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ORIGINAL ARTICLE

A phase II study of trastuzumab and capecitabine for patients with HER2-overexpressing metastatic breast cancer: Japan Breast Cancer Research Network (JBCRN) 00 Trial

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Abstract
Purpose To determine the response rate and toxicity profile of trastuzumab and capecitabine in women with HER2-overexpressing advanced breast cancer.
Patients and methods A total of 59 patients from 6 participating centers in Japan entered onto the study of trastuzumab and capecitabine. Eighty six percent of women had received prior chemotherapy as part of adjuvant (21.4%) or metastatic treatment (48.2%), or both (16.1%), including substantial portions of patients who had previously received either CMF (7.1%), anthracyclines (28.6%), taxanes (25.0%), or both types (25.0%) of chemotherapy.
Results Responses were observed in 28 of 56 patients (overall response rate, 50%). The response rate was 65.0% in patients treated with trastuzumab and capecitabine as first-line therapy for metastatic disease, and 62.5% among HER2 +3 positive patients, while high response rates were also seen in women treated with second- or third-line therapy. Patients receiving trastuzumab and capecitabine as first-line therapy had a longer TTP than did patients receiving this treatment as second- or third-line therapy (median TTP, 280 vs. 130 days, $P < 0.05$). Further, patients receiving trastuzumab and capecitabine as first-line therapy had longer OS than did patients receiving this treatment as second- or third-line therapy (median OS, 780 days vs. 480 weeks, $P < 0.05$). The treatment-related adverse events were hand–foot syndrome (30.4%), nausea (25%), diarrhea (10.7%), stomatitis (10.7%), fatigue (7.1%), and vomiting (5.4%). However, the majority were Grade 1–2 adverse events and only six patients experienced Grade 3 adverse events. Further Grade 1 cardiac toxicity was observed in one patient, while there were no cases of alopecia and treatment-related death.
Conclusion Trastuzumab in combination with capecitabine is highly active in women with HER2-overexpressing metastatic breast cancer and is well tolerated.

Keywords Trastuzumab · Capecitabine · Metastatic breast cancer

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Introduction

Breast cancer is one of the most common malignancies, and is the most common cause of cancer mortality in this population. Approximately 50% of all women diagnosed with breast carcinoma develop metastatic disease, and for these

patients the average survival time from the time of diagnosis of metastatic breast carcinoma ranges from approximately 18 to 30 months. In patients with metastatic disease, treatment is palliative, and pain relief and maintenance of the patient's quality of life are of paramount importance. In this situation, an ideal treatment would offer a reasonable prospect of response and would be well tolerated in an outpatient setting [1, 2].

Trastuzumab (Herceptin®; Chugai, Tokyo) is a humanized monoclonal antibody with specificity for the HER2 protein [3]. The original trials of trastuzumab selected patients whose tumors overexpressed HER2 as measured by immunohistochemistry (IHC). Trastuzumab given to such patients had therapeutic activity. As a single-agent first-line therapy, trastuzumab achieved response rates of 20–25% [4]. Among patients previously treated with chemotherapy for metastatic breast cancer, trastuzumab yielded response rates of 10–15% [4–6]. In retrospective analyses higher response rates to trastuzumab (31% as first-line, 18% as second- and third-line) were seen among patients whose tumors had more pronounced overexpression of HER2 [4–6].

The side effects of trastuzumab are mild, particularly in comparison to standard chemotherapy. There are few gastrointestinal side effects, and no alopecia. The most common treatment-related adverse effect is an infusion syndrome characterized by rigors, chills, or fever that may accompany the initial infusion of trastuzumab in approximately one-third of patients [6]. Preclinical models suggest that trastuzumab may potentiate the effects of chemotherapy when administered concurrently with chemotherapy [7, 8]. Clinical support for this observation comes from a randomized trial, in which women with HER2-positive metastatic breast cancer (IHC +2 or +3) received either chemotherapy or chemotherapy administered concurrently with trastuzumab [9–13]. The combination therapy was associated with higher response rates and longer time to progression (TTP), as well as statistically significant improvement in survival [9–13]. The use of trastuzumab in combination with anthracycline-based chemotherapy was associated with an unacceptably high incidence of cardiac dysfunction [6, 14]. Neither the optimal combination of trastuzumab with chemotherapy nor the optimal timing and sequencing of trastuzumab and chemotherapy have been determined.

