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Late Phase II Clinical Study of Vinorelbine Monotherapy in Advanced or Recurrent Breast Cancer Previously Treated with Anthracyclines and Taxanes

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Background: At present, it is one of the most important issues for the treatment of breast cancer to develop the standard therapy for patients previously treated with anthracyclines and taxanes. With the objective of determining the usefulness of vinorelbine monotherapy in patients with advanced or recurrent breast cancer after standard therapy, we evaluated the efficacy and safety of vinorelbine in patients previously treated with anthracyclines and taxanes.
Methods: Vinorelbine was administered at a dose level of 25 mg/m^2 intravenously on days 1 and 8 of a 3 week cycle. Patients were given three or more cycles in the absence of tumor progression. A maximum of nine cycles were administered.
Results: The response rate in 50 evaluable patients was 20.0% (10 out of 50; 95% confidence interval, 10.0–33.7%). Responders plus those who had minor response (MR) or no change (NC) accounted for 58.0% [10 partial responses (PRs) + one MR + 18 NCs out of 50]. The Kaplan–Meier estimate (50% point) of time to progression (TTP) was 115.0 days. The response rate in the visceral organs was 17.3% (nine PRs out of 52). The major toxicity was myelosuppression, which was reversible and did not require discontinuation of treatment.
Conclusion: The results of this study show that vinorelbine monotherapy is useful in patients with advanced or recurrent breast cancer previously exposed to both anthracyclines and taxanes.

Key words: breast cancer – vinorelbine – chemotherapy – phase II clinical trials

INTRODUCTION

The treatment of advanced or recurrent breast cancer is aimed at prolonging survival time rather than cure, with a focus on the relief of symptoms. At present, anthracycline-containing regimens are used as a first choice of chemotherapy for breast cancer, whereas taxanes are considered to play a leading role for patients previously treated with anthracyclines. However, there are no standard drugs or regimens that have been shown to provide a survival benefit for patients who have received both anthracyclines and taxanes.

Vinorelbine is a novel vinca alkaloid derivative developed in France (1). It exerts its antitumor activity by inhibiting microtubule polymerization (2), as opposed to taxanes' mechanism of action, i.e. the inhibition of depolymerization. As a single

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agent for first-line chemotherapy for advanced or recurrent breast cancer, vinorelbine yielded response rates of ⩾35% (3–11), and it is classified as an active chemotherapeutic agent for breast cancer (12).

Up to now, several studies have been conducted to evaluate the efficacy of vinorelbine monotherapy in patients with advanced or recurrent breast cancer after standard therapy. Livingstone *et al*. (13) reported that 25% of patients resistant to anthracyclines and paclitaxel responded to high-dose vinorelbine with granulocyte colony-stimulating factor (G-CSF) support (13). In the study performed by Zelek *et al*., patients who had previously received anthracyclines and taxanes were given vinorelbine intravenously once a week; the dose level was 30 mg/m^2 in the first six patients and then reduced to 25 mg/m^2 in the subsequent patients; vinorelbine yielded a response rate of 25% [10 partial responses (PRs) out of 40] (14).

With the objective of determining the usefulness of vinorelbine monotherapy in the aforesaid setting in Japan, we evaluated the efficacy and safety of vinorelbine in patients with advanced or recurrent breast cancer previously exposed to both anthracyclines and taxanes.

PATIENTS AND METHODS

PATIENTS

Inclusion criteria were: women with histologically diagnosed unresectable advanced breast cancer or recurrent breast cancer with distant metastasis; at least one evaluable disease (patients with bone metastasis only were not allowed); prior exposure to both anthracyclines and taxanes; an interval of at least 2 weeks (trastuzumab: 8 weeks) between the last dose of previous chemotherapy or radiotherapy and study start; Eastern Cooperative Oncology Group (ECOG) PS (performance status) of 0–2; estimated life expectancy >3 months; ages 20–75; adequate hepatic, renal and bone marrow function [NEU ⩾2000/mm^3 or white blood cells ⩾4000/mm^3; platelets ⩾100 000/mm^3; total bilirubin ⩽2.0 mg/dl; GOT, GPT ⩽2.5× the upper limit of normal (ULN) in each institution; serum creatinine ⩽1.5 mg/dl; PaO_2 ⩾60 mmHg or SaO_2 ⩾90%]; adequate cardiac function [cardiovascular (arrhythmia) ⩽grade 2 and cardiac-ischaemia/infarction ⩽grade 1 as defined by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC)]; no prior experience or suspicious symptoms of cardiac diseases; and no history of acute cardiac infarction within 12 months of enrollment. Written informed consent was obtained from all patients. Exclusion criteria were: past or current interstitial pneumonia or lung fibrosis; constipation ⩾grade 3; neuropathy ⩾grade 2 (excluding dysfunction resulting from local nerve pressure due to disease progression); symptomatic cerebral metastasis; pregnancy; dose intensive chemotherapy using hematopoietic stem cell transplantation; active double cancer; and enrollment in other clinical trials. This study was supported by Kyowa Hakko Kogyo Company in Tokyo.

