endocrine therapy, were not allowed. Pregnant women or women who might be pregnant were excluded from the study. Other exclusion criteria included contralateral breast cancer, uncontrolled concomitant disease, active concomitant malignancy (disease-free period <5 years), a history of myocardial infraction or clinically important cardiovascular disease, a left ventricular ejection fraction <50% or below the upper limit of normal, a New York Heart Association functional classification of II-IV, suspected infection with fever, motor paralysis or peripheral neuropathy, pleural or pericardial effusion requiring treatment, symptomatic brain metastasis, oedema of grade 2 or higher, interstitial pneumonia or lung fibrosis or an allergy to polysorbate 80.

Treatment procedure. Patients received docetaxel every 3 weeks and trastuzumab every week. In each cycle, 70 mg/m^2 docetaxel was administered intravenously (i.v.) over more than 60 min. Trastuzumab (2 mg/kg) was administered i.v. over 90 min, with the exception of the first treatment (day 1 of the first cycle) in which a loading dose of trastuzumab 4 mg/kg was administered i.v. over 90 min. For the first cycle, docetaxel was administered on day 2, and trastuzumab on days 1, 8 and 15. After the first cycle, docetaxel was administered on day 1 and trastuzumab on days 1, 8 and 15 of each cycle. Patients received 4 cycles of combination treatment, unless disease progression or unacceptable toxicity was observed.

Outcome measures. The primary endpoints were pathological response and clinical tumour response. Pathological response was assessed at the time of breast surgery according to the 'General Rules for Clinical and Pathological Recording of Breast Cancer: Histopathological Criteria for Assessment of Therapeutic Response in Breast Cancer' developed by the Japanese Breast Cancer Society (18). Hematoxylin and eosin (H&E) stained slides from the primary tumour were obtained. Slides were prepared by each institution as 5 mm interval gross tissue sections. A central review committee, consisting

Table II. Baseline characteristics of 21 women with HER-2-overexpressing breast cancer treated with a combination of docetaxel and trastuzumab.

Characteristic	Patients (n=21)
Median (range)	(33-69)
Age (years)	54
ECOG performance status, no. (%)	
0	18 (86)
1	3 (14)
Median (range) tumour size, cm	5.4 (1.3-15)
Clinical lymph nodes status, no. (%)	
N0	8 (38)
N1	12 (57)
N3	1 (5)
Pathological characteristics, no. (%)	
Ductal invasive carcinoma	20 (95)
Unknown	1 (5)
Postmenopausal, no. (%)	13 (62)
Receptor status, no. (%)	
Estrogen receptor positive	3 (14)
Progesterone receptor positive	0 (0)
Proposed surgery, no. (%)	
Mastectomy	17 (81)
Lumpectomy	4 (19)

of two pathologists working independently of local pathologists, assessed the pathological response to the therapy. The criteria are shown in Table I.

Evaluation of biological markers. All specimens obtained by core needle biopsy pre-treatment were fixed with 10% formalin-buffered solution and embedded in paraffin, and thin sections were used for FISH evaluation and immunohistochemistry.

FISH examination of HER-2 was performed using FISH kits for the evaluation of HER-2 gene status (Vysis Ltd., USA) according to protocol. The nuclei of 20 carcinoma cells in invasive lesions were identified, the numbers of fluorescent signal of both HER2 and CEP17 were counted and their signal ratios were calculated. We divided cases into high (>6.0) and low (≤6.0) groups according to signal ratio (19). FISH examination of c-MYC was also performed using c-MYC FISH kits (Dako Ltd., Denmark) According to the protocol, the numbers of c-MYC and CEP17 signals were counted and their signal ratios calculated. The cutoff line for the high and low groups was defined as 2.5 according to single color cut-off 5.0 (14). Immunohistochemistry for BRCA1 (Ab-1, Oncogene, USA) and Ki-67 (MIB1, Dako) was performed using specimens from core needle biopsy. The cutoff for IHC was defined ≥10% cells stained positive.

Table III. Pathological response of 19 women with HER-2-overexpressing breast cancer treated with a combination of docetaxel and trastuzumab.

Response[a]	No. of patients (%)
Grade 3	4 (21)[b]
Grade 2	7 (37)
Grade 1	8 (42)
Grade 0	0 (0)

[a]Classified according to the criteria of the Japanese Breast Cancer Society. [b]95% confidence interval, 6-46%.

Statistical consideration. The primary endpoint of this study was pCR response rate. The sample size was 20 patients, calculated based on binominal distribution (with a type I error of 5% and a study power of 80%). The correlation between pCR and each biomarker was assessed for significance in all analysis.

Results

Between July 2004 and March 2005, 21 women were enrolled. Table II summarises the baseline characteristics of all 21 patients. The median age was 54 years (range 33-69). Median pre-treatment tumour size was 5.4 cm (range 1.3-15 cm). Clinically-positive lymph nodes were observed in 13 patients (N1=12, N2=1). Tumours with invasive ductal carcinoma were present in 20 patients (95%) and mastectomy was recommended for 17 patients (81%).

All patients completed 4 cycles of combination treatment. No patients required docetaxel dose reduction. Two patients were later found to be inoperable owing to liver metastasis, and were therefore excluded from the efficacy analysis.

The overall clinical tumour response rate was 89% (95% CI, 67-99%) with complete response in 5 patients (26%), partial response in 12 (63%) and stable disease in 2 (11%). Eleven patients (52%) underwent breast-conserving surgery.