Capecitabine (Xeloda®; Chugai, Tokyo) is an oral, enzymatically activated fluoropyrimidine carbamate that was rationally designed to mimic continuous infusion 5-FU [15]. In clinical trials [16–18], capecitabine monotherapy has been well tolerated: the main and reversible adverse effects associated with the drug are hand–foot syndrome, diarrhea, and nausea. The favorable safety profile of capecitabine and the ability to readily manage drug-related toxicities by immediate treatment interruption and, if necessary, dose reduction to each patient's tolerable dose, suggest that this agent might play a major role in the management of metastatic breast cancer [16–18].

We conducted a phase II study to examine the clinical efficacy and side effect profile of trastuzumab and capecitabine in the treatment of women with HER2-positive metastatic breast cancer. The rationale for this particular combination stemmed from the preclinical and clinical data suggesting a favorable interaction between these two agents [8, 9]. In addition, no toxicities such as cardiac toxicity and alopecia all made the addition of capecitabine to trastuzumab a theoretically attractive combination.

Patients and methods

Eligibility

Eligible patients had +2 or +3 HER2-overexpressing metastatic breast cancer, with measurable disease according to the Response Evaluation Criteria in Solid Tumors Group criteria, and no CNS metastasis. Patients were required to be between 18 and 75 years of age, with Eastern Cooperative Oncology Group (ECOG) performance status <3, and provide written informed consent. Patient who had received any number or type of exogenous hormonal therapies, either for treatment of metastatic disease or as adjuvant therapy, were permitted to enroll onto the study, as were patients who had received no more than three prior chemotherapy regimens in the adjuvant or neoadjuvant setting or for treatment of metastatic disease. Prior trastuzumab therapy was not allowed. Patients were required to have a left ventricular ejection fraction (EF) of 50% or greater. Patients could not receive other concurrent antineoplastic therapy. The protocol was reviewed and approved by the institutional review boards at all participating centers.

Treatment plan

The initial trastuzumab infusion was 4 mg/kg intravenous (IV) administration for 90 min. Subsequently, trastuzumab was given weekly at 2 mg/kg IV administered for 60 min. If patients experienced an infusion syndrome, treatment was stopped and patients were assessed and given supportive measures (acetaminophen, diphenhydramine, H2-antagonists, dexamethasone, and meperidine) as needed.

Oral capecitabine was administered at a dose of 1,657 mg/m^2 twice daily on days 1–21 every 4 weeks. Patients were assessed with complete blood cell count and liver function tests every 4 weeks. Patients had left ventricular EF measured every 8 weeks. Patients with asymptomatic decrease in EF of more than 15% from baseline or to

less than the lower limit of normal, or with symptomatic congestive heart failure, were taken off the protocol. All adverse events considered to be possibly, probably, or definitely related to the study treatment were graded 1–4 according to the National Cancer Institute Common Toxicity Criteria. In patients experiencing Grade 2 or more severe toxicities, the standard capecitabine dose modification scheme, described in detail by Blum et al. [18], was applied. Once the dose had been reduced due to toxicity, it was not increased at a later time. Treatment was continued until disease progression or the appearance of prohibitively toxic effects.

Study analysis

After the results of our pilot study, showing a 41% response rate in 27 evaluable patients [19], the decision was made to extend the accrual to a total of 56 patients to better estimate the response rate and its confidence interval.

Patients were restaged every 8 weeks. Patient response to therapy and toxicity was determined according to standard criteria. Patients remained on the study until they withdrew by consent, experienced toxicity prompting cessation of therapy, or had progressive disease (PD). All patients who met the inclusion criteria and exclusion criteria and who were enrolled in the study were included in the intent-to-treat analysis. The primary study end point of this multi-center phase II trial was the overall response rate (complete response [CR] plus partial response [PR]). Disease responses (CR, disappearance of all measurable and nonmeasurable disease; PR, 50% decrease in the sum of bidimensionally measurable disease; PD, 25% increase in sum of bidimensionally measurable disease or appearance of new lesions; stable disease, neither CR, PR, or PD criteria met) were classified based on World Health Organization criteria.