TREATMENT

Vinorelbine was administered intravenously on days 1 and 8 of a 3 week cycle. The dose of vinorelbine was 25 mg/m^2, administered by slow intravenous injection over 6–10 min after dilution in about 50 ml of normal saline solution, followed by about 200 ml of normal saline infusion to flush the vein. Patients were given at least three cycles unless progressive disease was observed. All the data were cut off after nine cycles of treatment. Before each administration, patients were required to have NEU ⩾1000/mm^3. G-CSF support prior to administration was not allowed except in cases where NEU was <1000/mm^3. The dose level of vinorelbine will be reduced to 20 mg/m^2 when the day 1 administration is delayed more than 1 week or the day 8 administration is omitted in two consecutive cycles because of NEU <1000/mm^3.

EVALUATION

The primary end-points were objective response rate [complete response (CR) plus PR] and safety, and the secondary endpoint was TTP.

The efficacy of treatment was evaluated using the General Rules for Clinical and Pathological Recording of Breast Cancer (The Japanese Breast Cancer Society 14th edition), and extra-mural review for all patients was also carried out. Disease responses for patients with measurable and non-measurable but assessable disease were classified as follows: CR was defined as the complete disappearance of all clinical and radiological evidence of tumor. PR was defined as a decrease of at least 50% from baseline in the sum of bidimensionally measurable disease, or obvious improvement in non-measurable disease. CR and PR required confirmation by a second evaluation at least 4 weeks later. A response of lesser duration was considered a minor response (MR). Progressive disease (PD) was defined as an increase of ⩾25% from baseline in the sum of bidimensionally measurable disease, obvious increase in non-measurable disease or the appearance of any new disease. No change (NC) was defined as an evaluation that failed to qualify for any of these responses. All adverse events were graded according to NCI-CTC version 2.

RESULTS

PATIENT CHARACTERISTICS

Fifty patients were enrolled in this study between October 19, 2001 and February 3, 2003. The patient characteristics are shown in Table 1.

Six patients (12.0%) had advanced breast cancer, and 44 (88.0%) had recurrent disease. Five patients (10.0%) had a PS of 2. The number of prior chemotherapy regimens for metastatic disease was two in 22 patients (44.0%), three in 13 patients (26.0%) and five or more in three patients (6.0%). Hormone receptor status of the primary site was estrogen receptor positive in 22 patients (44.0%) and progesterone receptor positive in 16 patients (32.0%). Hormone receptor

Table 1. Patient characteristics

No. of patients	50	–
Age (years)		
Median (range)	55 (37–71)	
	<50	16 (32.0%)
	⩾50	34 (68.0%)
Performance status (ECOG)	0	38 (76.0%)
	1	7 (14.0%)
	2	5 (10.0%)
Diagnosis	Advanced	6 (12.0%)
	Recurrent	44 (88.0%)
Disease-free interval of recurrent cases (months)		
Median (range)	22.0 (2–97)	
	<1 year	10 (22.7%)
	1–5 years	28 (63.6%)
	⩾5 years	6 (13.6%)
No. of disease sites	1	13 (26.0%)
	2	16 (32.0%)
	3	11 (22.0%)
	4	7 (14.0%)
	⩾5	3 (6.0%)
Estrogen receptor status	+	22 (44.0%)
	–	25 (50.0%)
	Unknown	3 (6.0%)
Progesterone receptor status	+	16 (32.0%)
	–	30 (60.0%)
	Unknown	4 (8.0%)
No. of prior chemotherapy regimens for metastatic disease	0	3 (6.0%)
	1	3 (6.0%)
	2	22 (44.0%)
	3	13 (26.0%)
	4	6 (12.0%)
	⩾5	3 (6.0%)
Total dose of prior anthracyclines (mg/m^2)		
Median (range)	240.0 (30–1125)	
	⩽240	32 (64.0%)
	>240	18 (36.0%
Prior exposure to taxanes	Paclitaxel only	10
	Docetaxel only	24
	Both	16

status was examined according to the method used at each institution. The information on Her2 status was not collected, because it was not included in the general evaluation items when this study started. None of the patients had previously been treated with trastuzumab.

