Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: multicenter phase II and pharmacokinetic study in Japan

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Tolerability and response rate to weekly combination chemotherapy with trastuzumab and vinorelbine in Japanese women with HER2-overexpressing breast cancer not previously receiving either therapy were assessed. Tumor response was evaluated every 4 weeks and adverse events were graded. A total of 23 patients from six participating centers in Japan were enrolled. Median dose intensity of vinorelbine was 16.9 mg/m^2/week and response rate was 73% (complete response + partial response); complete response = 9%, partial response = 64%, and progressive disease = 5%. Time to progression was 361 days, with 75.0% of liver metastases and 60% of lung metastases responding to this treatment. The most common adverse events were leukocytopenia and neutropenia (96%); however, hematologic toxicity associated with vinorelbine was manageable by adjusting the dose. No pharmacokinetic differences for vinorelbine were found between single administration and combination with trastuzumab. This combination therapy produced high response rates and good tolerability, indicating a promising role in first-line chemotherapy for HER2-overexpressing metastatic breast cancer in Japan. *Anti-Cancer Drugs* **19:753–759 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

HER2 protein is a 185-kDa transmembrane tyrosine kinase with homology to the epidermal growth factor receptor. Approximately 25–30% of metastatic breast cancer patients overexpress HER2. Overexpression of HER2, as well as higher nuclear grade, increased tumor cell proliferation, and hormone receptor-negative status, are unfavorable prognostic factors in patients with breast cancer [1].

Trastuzumab is an anti-HER2 humanized monoclonal antibody, showing therapeutic activity in patients with HER2-overexpressing tumors. As first-line therapy, response rate to trastuzumab monotherapy is 26% [2]; however, second-line response rates are only 12–15% [3,4]. If HER2 is overexpressed strongly (+ 3 immunohistochemistry), patients yield better response rates (35% as first-line, 18% as second- and third-line therapies). Trastuzumab exhibits additive or synergistic effects when administered concurrently with chemotherapy [5–7]. Some combination chemotherapy regimens that included trastuzumab resulted in higher response rates, longer time to progression, and significant improvement in survival [5,7]; however, optimal regimens have not been characterized. Synergistic interaction of trastuzumab and vinorelbine, carboplatin, docetaxel, or 4 hydroxycyclophosphamide have been observed [6].

Vinorelbine is a semisynthetic vinca alkaloid that inhibits tubulin polymerization, with response rates of 35–50% as first-line therapy [8–11] and 16–36% as second- or third-line treatment [11–15]. Vinorelbine and trastuzumab combination therapy produced an overall response rate of 68–78%, 68–84% in patients treated with this combination as first-line therapy [16–18]. High response rates (67%) were also observed in women with second- or third-line therapy after pretreatment with anthracyclines and taxanes [16].

The present study was designed to assess safety and tolerability of vinorelbine in combination with trastuzumab in Japanese HER2-overexpressing metastatic breast cancer patients with no earlier chemotherapy for metastatic lesions. Secondary objectives were to evaluate

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tumor response to this combination and characterize vinorelbine pharmacokinetics.

Patients and methods

Eligibility

Eligible patients had stage-IV breast cancer with evidence of HER2 overexpression. Metastatic breast cancer was demonstrated histologically or cytologically to be advanced breast cancer at stage IV or recurrent breast cancer with clinically identified distant metastasis. HER2 overexpression (3+ positive) was determined by immunohistochemistry or HER2/neu gene amplification with fluorescence in-situ hybridization. Before enrollment, an interval of at least 4 weeks from final dose was required if earlier therapy had been received (for luteinizing hormone-releasing hormone agonist 6 weeks). In patients with earlier exposure to anthracyclines, cumulative dose of adriamycin was required to be less than 240 mg/m^2, and patients could not have previously received vinca alkaloids, including vinorelbine or trastuzumab.

