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ORIGINAL ARTICLE

Efficacy and safety of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive metastatic breast cancer

Tomo Osako · Yoshinori Ito · Shunji Takahashi · Nahomi Tokudome · Takuji Iwase · Kiyohiko Hatake

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Abstract
Purpose We retrospectively evaluated the efficacy and safety of combination therapy of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive metastatic breast cancer (MBC).
Methods Patients with HER2-positive MBC who had been administered the combination therapy between July 2003 and July 2006 at the Cancer Institute Hospital, Tokyo, were retrospectively reviewed. Capecitabine (828 mg/m^2) was given twice daily for 3 weeks followed by a 1-week rest period; this was repeated every 4 weeks. Trastuzumab was given at 4 mg/kg as an initial loading dose intravenously, followed by 2 mg/kg weekly. We investigated objective response rate (ORR), clinical benefit rate (CBR), and time-to-treatment failure (TTF) according to the Response Evaluation Criteria in Solid Tumors guidelines. Adverse events were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0.
Results A total of 49 patients were assessed and median follow-up time of patients was 16.2 months (1.4–43.5 months). ORR was 16% (95% confidence interval: 7–30%) and CBR was 47% (95% confidence interval: 32–62%). Median TTF was 5.4 months. Common adverse effects were hand–foot syndrome, liver dysfunction, and bone marrow suppression. Grade 3 adverse events were observed in nine patients (18%). One patient (2%) suffered from symptomatic chronic heart failure, which improved after discontinuation of trastuzumab.
Conclusions The combination therapy of trastuzumab plus capecitabine is effective and tolerable for heavily pretreated patients with HER2-positive MBC.

Keywords Capecitabine · Trastuzumab · HER2-positive · Metastatic breast cancer

T. Osako (✉) · Y. Ito · S. Takahashi · N. Tokudome · K. Hatake
Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-10-6, Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: tomo.osako@jfcr.or.jp

T. Osako · T. Iwase
Department of Breast Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-10-6, Ariake, Koto-ku, Tokyo 135-8550, Japan

Introduction

HER2/neu is a surface membrane protein, member of the type I epidermal growth factor receptor family, encoded by the c-erb-b2 gene. In human breast cancer, c-erb-b2 gene amplification occurs in 25–30% of patients [1, 2]. The gene amplification induces HER2/neu protein overexpression. The overexpression results in a constitutive activation of the HER2/neu signaling pathways and an increase of cell proliferations [3]. Clinically, HER2/neu alteration is associated with an adverse prognostic profile, including shortened time to progression and overall survival in patients whose primary breast tumors contain the HER2/neu abnormality [1, 2, 4].

Trastuzumab is a humanized monoclonal antibody that binds with a specific epitope of the HER2 protein [1, 2, 4]. Trastuzumab as a single agent induced responses in 15–20% of patients with HER2-overexpressing breast cancer [5–7]. Furthermore, there is clear synergism between trastuzumab and several chemotherapeutic agents including cisplatin [8], docetaxel [9], paclitaxel [10], and vinorelbine [11, 12]. So, many clinicians continue trastuzumab therapy and change one chemotherapeutic agent for another sequentially in patients with HER2-positive metastatic

breast cancer (MBC), when the disease has progressed during treatment, in the hope of taking advantage of this possible synergy.

Capecitabine is an oral fluoropyrimidine carbonate, which is converted to 5FU selectively in tumors through a cascade of three enzymes [13]. Based on the differential distribution of these three enzymes in different tissues, this drug is designed to yield more 5FU in cancer cells than in bone marrow cells or gastrointestinal epithelial cells [13]. Capecitabine is effective and well tolerated for MBC patients who have failed anthracycline- and taxane-containing regimen [14–19]. Therefore, capecitabine is one of key drugs for patients with MBC.

However, for patients with HER2-positive MBC, there are not enough data about the efficacy and safety of the combination therapy of trastuzumab plus capecitabine. Therefore, the purpose of the present single-institute retrospective study is to evaluate efficacy and safety of combination therapy of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive MBC.