Table 2. Tumor response

Disease site	*n*	Efficacy						Overall response (%) (95% CI)
		CR	PR	MR	NC	PD	NE	
Breast	3	0	0	0	3	0	0	0.0
Skin	9	0	1	1	5	2	0	11.1
Lymph node	23	1	3	6	7	5	1	17.4
Mediastinum	1	0	0	0	1	0	0	0.0
Subtotal (soft tissues)	36	1	4	7	16	7	1	13.9
Bone	13	0	0	1	7	2	3	0.0
Lung	24	0	5	4	12	2	1	20.8
Pleura	13	0	2	0	6	2	3	15.4
Liver	13	0	2	0	8	3	0	15.4
CNS	2	0	0	0	0	2	0	0.0
Subtotal (visceral organs)	52	0	9	4	26	9	4	17.3
Other	1	0	0	0	0	0	1	0.0
Total	50	0	10	1	18	18	3	20.0 (10.0–33.7)

CR, complete response; PR, partial response; MR, minor response; NC, no change; PD, progressive disease; NE, not evaluable; CNS, central nervous system.

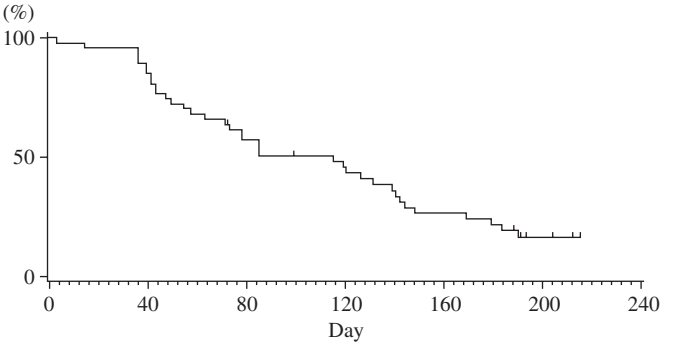

Figure 1. Time to progression.

EFFICACY

The response rate as the primary end-point was 20.0% (10 PRs out of 50; 95% confidence interval, 10.0–33.7%) (Table 2). The response rate in the visceral organs was 17.3% (nine PRs out of 52). The Kaplan–Meier estimate (50% point) of TTP was 115.0 days (Fig. 1).

The response rates by type of prior taxane exposure were as follows: all of the 16 patients previously treated with both paclitaxel and docetaxel failed to respond to vinorelbine, whereas responses were observed in 37.5% of the patients who had received docetaxel only (nine PRs out of 24) and 10.0% of the patients previously treated with paclitaxel only (one out of 10). Therefore, the response rate of the patients with prior exposure to only one taxane was 29.4% (10 PRs out of 34).

Table 3. The incidence and severity of adverse drug reactions

	Total		Grade (no.)				Grade 3–4	
	n	%	1	2	3	4	*n*	%
Hematological								
Leukocytes	46	92	0	15	24	7	31	62
Neutrophils	47	94	1	9	17	20	37	74
Hemoglobin	38	76	13	20	3	2	5	10
Platelets	7	14	5	1	0	1	1	2
Febrile neutropenia	6	12	0	0	6	0	6	12
Transfusion:pRBCs	2	4	0	0	2	0	2	4
Non-hematological								
Nausea	32	64	25	6	1	0	1	2
Vomiting	20	40	13	6	1	0	1	2
Diarrhea	15	30	13	2	0	0	0	0
Anorexia	31	62	22	5	4	0	4	8
Stomatitis/pharyngitis	21	42	14	7	0	0	0	0
Fatigue (lethargy, malaise and asthenia)	36	72	26	8	2	0	2	4
Infection with grade 3–4 neutropenia	6	12	0	0	6	0	6	12
Phlebitis (superficial)	30	60	0	30	0	0	0	0
Injection site reaction	29	58	17	12	0	0	0	0
SGOT (AST)	17	34	11	4	1	1	2	4
SGPT (ALT)	18	36	10	5	2	1	3	6
Neuropathy-sensory	15	30	11	4	0	0	0	0
Headache	20	40	17	3	0	0	0	0

SAFETY

The incidence and severity of adverse drug reactions are shown in Table 3. The major toxicity was myelosuppression; neutropenia (94%), leukopenia (92%), erythrocytopenia (78%) and decreased hemoglobin (76%) were observed frequently. Grade 3 or 4 neutropenia and leukopenia affected 74 and 62% of the patients, respectively. Other grade 3 or 4 toxicities included febrile neutropenia (12%), infection with grade 3 or 4 neutropenia (12%), decreased hemoglobin (10%), anorexia (8%), SGPT (ALT) increased (6%), fatigue (lethargy, malaise and asthenia) (4%), SGOT (AST) increased (4%), and transfusion:pRBCs (4%).

