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ORIGINAL ARTICLE

Paclitaxel combined with ifosfamide in anthracycline- and docetaxel-pretreated metastatic breast cancer: activity independence of prior docetaxel resistance

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Abstract
Background We evaluated the efficacy and tolerability of combined paclitaxel and ifosfamide in anthracycline- and docetaxel-pretreated metastatic breast cancer (MBC).
Methods Patients received paclitaxel (175 mg/m^2 i.v. in a 3-h infusion) on day 1 and ifosfamide (1.5 g/m^2 i.v. in a 15-min infusion) on days 1–3, every 3 weeks for a maximum of nine cycles. The tumor response was assessed every two cycles.
Results We enrolled 34 patients with a median age of 50 years. Thirty patients had visceral metastases. Anthracycline- and docetaxel-based chemotherapy had previously been administered to 18/13 and 13/21 patients, respectively, in (neo)adjuvant/metastatic settings. Three patients had not previously received anthracycline due to abnormal cardiac functions. A total of 174 cycles of chemotherapy were delivered with a median of six cycles. The response rate under the intent-to-treat analysis was 23.5% (all partial responses) with a median response duration of 14 months. The disease control rate was 70.6%. The median progression-free and overall survival were 5.9 and 8.5 months, respectively. There was no apparent relationship between activity and prior docetaxel resistance. The incidence of grade III/IV neutropenia was 46.6% (81 of 174 cycles) with febrile neutropenia of only 1.7%. Major grade III/IV non-hematological toxicities included peripheral neuropathy (6 of 34 patients) and infection (4 of 34 patients). There were no treatment-related deaths.
Conclusion Paclitaxel combined with ifosfamide was effective and tolerable in anthracycline-/docetaxel-pretreated MBC. Overcoming docetaxel resistance by using paclitaxel in combination with ifosfamide needs to be addressed through further investigation.

Keywords Anthracyclines · Breast cancer · Docetaxel · Paclitaxel · Ifosfamide

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Introduction

Breast cancer is the most prevalent malignancy in women and metastatic breast cancer (MBC) is a leading cause of mortality, accounting for more than 400,000 deaths annually worldwide [1]. Even though anthracyclines and taxanes are the most active agents, resistance to these essential antineoplastic drugs is one of the most limiting factors in the treatment of breast cancer. In high-risk early breast cancer, the addition of a taxane to an anthracycline-based regimen has been shown to improve disease-free and overall survival in an adjuvant setting [2] and to increase pathological complete response in a neoadjuvant setting [3]. Furthermore, the use of taxanes as a first-line treatment for MBC significantly improved response rates (RRs) and progression-free survival (PFS) compared to treatment

without taxane [4, 5]. Under these circumstances, many breast cancer patients are being exposed to both anthracyclines and taxanes early in the course of the disease. As a consequence, the number of patients whose disease is resistant or refractory to anthracyclines and taxanes, or who can no longer tolerate these agents, is increasing.

Paclitaxel and docetaxel are taxanes that exert their antitumor activity by binding tubulin and stabilizing non-functional microtubule bundles, thereby blocking normal mitotic spindle development and causing cell cycle arrest in the G2 phase. The mechanisms of action of paclitaxel and docetaxel are similar. However, docetaxel has shown more potent antitumor activity in in vitro [6] and in vivo [7] models, so it is chosen more frequently than paclitaxel in our routine practice and clinical trials for treatment of breast cancer, although superior efficacy of docetaxel to paclitaxel has not been firmly proven in clinical studies [8–10]. Accordingly, anthracycline- and docetaxel resistance are commonly encountered clinical situations in our routine practice.

Paclitaxel alone showed activity in both docetaxel- and anthracycline-resistant MBC patients (RR 17–32%) [11–13], as well as in anthracycline-resistant patients (RR 33–56%) [14, 15] with various dosing schedules. Ifosfamide, an alkylating agent, has been reported to produce single-agent objective RRs in about 15–30% of patients with MBC, and has been used in various drug combinations for the palliative treatment of patients previously exposed to cytotoxic agents [16, 17]. Considering the single-agent activity of both paclitaxel and ifosfamide in MBC patients, their different mechanisms of action, and their distinct non-hematological toxicity profiles, we performed a retrospective study to evaluate the efficacy and tolerability of combined paclitaxel and ifosfamide treatment in anthracycline- and docetaxel-pretreated MBC.