Materials and methods

Patients

Patients with HER2-positive MBC who had been administered combination therapy of trastuzumab plus capecitabine between July 2003 and July 2006 at the Cancer Institute Hospital, Tokyo, were retrospectively reviewed. The eligibility criteria were as follows: (1) trastuzumab plus capecitabine, (2) metastatic breast cancer, (3) HER2-positive cancer (HER2 protein scored as 3+ in immunohistochemistry or HER2 gene-amplified twofold or greater in fluorescence in situ hybridization), (4) lesion(s) measurable according to the Response Evaluation Criteria in Solid Tumors guidelines, (5) performance status of three or less according to the Eastern Cooperative Oncology Group's scale.

Treatment plan

Capecitabine was given orally at a dosage of 828 mg/m^2, twice daily for 3 weeks followed by a 1-week rest period. This was repeated every 4 weeks. The dose was calculated on the basis of body surface area at baseline (Table 1). The schedule of trastuzumab is 4 mg/kg as an initial loading dose intravenously, followed by 2 mg/kg weekly. This regimen was registered with the hospital.

Patients with an objective response or stable disease (SD) could continue to receive the combination treatment until progressive disease (PD) or unacceptable toxicity developed.

Table 1 Determination of capecitabine dose according to body surface area

Body surface area (m^2)	Dose (mg, twice daily)
<1.31	900
1.31–1.64	1,200
≥1.64	1,500

Treatment interruption and/or individual dose adjustment of capecitabine was considered when patients experienced any adverse events assessed at grade 2 or more as defined by the National Cancer Institute, Common Toxicity Criteria, version 3.0.

Evaluation of efficacy and safety

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines by the investigators and the independent reviewers, with computed tomography scans at baseline and every 2 or 3 months. Complete response (CR) was defined as the disappearance of all known lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of the sum of all measurable lesions by at least 30%. PD was defined as an increase of the sum of all measurable lesions by than greater 20% or as the appearance of a new lesion and stable disease (SD) was defined as neither CR, PR, nor PD. Long SD was defined as SD lasting for more than 24 weeks.

Objective response rate (ORR) was defined as the sum of CR and PR rates. Clinical benefit rate (CBR) was defined as the sum of CR, PR, and long SD rates. Time-to-treatment failure (TTF) was defined as the period from the commencement of capecitabine to discontinuation of capecitabine and/or trastuzumab due to PD or unacceptable toxicity.

All adverse events and laboratory parameters were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0. Objective and subjective adverse events were assessed every week and laboratory parameters were assessed every 4 weeks.

Statistical analysis

Calculation of TTF was done by the Kaplan–Meier method, in order to analyze censored data. Confidence intervals (CI) were set at the 95% level.

Results

Patient characteristics

In the present study, 49 patients were assessed. Median follow-up time of patients was 16.2 months and the range was

1.4–43.5 months. All patients were Japanese women. The demographic characteristics of the present study population are presented in Table 2. Regarding hormonal status, 59% of patients were both estrogen and progesterone receptors negative. With regard to HER2 status, 86% of the patients were HER2 protein 3+ in immunohistochemistry and 14% were HER2-gene amplified in FISH.

The patients in the present study ailed from advanced disease. More than half of the patients (57%) had three or more metastatic organs. Approximately half of the patients had visceral metastasis of either the lung (49%) or liver (39%).

Table 2 Baseline patient and disease characteristics ($n = 49$)

Characteristics	No. of patients	%
Mean age (range)	54.3 (33–72)	
Performance status		
0	42	86
1	5	10
2	2	4
Estrogen receptor/progesterone receptor status		
+/+	9	18
+/−	9	18
−/+	2	4
−/−	29	59
HER2 status		
IHC 3+	42	86
FISH positive	7	14
No. of metastases		
Mean (range)	2.6 (1–5)	
1	8	16
2	13	27
3	28	57
Sites of metastases		
Lymph node	33	67
Lung	24	49
Bone	20	41
Liver	19	39
Chest wall/skin	19	39
Chemotherapeutic pretreatment	49	100
Adjuvant or neoadjuvant setting	24	49
Anthracyclines	20	41
Taxanes	12	24
Metastatic setting	47	96
1 prior regimen	8	16
2 prior regimens	17	35
Mean number of regimens (range)	2.7 (0–8)	
Anthracyclines	26	53
Taxanes	42	86
Trastuzumab	43	88