Sample size

The sample size calculation is based on the assumption that the true dropout rate in this study by adverse events before completing eight doses was 33.3% or less. Under this assumption, we considered the sample size having 80% probability in which the 95% upper confidence limit of the dropout proportion calculated using the F distribution does not exceed the unacceptable threshold of 66.7%. Nineteen patients or more are enough to demonstrate the tolerance of the administration prescribed by this protocol. In addition, we added three more patients who might not complete eight doses by the progressive disease (PD) on the basis of the PD rate of 15%, which was reported in another clinical study among the patients who had same background. At total 22 patients is the planned sample size and this number is enough to have 19 who are appropriate to evaluate the probability of completing eight doses.

Inclusion criteria

The criteria for inclusion in the study were 20–74 years at the time of informed consent, Eastern Cooperative Oncology Group performance status of 0–2, life expectancy of at least 3 months, absolute neutrophil count greater than 2000/μl or white blood cell count greater than 4000/μl, platelet count greater than 100 000/μl, total bilirubin less than 1.5 × upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase less than 2.5 × ULN, creatinine less than 1.5 × ULN, and po_2 greater than 60 mmHg or SaO_2 greater than 90%. Cardiac function criteria were ECG grade 0–1 cardiac dysrhythmia, National Cancer Institute common toxicity criteria ver. 2.0 grade 0–1 cardiac-ischemia/infarction and left ventricular ejection fraction (LVEF) determined by multigated acquisition scan (MUGA) or echocardiography greater than 50%.

The protocol was reviewed and approved by the ethics committee and institutional review board of each participating institution. All patients gave voluntary written informed consent to participate in this study.

Pharmacokinetics

Sampling

Blood sampling was performed in the first five patients after the first and second doses of vinorelbine. Samples (3 ml) were collected in heparinized silicon-coated tubes from veins different to the veins used to administer vinorelbine at 30 min, plus 1, 2, 4, and 24 h after the start of infusion. Samples were centrifuged; plasma was collected, then immediately frozen, and stored at −20°C until analysis.

Drug bioanalysis

Vinorelbine was extracted from biological fluids containing 500 μl of 1 mol/l glycine–NaCl–NaOH buffer (pH 10) and 4 μl diethylether together with vinblastine, used as internal standard, plus 500 μl plasma sample. After vortex mixing, samples were centrifuged at 2153 rpm for 5 min. Trifluoroacetate (100 μl of 0.05% v/v) was added to the organic phase then mixed and reverse phase extraction performed. The organic phase was removed by centrifugation at 2200*g* for 5 min. Diethylether was removed under a nitrogen stream at 25°C, then 25 μl methanol added to the water phase. Plasma vinorelbine levels were quantified by high performance liquid chromatography assay with ultraviolet detection (optical density = 268 nm; quantification limit = 1 ng/ml). Pharmacokinetic parameters were estimated using noncompartmental analysis software, WinNonLin ver 3.1 (Pharsight; Mountain View, California, USA).

Treatment plan

Vinorelbine and trastuzumab were administered intravenously (i.v.) at weekly intervals. Except for the first dosing, both drugs were administered on the same day as a rule. The first dose of trastuzumab was administered on the day subsequent to first dosing of vinorelbine (after blood sampling) and monitored in a hospital setting for 24 h after the start of dosing. Subsequent administration started after completion of vinorelbine administration on respective dosing days. As mentioned above, inclusion criteria required a neutrophil count > 2000/μl, therefore, at the first administration day, a patient's neutrophil count should be > 2000/μl. After starting treatment, administration of vinorelbine was only performed if the patient had a neutrophil count greater than or equal to 1000/μl.

Vinorelbine (25 mg/m^2) was administered through a free-flowing IV line as a 6–10-min i.v. infusion, followed by 200 ml of saline solution. The initial trastuzumab infusion was 4 mg/kg i.v., administered over 90 min. Subsequent trastuzumab doses were 2 mg/kg i.v., administered over

90 min. Except for the first dosing, trastuzumab was given after vinorelbine administration. The first dose of trastuzumab was administered on the day after the first vinorelbine infusion, to perform pharmacokinetic evaluation of vinorelbine.