Patient progress followed up every 4 weeks for information about survival status. The Kaplan–Meyer product product limit method was used to determine: (1) time to progression, which was calculated from the date of the first dose of capecitabine and trastuzumab to the date of the first documented tumor progression or death in the absence of tumor progression, (2) time to treatment failure, which was calculated from the date of first dose of capecitabine and trastuzumab to the date of discontinuation for any reason, progression or death in the absence of tumor progression; response duration, which was calculated, in patients achieving a CR or a PR, from the date of the first dose of capecitabine and trastuzumab to the date of documented tumor progression, and overall survival, which was calculated from the first date of the first dose of study drugs to the date of documented death of the patients. Surviving patients were assessed at the date of their most recent follow-up visit.

Results

Patient and treatment characteristics

A total of 59 patients from 6 participating centers in Japan entered onto the study. Two women who were ineligible did not receive the protocol-based study, and one woman who experienced decline in EF (Grade 1) during therapy was taken off the study according to the protocol criteria. Therefore they were not included in the study analysis; the data analyses reflect the experience of the other 56 patients. The patient characteristics are listed in Table 1. Median age was 55 years; most women had good performance status (Eastern Cooperative Oncology Group, 0 or 1). HER2 overexpression was determined by IHC. Thirty-two of the patients on study (57.1%) were +3 overexpressors, 24 had tumors with +2 overexpression.

The majority of women had visceral disease and bone metastasis as shown in Table 1. Most of them (85.7%) had received prior chemotherapy in either the metastatic or/and adjuvant/neoadjuvant setting, with a variety of regimens as indicated. Most patients had previously been treated with either anthracycline-based, taxane-based, or CMF regimens.

Efficacy

The principal end point for the study was the overall response rate on an intent-to-treat basis for the 56 patients in the study, the overall response rate was 50.0% (Table 2). Four complete and 24 partial responses were observed. An additional 20 patients had stable disease in excess of 6 months. Response rates among subgroups of patients defined by clinical characteristics and tumor features are listed in Table 3. As first-line therapy for metastatic breast cancer, trastuzumab and capecitabine had a 65.0% response rate, while the response rate was 41.7% among patients receiving this regimen as second- or third-line therapy. Further response rates were analyzed as a function of the level of HER2 overexpression. For those patients with +3 overexpression, the response rate was 62.5% (20/32), whereas among those patients with +2 overexpression, the response rate was 33.3% (8/24). Tumors were not analyzed for *HER2* gene amplification for fluorescence in situ hybridization.

The TTP for patients on study is shown in Fig. 1. Patients receiving trastuzumab and capecitabine as first-line therapy had longer TTP than did patients receiving this treatment as second- or third-line therapy (median TTP, 280 vs. 130 days, log-rank $P < 0.05$). Of those patients with PD, four (7.1%) were discovered to have new CNS metastases as their site of disease progression. The OS for patients on study is shown in Fig. 2. Patients receiving trastuzumab and capecitabine as first-line therapy had longer OS than did patients receiving this treatment as

Table 1 Patient characteristics

Characteristics	No. of patients (%)
Age, years	
Median (range)	55 (42–70)
ECOG-PS	
0	48 (85.7)
1	8 (14.3)
HER2 expression status	
+2	24 (42.9)
+3	32 (57.1)
No. of metastatic organ sites	
1	26 (46.2)
2	28 (50.0)
3	2 (3.6)
Actual metastatic sites	
Liver	12 (21.4)
Bone	22 (39.3)
Lung/pleura	18 (32.1)
Lymph node	16 (28.6)
Breast/chest wall	14(25.0)
Prior chemotherapy	
None	8 (14.2)
Adjuvant only	12 (21.4)
Metastatic only	27 (48.2)
Adjuvant and metastatic	9 (16.1)
No. of prior regimens for metastatic breast cancer	
0	20 (35.7)
>1	36 (64.3)
Type of prior chemotherapy	
None	8 (14.3)
CMF	4 (7.1)
Anthracycline based	16 (28.6)
Taxane based	14 (25.0)
Anthracycline and Taxane based	14 (25.0)
Disease free interval (month)	
0–24	44 (78.6)
>24	12 (21.4)