IHC Immunohistochemistry, *FISH* fluorescence in situ hybridization

Moreover, they had been heavily pretreated. Approximately 90% of the patients were pretreated with anthracyclines (42 of 49; 86%) and taxanes (43 of 49; 88%) in the adjuvant, neoadjuvant, and/or metastatic settings, and 88% (43 of 49) of the patients were pretreated with trastuzumab-containing regimens in the metastatic setting. The mean number of chemotherapeutic pretreatment regimens was 2.7 (range 0–8, median 2) in the metastatic setting.

Efficacy

Of the 49 patients, response was assessable in 44 patients. One patient achieved CR (2%), and seven patients achieved PR (14%). Therefore, ORR for capecitabine was 16% (95% CI: 7–30%). Moreover, 16 patients achieved SD, and of these, 15 achieved long SD (31%); hence, CBR for capecitabine was 47% (95% CI: 32–62%) (Table 3). Median TTF was 5.4 months (Fig. 1). Median overall survival (OS) has not been reached.

Safety (Table 4)

Grade 3 adverse events were observed in nine patients (18%). No grade 4 event was observed. Treatment interruption and/or individual dose adjustment of capecitabine was required in 15 patients (31%).

Table 3 Response to trastuzumab plus capecitabine ($n = 49$)

	No. of patients	%
Response		
Complete response	1	2
Partial response	7	14
Stable disease	16	33
(Long stable disease)	(15)	(31)
Progressive disease	21	43
Not evaluable	4	8
Objective response rate	8	16
Clinical benefit rate	23	47

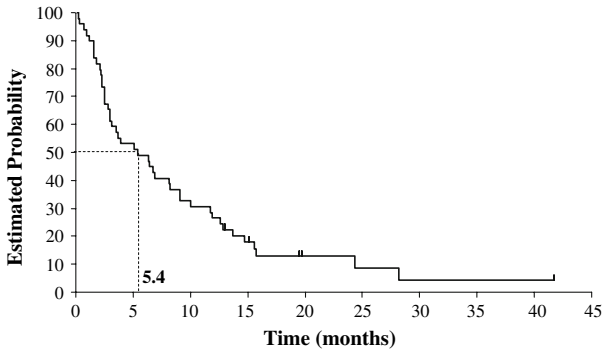

Fig. 1 Time-to-treatment failure ($n = 49$)

Table 4 Summary of adverse events worst by patient ($n = 49$)

	Total		Grade 1		Grade 2		Grade 3	
	No.	%	No.	%	No.	%	No.	%
Hand-foot syndrome	32	65	15	31	13	27	4	8
Fatigue	18	37	18	37				
Nausea	12	24	11	22	1	2		
Diarrhea	10	20	8	16	1	2	1	2
Anorexia	4	8	3	6	1	2		
Vomiting	4	8	4	8				
Interstitial pneumonia	1	2					1	2
Chronic heart failure	1	2					1	2
Leukopenia	27	55	20	41	7	14		
Neutropenia	13	27	7	14	6	12		
Anemia	14	29	8	16	4	8	2	4
Thrombocytepenia	1	2			1	2		
AST elevation	27	55	25	51	1	2	1	2
ALT elevation	15	31	10	20	4	8	1	2
Total bilirubin elevation	17	35	11	22	6	12		
Creatinine elevation	1	2	1	2				
All events	47	96	12	24	26	53	9	18

No grade 4 event was observed

Common adverse effects of the combination therapy were hand–foot syndrome, liver dysfunction, and bone marrow suppression. First, 32 patients had hand–foot syndrome (65%). This was classified as grade 3 in four patients (8%). Second, elevation of AST, ALT, and total bilirubin were noted in 27 (55%), 15 (31%), and 17 patients (35%), respectively. Grade 3 liver dysfunction occurred in one patient (2%). Third, effects of bone marrow suppression as leukopenia, anemia, and neutropenia were seen in 27 (55%), 14 (29%), and 13 patients (27%) at all grades; however grade 3 occurred in 2 patients (4%).