Vinorelbine administration was delayed if neutrophil count was less than 1000/μl. If neutrophil count was below this level for more than 2 consecutive weeks, the dose was reduced to 20 mg/m^2; however, no further dose modification was made. The neutrophil count was shown to be below the minimum required level for more than 3 consecutive weeks during the administration at a dose level of 25 mg/m^2 and for more than 2 consecutive weeks even after dose reduction to 20 mg/m^2, the administration of vinorelbine was discontinued.

Trastuzumab administration was delayed if LVEF on the day of treatment was 45–50%, with a 10% or greater reduction compared with baseline, or less than 45%. LVEF was reexamined every 2 weeks to check LVEF level carefully in expectation of early resumption; and if the patient had recovered from toxicity, treatment was resumed. If trastuzumab could not be resumed within 4 weeks, it was discontinued and the patient was withdrawn from the study. No dose reduction of trastuzumab was made.

Investigational drugs were administered at weekly intervals. At least eight doses of vinorelbine were administered, but not in patients with disease progression.

Study analysis

Tumor response was evaluated every 4 weeks for measurable or evaluable lesions according to the General Rules for Clinical and Pathological Recording of Breast Cancer (14th edition) of The Japanese Breast Cancer Society (JBCS), consistent with WHO criteria. Each lesion was reevaluated by Response Evaluation Criteria in Solid Tumors (RECIST). Adverse events were graded using National Cancer Institute common toxicity criteria ver.2.

Results

Patients and treatment characteristics

A total of 23 patients from six participating centers in Japan were enrolled between March 2003 and March 2004. One patient was excluded from efficacy analysis owing to a short treatment period. Clinical characteristics of patients are listed in Table 1. Median age was 57 years, and all had good performance status (Eastern Cooperative Oncology Group, 0 or 1). Nine patients (39%) were diagnosed with stage-IV breast cancer and 14 patients (61%) had recurrences. Seventeen patients (74%) had visceral metastases, such as hepatic and/or pulmonary lesions. Thirteen patients (57%) with recurrent tumor had been pretreated with chemotherapy and/or endocrine therapy in an adjuvant setting: five patients received anthracycline-based regimens; two patients received anthracycline-based and taxane-based regimens; three patients received cyclophosphamide, methotrexate, and 5-fluorouracil combination regimen; one patient received carmofur; and two patients received endocrine therapy only. Vinorelbine and trastuzumab were administered as first-line chemotherapy for all nine patients with stage-IV advanced breast cancer at diagnosis.

Table 1 Patient characteristics

	No. of patients	%
Age, years		
Median (range)	57.0 (31–74)	
<50	5	22
≥ 50	18	78
ECOG performance status		
0	21	91
1	2	9
Diagnosis		
Advanced	9	39
Recurrent	14	61
No. of metastatic sites		
1	6	26
2	5	22
3	6	26
4	6	26
Actual metastatic sites		
Lymph node	17	74
Lung	11	48
Liver	9	39
Breast	9	39
Bone	6	26
Skin	6	26
HER2 expression status		
IHC 3+ positive	19	83
FISH positive (IHC 1, 2+)	4	17
Estrogen receptor status		
Positive	12	52
Negative	11	48
Progesterone receptor status		
Positive	6	25
Negative	17	43
Earlier chemotherapy type (adjuvant in 14 recurrent patients)		
None	3	22
Anthracycline-based	5	36
Taxane-based	0	0
Both anthracycline and taxane-based	2	14
Nonanthracycline and taxane-based	4	29

Total dose of anthracyclines in seven patients (mg/m^2); median: 150, range: 70–213. ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in-situ hybridization; IHC, immunohistochemistry.

At the time of analysis, a total of 750 weekly trastuzumab and 600 weekly vinorelbine treatments had been administered. In six patients, the vinorelbine dose needed to be reduced to 20 mg/m^2 owing to hematologic toxicity. Four patients required granulocyte colony-stimulationg factor administration. Median dose intensity of vinorelbine was 16.9 mg/m^2/week. Dose modification of trastuzumab was not allowed.