Patients and methods

Patients

Patients with metastatic and/or relapsed breast cancer who were treated at Yonsei Cancer Center from June 2005 to December 2008 were included if the following criteria were met: (i) histologically- or cytologically proven breast cancer, (ii) anthracycline- and docetaxel pretreatment or intolerance, (iii) no prior treatment with paclitaxel- or ifosfamide-containing regimens, (iv) no indication for human epidermal growth factor receptor-2 (HER-2)-targeted therapy, (v) at least one bidimensionally measurable lesion, (vi) age $\geq$18 years, (vii) Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2, (viii) adequate bone marrow (neutrophils $\geq 1.5 \times 10^3/\mu l$, platelets $\geq 100 \times 10^3/\mu l$, and Hb $\geq$ 10.0 g/dl), renal (serum creatinine $\leq 1.5 \times$ upper normal limit), and liver function (serum bilirubin $\leq 1.5 \times$ upper normal limit and aspartate aminotransferase and alanine aminotransferase $\leq 1.5 \times$ upper normal limit), and (viii) no history of other malignancies excluding non-melanoma skin cancer or carcinoma in situ of the uterine cervix. Any hormonal therapy was discontinued at least 2 weeks prior to initiation of the study. There were no other restrictions on the prior number of therapies. Docetaxel or anthracycline resistance was classified as 'primary resistance' if the disease recurred within 6 months after the completion of neo-/adjuvant chemotherapy or progressed within 6 months of the start of palliative chemotherapy. 'Secondary resistance' was the classification if the disease recurred after 6 months from the last dose of neo-/adjuvant chemotherapy or progressed after 6 months from the start of palliative chemotherapy. This retrospective study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea.

Treatment plan

Treatment consisted of paclitaxel 175 mg/m^2 i.v. for a 3-h infusion on day 1. Premedication to avoid acute allergic reactions included dexamethasone 10 mg i.v., pheniramine maleate 2 mg i.v. and cimetidine 300 mg i.v., 30 min before paclitaxel infusion. Ifosfamide was given at 1.5 g/m^2 i.v. for a 15-min infusion on days 1–3, with mesna 300 mg/m^2 i.v. prior to and 4 and 8 h following each dose of ifosfamide. This treatment was repeated every 3 weeks for a maximum of nine cycles.

If the neutrophil count was $\geq 1.5 \times 10^3/\mu l$ and the platelet count was $\geq 100 \times 10^3/\mu l$, we would begin the next cycle. If these values were not reached by the scheduled retreatment, therapy was delayed by weekly intervals. If grade III/IV non-hematologic toxicity was observed, therapy was also delayed until the toxicity was reduced to at least grade I. If these hematological and non-hematological criteria were still not fulfilled even after 3 weeks of delay, the patient was removed from the protocol. The doses of paclitaxel and ifosfamide were reduced by 20% in the subsequent cycle if febrile neutropenia or grade III/IV non-hematologic toxicity occurred. Dose reduction was only allowed once. Granulocyte colony-stimulating factor (G-CSF) was administered only in the case of febrile neutropenia and prophylactic G-CSF usage was also allowed in this case.

Endpoints evaluation and statistical considerations

The tumor response was assessed using chest CT scan, abdominal CT scan and/or bone scan every two cycles. Tumor response was classified according to the Response

Evaluation Criteria for Solid Tumors (version 1.0) [18] as follows: complete response (CR), disappearance of all target and non-target lesions; partial response (PR), a minimum of 30% decrease in the sum of the longest diameter of the target lesions; progressive disease (PD), a minimum of 20% increase in the sum of the longest diameter of the target lesions, appearance of one or more new lesions, or unequivocal progression of existing non-target lesions; stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Patients who achieved a response were required to take a confirmative CT scan at least 4 weeks later. PFS was defined as the time from commencement of the treatment until disease progression or death. Overall survival (OS) was measured from the first date of the treatment to a death due to any cause. The toxicity was graded based on the National Cancer Institute's Common Terminology Criteria version 3.0.

Chi-square or Fisher's exact tests were used for comparison of categorical variables. Survival was calculated using the Kaplan–Meier method. A log-rank test was used to compare survivals between the groups. All P values were two-sided, and the α value was set at 0.05. All statistical calculations were carried out using SPSS for Windows, version 12.0 (SPSS, Chicago, IL, USA).