Table 2 Patient characteristics overall activity rate for trastuzumab and capecitabine therapy

Clinical category	Response	
	No.	Rate (%)
CR + PR	28	50
Complete response	4	7.1
Partial response	24	42.9
Stable disease >6 months	20	35.7
Progressive disease	8	14.3

Table 3 Response rates among subgroups of patients treated with trastuzumab and capecitabine

Category	No. of Responses/ No. of Patients	Response (%)
HER2 expression status		
+2	8/24	33.3
+3	20/32	62.5
No. of prior regimens for metastatic breast cancer		
0	13/20	65.0
>1	15/36	41.7
Prior chemotherapy		
None	4/8	50.0
Adjuvant only	8/12	66.7
Metastatic only	12/27	44.4
Adjuvant and metastatic	4/9	44.4
Type of prior chemotherapy		
None	4/8	50.0
CMF	4/4	100
Anthracycline based	4/16	25
Taxane based	8/14	57.1
Anthracycline and Taxane based	8/14	57.1
Disease free interval (months)		
0–24	18/44	40.9
>24	10/12	83.3

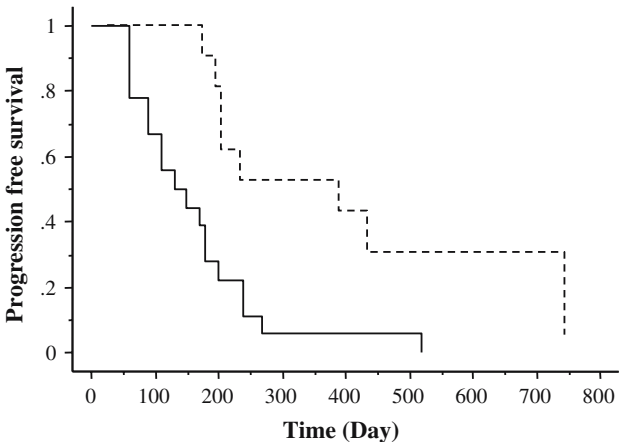

Fig. 1 Proportion of patients without disease progression as a function of the number of prior chemotherapy regimens received for metastatic breast cancer is shown. The *dashed lines* show 0 prior regimen and the *solid lines* show 1 or 2 prior regimens (log-rank $P < 0.05$)

second- or third-line therapy (median OS, 780 days vs. 480 weeks, log-rank $P < 0.05$).

Toxicity

All patients who received trastuzumab and capecitabine (282 cycles) were evaluated for toxicity (Table 4): the

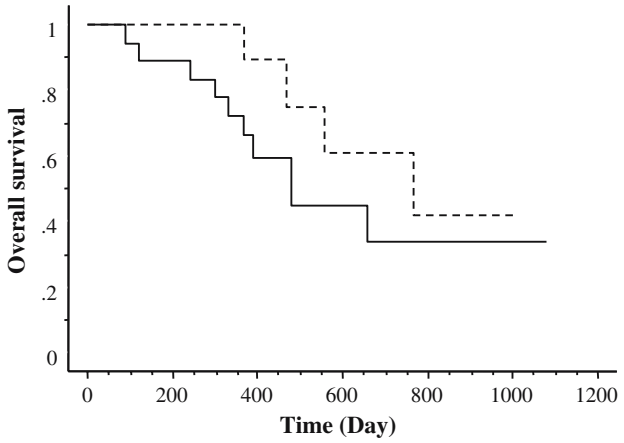

Fig. 2 Proportion of patients surviving as a function of the number of prior chemotherapy regimens received for metastatic breast cancer is shown. The *dashed lines* show 0 prior regimen and the *solid lines* show 1 or 2 prior regimens (log-rank $P < 0.05$)