Clinical efficacy

Data from all but one patient were extramurally reviewed. This patient's data could not be collected because she had withdrawn from the study because of a severe persecution

complex and manic state before evaluation. With General Rules for Clinical and Pathological Recording of Breast Cancer (14th edition), JBCS, two patients had complete response (CR) (9%), 14 had partial response (PR) (64%), and one had PD (5%). Overall, response rate (CR + PR) was 73% [95% confidence interval: 50–89]. Time to progression was 12 months (361 days) (range: 57–400 days) (Fig. 1). Response of each lesion is shown in Table 2. Results indicate that 75.0% (6/8) of liver metastases and 60% (6/10) of lung metastases responded to this treatment. With the RECIST criteria, another patient's data could not be evaluated because she had a nontarget lesion only, hence we had to evaluate the efficacy on the basis of the data from 21 evaluable patients. When assessed by the RECIST criteria, no patient had CR, as the tumor markers did not fall within normal limits. In evaluable patients, 16 of 21 had PR (76%), resulting in a response rate of 76% (95% confidence interval: 53–92) and no patient had PD.

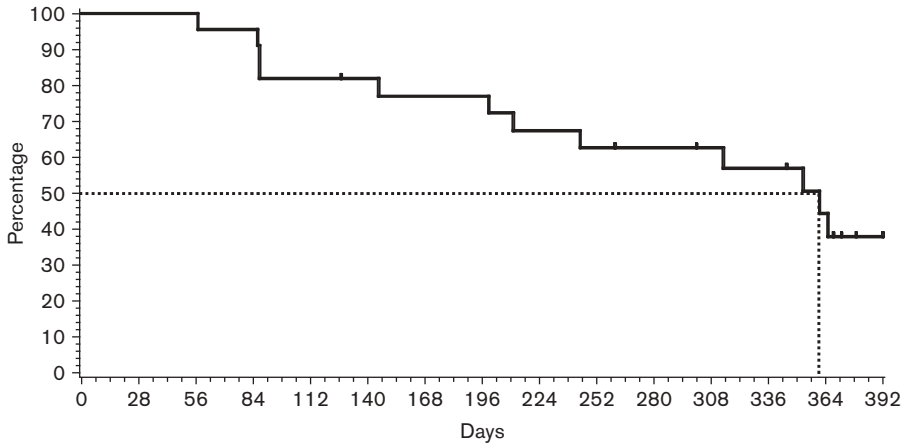
Toxicity

Adverse events observed in greater than 50% of patients are listed in Table 3. Most adverse events were of grade 1 or 2. The most frequent was bone marrow suppression, with grade 4 adverse events observed in this category only: 16 patients (70%) and 19 patients (83%) were affected by grade 3 or 4 leukocytopenia and neutropenia, respectively. Febrile neutropenia occurred in one patient (4%) and infection with grade 3 or 4 neutropenia was observed in three patients (13%); however, all resolved without any complications.

Several nonhematologic adverse events were observed in this therapy. Grade 1 or 2 allergic reaction and fever related to trastuzumab were observed in 17 (74%) and 16 (70%) patients, respectively. Inflammatory reaction at the injection site was the most common adverse event associated with vinorelbine. Grade 1 or 2 toxicity was observed in 17 patients (74%). Gastrointestinal toxicity related to these drugs was usually mild: 14 patients (61%) had anorexia, one (4%) had a grade 3 event, and mild stomatitis affected 18 patients (78%). As many as 12 patients (52%) complained of mild alopecia, contrary to expectations. Neurotoxicity was also mild; neuropathic sensory grade 1 or 2 toxicity was observed in 10 patients (44%) and one had (4%) a grade 2 event.

According to the study protocol, cardiac function should be examined every 4 weeks with MUGA or echocardio-

Fig. 1



Time to progression (Kaplan–Meier).

Table 2 Therapeutic effects

	No. of patients						
Site	Total	CR	PR	MR	NC	PD	Response rate (%) (95% CI)
Overall	22	2	14	2	3	1	73 (50–89)
Lymph node	16	5	6	3	2	0	69
Lung	10	1	5	0	4	0	60
Breast	9	1	6	1	1	0	78
Liver	8	0	6	0	2	0	75
Skin	4	1	3	0	0	0	100
Bone	3	0	3	0	0	0	100

CI, confidence interval; CR, complete response; MR, minor response; NC, no change; PD, progressive disease; PR, partial response.