Table III shows the results of pathological response. Four of 19 cases (21%) were grade 3 (pCR), 7 (37%) were grade 2 and 8 (42%) grade 1. The pCR rate was 21%

Table IV shows the relationship between the pCR rate and the biomarkers (HER-2, c-MYC, BRCA1 and Ki-67). Four cases (4/13, 29%) with high HER-2 expression achieved pCR, whereas none with low expression did. Three cases (3/10, 30%) with high c-MYC expression achieved pCR, whereas only one case (1/9, 11%) with low c-MYC did. Patients with high c-MYC expression also seemed to have a high pCR rate compared to patients with low expression. Three cases (3/14, 21%) were positive for Ki-67 and 1 (1/5, 20.0%) was negative. Three cases (3/13, 23%) were positive for BRCA1 and one (1/6, 16%) was negative. No significant difference in pCR rate was shown based on the predefined cutoff of all the biological markers.

Table IV. Association between pathological response and the expression of biological markers in 19 women with HER-2-overexpressing breast cancer treated with a combination of docetaxel and trastuzumab.

Biological marker	No. of patients	No. who achieved pCR (%)
HER2		
High (>6)	14	4 (29)
Low (<6)	5	0 (0)
c-MYC		
High (>2.5)	10	3 (30)
Low (<2.5)	9	1 (11)
BRCA1		
Positive (≥10%)	13	3 (23)
Negative (<10%)	6	1 (17)
Ki-67		
Positive (≥10%)	14	3 (21)
Negative (<10%)	5	1 (20)

pCR, pathological complete response.

Discussion

Previous studies have indicated the efficacy and safety of the docetaxel/trastuzumab combination in patients with HER-2-overexpressing metastatic breast cancer (20-23). In our trial, the results showed that this pairing is promising as neoadjuvant chemotherapy with a pCR rate of 21% and an overall clinical tumour response rate of 89%.

The pCR and overall clinical tumour response rates in our trial are within the ranges of those achieved by docetaxel- or trastuzumab-containing regimens in this setting. Trudeau *et al* reviewed the published results of randomised controlled trials of neoadjuvant taxane chemotherapy, and reported the pCR and overall clinical tumour response rates of docetaxel-containing regimens as ranges of 5-31 and 25-91%, respectively (24). Although participants in these trials were not patients with HER-2-overexpressing cancer, these results in part support the efficacy of our regimen. Montemurro and Aglietta reported that the pCR and overall clinical tumour response rates of trastuzumab-containing neoadjuvant therapy ranged between 12 and 65% and 60 and 93%, respectively (11). The pCR rate in our trial is not low considering that relatively large tumours (median, 5.4; range, 1.3-15 cm) were included.

Trastuzumab is a humanised monoclonal antibody directed against HER-2 protein. Thus, it is reasonable to consider that HER-2 would predict response to a trastuzumab-containing regimen. It has been reported that trastuzumab is more effective in cases with a high signal ratio of HER-2/CEP17. Response rates in a Genentech H0649 clinical trial of trastuzumab were as follows: the response rate was 0% in cases with <2.0 signal ratio, 13% in cases with 2.0-6.0 and 25% in cases with >6.0. In this study, 4 cases (4/13, 29%) with high HER-2 expression achieved pCR, whereas no cases with low expression did (14).

Overexpression of c-MYC may be correlated with better treatment outcome, considering that proliferating cells are usually more sensitive to chemotherapy. A high signal ratio of c-MYC/CEP17 is known to be more sensitive to trastuzumab therapy. c-MYC plays two conflicting roles in both apoptosis and cell proliferation. Under HER-2 overexpression, the survival signals suppress only the apoptotic role of c-MYC, resulting in its cell proliferation role dominating. Trastuzumab, however, blocks the survival signals of HER-2 so that c-MYC can induce apoptosis (13). In the present study, 3 cases (3/10, 30%) with high c-MYC expression achieved pCR, whereas only one case (1/9, 11%) with low c-MYC did. Patients with high c-MYC expression also had a higher pCR rate than did patients with low expression.

Based on these results, we can suggest that the signal ratios of HER2/CEP17 and c-MYC/CEP17 might be useful factors in predicting sensitivity to docetaxel/trastuzumab-combination therapy. If patients with a high signal ratio of HER2/CEP17 or c-MYC/CEP17 were treated with this regimen, a higher rate of pathological complete response could be expected.

We found few patients bearing tumours negative for Ki-67 or BRCA1. This sample size is too small to be considered for its correlation with pCR. Pre-clinical study results suggested that BRCA1 might be required for the response to spindle poisons (25), and a recent retrospective study showed that increased BRCA1 expression is correlated with a longer time-to-progression in patients with metastatic breast cancer treated with taxane-containing chemotherapy (26). However, another clinical trial showed no significant correlation between the expression of BRCA1 and response to docetaxel (27). The role of BRCA1 in predicting response to taxane therefore remains to be clarified.

This was a small sample size single arm phase II trial. In the absence of a control group, we cannot draw any definite conclusions from the results. Although pCR has been shown to predict disease-free and overall survival (4,12), the effect of combination docetaxel and trastuzuman on survival should be confirmed by a clinical trial with long-term follow-up. In addition, the predictive biomarkers of response to this combination should be confirmed by a large-scale randomised controlled trial. Considering that no reliable predictive bio-marker of response to chemotherapy in early-stage breast cancer has been found to date, a clinical trial prospectively designed to investigate the association between biomarker expression and chemotherapeutic response will be needed.

Despite these limitations, we conclude that combination treatment with tri-weekly docetaxel and weekly trastuzumab is a promising regimen in patients with HER-2-overexpressing operable breast cancer. Further study is warranted.

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