Table 4 Frequency of treatment-related toxicity

Event	Grade 1–2	Grade 3
	No. of patients (%)	No. of patients (%)
Hematologic		
Neutropenia	1 (1.8)	0
Anemia	1 (1.8)	0
Thrombocytopenia	0	0
Non-hematologic		
Hand–foot syndrome	16 (28.6)	1(1.8)
Diarrhea	5 (8.9)	1(1.8)
Fatigue	4 (7.1)	0
Nausea	11 (19.6)	3(5.4)
Pain	0	0
Stomatitis	5 (8.9)	1(1.8)
Vomiting	3 (5.4)	0
Cardiac, LVEF	1 (1.8)	0

median number of cycles per patient was six (range, 1–8 cycles). The capecitabine dose was reduced to 75% of the starting dose in 6 patients (10.7%). The adverse events leading to dose reduction were nausea (three patients), diarrhea (one patient), hand–foot syndrome (one patient), and stomatitis (one patient). Overall, dose modifications were required after a median of two cycles (range 1–4 cycles). Cardiac function was monitored every 8 weeks by echocardiogram (data not shown). No patient developed symptomatic congestive heart failure during the study. One patient experienced a decline in EF (Grade 1) and was taken off the study according to protocol criteria. In subsequent follow-up, off of trastuzumab treatment, the patient's EF recovered to baseline levels and she was not subsequently retreated with trastuzumab.

Discussion

The results of this multicenter phase II study suggest that treatment with trastuzumab and capecitabine is highly active and well tolerated among women with HER2-overexpressing metastatic breast cancer who have not previously received either therapy. The overall response rate was 50%, with a suggestion of higher response rates observed in subgroups of patients with HER2 +3 positive tumors, and among patients receiving the combination regimen as first-line chemotherapy for metastatic breast cancer. In addition, response rates in excess of 40% were observed for patients receiving the regimen as second- or third-line therapy for metastatic cancer.

Other phase II trials have demonstrated response rates in the order of 60–80% for combinations of trastuzumab with taxanes [6, 11, 12] and vinorelbine [10]. The analysis of a randomized trial of trastuzumab with paclitaxel versus trastuzumab in combination with paclitaxel and carboplatin indicates improvement in time to progression with the triplet combination [13]. The optimal combination of trastuzumab with chemotherapy is not known; comparisons among trials are fraught with difficulty, owing to different definitions of HER2 overexpression and varying degrees of prior therapy. Given these limitations, the results of treatment, in this study, with trastuzumab and capecitabine are generally comparable in terms of response rate and time to progression with other reports of single-agent chemotherapy with trastuzumab. A substantial fraction of patients elected to end the study treatment before experiencing disease progression in favor of trastuzumab monotherapy or trastuzumab with hormonal therapy; this result is a testimony to the palliative efficacy of the regimen. However, neither the clinical benefit of ongoing trastuzumab therapy in such circumstances nor the impact of discontinuation of chemotherapy is known.

The toxicity observed when using trastuzumab in combination with capecitabine did not differ appreciably from that expected from historical experience when using either agent alone. Most toxicities were quite mild and manageable. Gastrointestinal side effects were modest. Sustained therapy with capecitabine and trastuzumab was feasible without encountering cumulative side effects. There were no side effects that emerged with prolonged therapy, and no need for concurrent corticosteroid administration. Cardiomyopathy, a serious toxicity associated with trastuzumab-based therapy, has been reported in 13% of patients receiving paclitaxel and trastuzumab (including severe events in 2% of patients) [6]. However, in this study, only one patient (1.8%) developed Grade 1 cardiac toxicity and her cardiac function recovered to baseline with cessation of trastuzumabtherapy. Therefore trastuzumab in combination with capecitabine is well tolerated in women with HER2-overexpressing metastatic breast cancer.

Although the optimal use of trastuzumab in the treatment of metastatic breast cancer is under active investigation, the combination of trastuzumab and capecitabine may be effective and safe for metastatic breast cancer patients.

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