Table 3 Toxicity per patient

	No. of patients (%)				
Toxicity	Total	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	22 (96)	1 (4)	5 (22)	15 (65)	1 (4)
Neutrophils	22 (96)	0	3 (13)	10 (43)	9 (39)
Hemoglobin	20 (87)	8 (35)	12 (52)	0	0
Allergic reaction/ hypersensitivity	17 (74)	4 (17)	13 (57)	0	0
Fatigue	17 (74)	11 (48)	6 (26)	0	0
Fever	16 (70)	11 (48)	5 (22)	0	0
Rigors, chills	15 (65)	15 (65)	0	0	0
Alopecia	12 (52)	10 (44)	2 (9)	0	0
Injection site reaction	17 (74)	11 (48)	6 (26)	0	0
Anorexia	14 (61)	8 (35)	5 (22)	1 (4)	0
Nausea	13 (57)	9 (39)	4 (17)	0	0
Stomatitis/pharyngitis	18 (78)	16 (70)	2 (9)	0	0
SGPT (ALT)	12 (52)	4 (17)	6 (26)	2 (9)	0
Headache	12 (52)	11 (48)	1 (4)	0	0

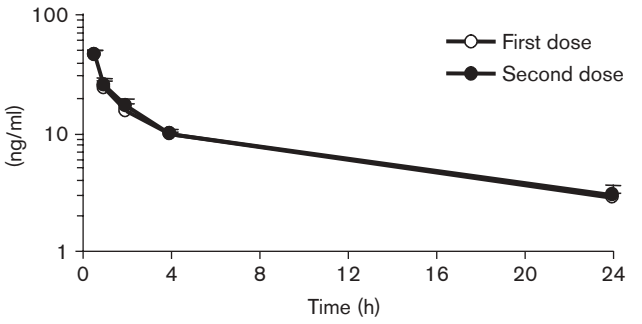
ALT, alanine aminotransferase; SGPT, serum glutamic pyruvate transaminase.

graphy. In all cases, cardiac function was examined with echocardiography. Patients discontinued treatment if LVEF was 45–50% with a 10% or greater reduction compared with baseline or if LVEF was less than 45%. A total of six patients (26%) had grade 1 or 2 deterioration of LVEF. Only one patient with grade 2 LVEF reduction needed a 2-week rest from trastuzumab and resumed treatment according to protocol criteria. No patient developed symptomatic congestive heart failure.

Pharmacokinetics

Plasma vinorelbine profiles are presented in Fig. 2 and Table 4. A gradual decrease in plasma vinorelbine levels was observed in each patient, with no differences among individual patients. No pharmacokinetic differences were observed between the first dose (single administration of vinorelbine) and second dose (combination of vinorelbine and trastuzumab).

Fig. 2



Plasma concentration of vinorelbine.

Discussion

The present study aimed to determine tolerability and response rate to combination chemotherapy of weekly trastuzumab and vinorelbine in women with HER2-overexpressing breast cancer that had not previously received either therapy. Burstein *et al.* [16] reported that the overall response rate to the same combination was 75% with a CR rate of 8% and Jahanzeb *et al.* [17] reported similar results [18]. Using the same strategy, efficacy and tolerability of this treatment in Japanese patients were evaluated. Response rate was 73%, with a CR rate of 9% and a PR rate of 64%. These results were classified using the General Rules for Clinical and Pathological Recording of Breast Cancer (14th edition) of JBCS, therefore, resembling other reports. In contrast, using RECIST criteria, no patient was classified as having CR owing to continuous elevation of tumor markers.