One patient suffered from grade 3 interstitial pneumonia, which improved after discontinuation of trastuzumab plus capecitabine.

Another patient without past medical history of cardiac dysfunction suffered symptomatic chronic heart failure (CHF), which improved after discontinuation of trastuzumab. She had been given doxorubicin in the neoadjuvant setting (total dose 300 mg/m^2). And also, she had been given trastuzumab in the metastatic setting for 1 year and 7 months. The interval between anthracycline and trastuzumab/capecitabine therapy was 2 year and 11 months.

Discussion

This retrospective study showed that the combination therapy of trastuzumab plus capecitabine is effective and safe for heavily pretreated patients with HER2-positive MBC. ORR was 16% and CBR was 47% (Table 3). Median TTF was 5.4 months (Fig. 1). Grade 3 adverse events were observed in 18% of the patients, but symptoms were improved after discontinuation of the therapy (Table 4).

Preclinical data investigating the combination of trastuzumab with 5FU showed that this combination was less effective than either drug alone, suggesting antagonism in vitro, whereas it may be synergic (cisplatin, thiopeta, etoposide) or additive (doxorubicin, paclitaxel, methotrexate, vinblastin) [20]. However, further studies indicated that trastuzumab and 5FU prodrug capecitabine had at least additive antitumor activity in in vivo models [21]. The reason for the discrepancy between the in vivo and in vitro results has not been clarified [21].

In the clinical setting, the combination therapy of trastuzumab plus capecitabine is effective for patients with HER2-positive MBC. In German multicenter phase II study of weekly trastuzumab with capecitabine (1,250 mg/m2 twice daily on days 1–14, tri weekly) in patients with pretreated MBC ($n = 27$), ORR was 45%, CBR was 68%, median progression-free survival time was 6.7 months, and median OS was 28 months [22]. Using the same treatment regimen as the German trial, this high ORR was mirrored in Chinese phase II study of the first-line therapy ($n = 43$), in which an ORR of 63% was recorded [23]. In Japanese phase II trial ($n = 27$), using the same regimen as the present study, ORR was 41%, median time to progression was 5.2 months, and median OS was 16.1 months [24]. In the present study, although ORR was inferior to these studies, tumor was

controlled for a relatively long time, considering the poor prognosis of the patients in the study population who had been heavily pretreated for the multiple metastases.

Furthermore, the combination therapy of trastuzumab plus capecitabine is well tolerated. The German trial showed that grade 3/4 adverse events were general pain (28%), motor dysfunction (16%), hand-foot-syndrome (16%), nausea (12%), anemia (8%), and leucopenia (4%) [22]. The Chinese trial showed that grade 3 hand–foot syndrome occurred in 9% and myelosupression occurred in 1% of patients [23]. The Japanese trial, same regimen as the present study showed no reports of grade 3/4 events [24]. Our results of adverse events are in the range of these prior studies.

The most clinically significant adverse event of trastuzumab was cardiac dysfunction. Patients ranging 2–5% who were treated with trastuzumab alone developed CHF [6, 7] and 0–2% of patients who were treated with trastuzumab plus non-anthracycline containing combination regimens developed CHF [9–11]. In the present study, grade 3 CHF was observed in one patient (2% Table 4), although approximately 90% of the patients pretreated with anthracycline (Table 2). Therefore, capecitabine added to trastuzumab does not increase CHF. Moreover, the clinically significant adverse events of capecitabine were hand-foot syndrome, liver dysfunction, and bone marrow suppression [14–18, 25, 26]. In the present study, the safety profile is not inferior to that seen in previous studies of capecitabine alone [14–18, 25, 26]. Therefore, trastuzumab added to capecitabine does not increase the adverse events of capecitabine.

In conclusion, the results of the present single-institute retrospective study confirm that the combination therapy of trastuzumab plus capecitabine is effective and tolerable in heavily pretreated patients with HER2-positive MBC.

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