Phlebitis was seen more frequently than in the previous study (3). In this study, all patients had previously been treated with anthracyclines and taxanes, and had experienced more prior chemotherapy regimens than in the previous study. We thus suspect that phlebitis might be due to heavy prior chemotherapy regimens. Other events were clinically tolerable, and were not frequent.

Forty-eight patients (96%) received more than three cycles of treatment that was provided by the protocol. The median number of cycles was five (range, 1–9). The dose was reduced in one patient due to neutropenia, and none of the patients discontinued treatment due to adverse drug reactions. Neither interstitial pneumonia nor ileus was observed. There were no treatment-related deaths.

DISCUSSION

Several drugs or regimens have been evaluated for the treatment of patients with metastatic breast cancer previously treated with anthracyclines and taxanes. Capecitabine, when used as a single agent, yielded response rates of 20.0–24.6% in taxane-resistant patients (15,16). Two studies were conducted to evaluate the efficacy of vinorelbine monotherapy in a similar setting, both of which reported a response rate of 25.0% (13,14). At present, however, there are no standard drugs or regimens which have been shown to provide a survival benefit.

In patients previously treated with anthracyclines and taxanes, therefore, evidence of the drug being at least effective would justify its existence. In the present study, vinorelbine achieved a response rate of 20.0% (10 PRs out of 50) with a lower 95% confidence limit of 10.0%. These results show that vinorelbine is also effective for this setting in Japan.

However, this response rate was lower than the results reported for vinorelbine monotherapy in patients with similar characteristics. To compare these data, the differences in prior taxane exposure should be taken into consideration. The study by Livingstone *et al*. involved paclitaxel-resistant patients (13), and the study by Zelek *et al*. involved patients previously exposed to taxanes (14); in both of the studies, prior taxane exposure was limited to only one regimen. On the other hand, the protocol of this study did not specify the number of prior taxane regimens; 16 of the 50 patients had previously received two different taxanes, all of whom failed to respond to vinorelbine. Patients receiving a taxane followed by another taxane are at risk of experiencing overlapping toxicities. Drugs which have different mechanisms of action and toxicity profile, such as vinorelbine, should thus be considered for use in the patients who have received only a single taxane. It should also be noted that the response rate in the subset of patients previously treated with only one taxane was as high as 29.4% (10 PRs out of 34).

In this study, one patient showed MR, and 18 showed NC. Responders plus those achieving MR or NC accounted for 58.0% (10 PRs + one MR + 18 NCs out of 50). In three of the NC cases, disease remained stable for as long as 24 weeks or more. The Kaplan–Meier estimate (50% point) of TTP was 115.0 days. In situations where there are few treatment options left because of the prior exposure to standard therapy, it is important at least to prevent disease progression. From this viewpoint, those results strongly support the usefulness of vinorelbine.

The major toxicity was myelosuppression, with grade 3 or 4 neutropenia and leukopenia affecting 74.0 and 62.0% of patients, respectively. However, none of these events led to discontinuation of treatment, with G-CSF support, if needed, resulting in rapid recovery. It should be noted that no patient experienced interstitial pneumonia or ileus which we had sometimes experienced as the toxicities of vinorelbine. These

findings show that the vinorelbine monotherapy regimen used in this study is well tolerated and feasible. However, in this study, we paid a lot of attention to pulmonary toxicity using the observation of pulmonary function as part of the inclusion and exclusion criteria. Precautions against pulmonary toxicity of vinorelbine will still be needed in clinical practice.

At present, it is generally agreed that patients who have had disease recurrence or progression during or after standard therapy should be given another regimen using drugs with different mechanisms of action. However, the main treatment options now available for these patients refractory to standard therapy are prodrugs of 5-fluorouracil, which is often used in combination with anthracyclines, and another taxane. The results of this study indicate that single-agent vinorelbine with a mechanism of action different from drugs used as standard therapy may offer an important new option in these clinical settings.

In addition, there have been a lot of studies showing the synergistic effect of vinorelbine and other chemotherapeutic (17–27) or molecular targeting agents including trastuzumab (28,29) *in vitro* or *in vivo*. In fact, favorable results have been achieved in some clinical studies of combination therapy using vinorelbine and trastuzumab (30–33). Furthermore, the toxicity profile of vinorelbine suggests its potential to be used in combination with other chemotherapeutic drugs. Therefore, vinorelbine also appears to be a promising candidate for combination therapy in breast cancer, warranting further evaluation.

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