Median dose intensity of vinorelbine was 16.9 mg/m^2/week; however, Burstein reported 21.3 mg/m^2/week. In that study, vinorelbine dose was reduced to 15 mg/m^2 in 13% of weekly treatments and vinorelbine was omitted in 7% of weekly treatments [16]. Differences in the median dose are most likely derived from differences in criteria. Their protocol specified dose adjustment on the basis of neutrophil count, but that weekly treatment should be maintained in principle. In this study, if neutrophil count criteria were not satisfied, vinorelbine administration was postponed for 1 week and if treatment delay exceeded 2 weeks, dose level was reduced. Thereafter, the same dose was administered until the patient was withdrawn. Despite relatively low-dose intensity for vinorelbine, this study produced a high response rate of 73%, as good as previously reported.

Some investigators of vinorelbine and trastuzumab combination therapy describe good tolerability. The most common adverse events were leukocytopenia and neutropenia, with 96% of patients in this study experiencing those adverse events. Grade 3/4 leukocytopenia and neutropenia were experienced by 70 and 83%, respectively. Although one patient (4%) had febrile neutropenia, hospitalization was not necessary and resolved without any complications. Hematologic toxicity associated with

Table 4 Pharmacokinetics

	$t_{1/2}$ (h)	AUC (ng × h/ml)	Vdss (l/m^2)	MRT (h)	CL (l/h/m^2)
First dose	11.7 ± 1.5	275 ± 38	1080 ± 80	11.9 ± 1.9	92.2 ± 13.5
Second dose	11.2 ± 0.9	268 ± 29	1060 ± 150	11.2 ± 0.9	94.2 ± 11.1
Overall	11.5 ± 1.2	272 ± 32	1070 ± 120	11.6 ± 1.5	93.2 ± 11.7

AUC, area under the curve; CL, clearance; MRT, mean residence time; Vdss, the volume of distribution at steady state.

vinorelbine was manageable by adjusting dose, with six patients (27%) requiring dose modification. Adjustments to trastuzumab dose were not necessary.

Vinorelbine causes less neurotoxicity with its higher selectivity for non-nervous tissue microtubules than for axonal microtubules. Incidence of neurotoxicity with vinorelbine was 44%, with no grade 3/4 severe toxicity observed. Vinorelbine can cause injection site reactions that increase intravenous cannulation difficulties. In this study, 74% of patients developed this reaction; however, no grade 3 severe injury leading to ulceration was observed.

Burstein *et al.* [16] reported low–normal LVEF together with earlier cumulative doxorubicin exposure in excess of 240 mg/m^2 as important predictors of grade 2 cardiac toxicity. Therefore, eligibility criteria in this study specified that earlier cumulative doxorubicin dose should be less than 240 mg/m^2. A decline in left ventricular function associated with trastuzumab, a manifestation of cardiac toxicity, was experienced in 26% of patients. Most LVEFs were well tolerated. All LVEF-decreased cases were not improved by the continuous existence and there was no influence for the administration. None had symptomatic cardiac failure, although grade 2 cardiac toxicity (LVEF decline of at least 20%) occurred in three patients (13%), one pretreated with an anthracycline. Of the seven patients pretreated with doxorubicin in an adjuvant setting, three patients (43%) experienced LVEF depression. For patients that had not used doxorubicin, three of 16 (19%) developed LVEF depression. Despite strict eligibility criteria, incidence of cardiac toxicity was higher than previously reported for the same combination therapy. However, LVEF declined by less than 15% in 15 patients (65%) and by 15% or greater in four patients (17%), results comparable to a randomized study of trastuzumab combined with docetaxel [7]. The relatively high incidence of cardiac toxicity in this study is likely as a result of the more sensitive ultrasound cardiography used to evaluate LVEF function, compared with the MUGA scan used in other investigations.

To the best of our knowledge, this is the first pharmacokinetic analysis of vinorelbine and trastuzumab in combination. Plasma concentration of vinorelbine decreased gradually with no obvious differences between patients. Importantly, there were no differences in pharmacokinetics between single administration of vinorelbine earlier to trastuzumab and concurrent administration of these two drugs.

In conclusion, the combination of trastuzumab and vinorelbine produced high response rates and good tolerability. Vinorelbine and trastuzumab in combination are promising first-line chemotherapy for HER2-overexpressing metastatic breast cancer in Japan.

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