Results

Patients characteristics

Thirty-four patients (33 with metastatic and one with locoregional disease in the chest wall) were enrolled in the study. The median age was 50 years (range 26–69). The ECOG performance status was 0–1 in 29 patients (85%) and 2 in 5 patients (15%). Thirty patients (88%) had visceral metastases (Table 1). Seven of them had brain metastases and they all received therapy for brain metastases before entering the study (4 gamma knife surgery, 3 whole brain radiotherapy). As listed in Table 2, 29, 24, and 15% of patients previously received 1, 2, and 3 sets of chemotherapy for metastasis, respectively. All patients had previously been treated with docetaxel-based chemotherapy in a neoadjuvant ($n = 1$), adjuvant ($n = 12$), and metastatic setting ($n = 21$). Thirty-one patients (91.2%) had previously been treated with anthracycline-containing regimens in a neoadjuvant ($n = 1$), adjuvant ($n = 17$) and palliative setting ($n = 13$). The median time between the last dose of docetaxel and anthracycline and the first dose of paclitaxel/ifosfamide was 7.9 months (range 0.8–52.7) and 10.2 months (range 0.3–120), respectively. Eleven of 34 patients (32%) showed primary resistance to prior docetaxel treatment and the remaining patients had secondary resistance. Eleven (32%) and 20 (59%) patients showed primary and secondary resistance to prior anthracycline, respectively. Anthracycline resistance was not determined in the remaining three patients because they had not previously received anthracycline due to abnormal

Table 1 Patient characteristics

Characteristics	Number	(%)[a]
Number of patients	34	(100)
Median age, years (range)	50.0 (26–66)	
ECOG performance status		
0/1/2	3/26/5	(9/77/15)
Number of metastatic organs		
1/2/3/≥4	11/9/12/2	(32/27/35/6)
Metastatic organs		
Liver	21	(62)
Lung or pleura	18	(53)
Bone	14	(41)
Brain	7	(21)
Others	9	(27)
Visceral metastasis		
Present/absent	30/4	(88/12)
Menstruation		
Pre-/peri-/post-menopause	11/8/15	(32/24/44)
Histology		
Ductal/lobular carcinoma	33/1	(97/3)
ER		
Positive/negative/unknown	16/12/6	(47/35/18)
PR		
Positive/negative/unknown	17/10/7	(50/29/21)
HER-2		
Positive/negative/unknown	6/20/8	(18/59/24)

ECOG Eastern Cooperative Oncology Group, *ER* estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor receptor

[a] Sums may not be 100 due to rounding

Table 2 Summary of prior systemic treatment

Chemotherapy	Number	(%)
No. of chemotherapy for metastasis		
0/1/2/3	11/10/8/5	(32/29/24/15)
Prior anthracycline	31	(91)
Neo-/adjuvant aim	18	(53)
Palliative aim	13	(38)
Prior docetaxel	34	(100)
Neo-/adjuvant aim	13	(38)
Palliative aim	21	(62)
Prior capecitabine	10	(29)
Prior hormonal treatment	14	(41)

Table 3 Efficacy of paclitaxel/ifosfamide based on prior docetaxel or anthracycline resistance

Efficacy	Docetaxel resistance			Anthracycline resistance		
	Primary ($n = 11$)	Secondary ($n = 23$)	P value	Primary ($n = 11$)	Secondary ($n = 20$)	P value
RR	27.3%	21.7%	1.0	27.3%	25.0%	1.0
DCR	72.7%	76.2%	1.0	63.3%	94.4%	0.054
Median PFS (95% CI)	3.2 months (0.8–5.6)	6.7 months (3.0–10.4)	0.252	2.6 months (0–7.6)	6.7 months (2.8–10.6)	0.152
Median OS (95% CI)	8.4 months (3.5–13.3)	8.5 months (7.0–10.7)	0.180	9.6 months (6.3–12.9)	8.1 months (3.2–13.0)	0.265

RR response rate, *DCR* disease control rate, *PFS* progression-free survival, *OS* overall survival, *CI* confidence interval

cardiac functions. Six patients (18%) had HER-2 overexpression and they had already been on treatment with trastuzumab before entering the study. HER2 status was not determined in eight patients (24%) because tissues were not available.

Treatment delivery and dose-intensity

The median number of cycles administered was six (range 1–9), and a total of 174 cycles of chemotherapy were delivered. The ratio of delayed cycles per total cycles was 9.2% (16/174 cycles). Dose reduction was performed in one patient. Planned dose-intensities for paclitaxel and ifosfamide were 58.3 mg/m^2/week and 1.5 g/m^2/week, respectively. The median relative dose-intensities for paclitaxel and ifosfamide were 1.0 (range 0.86–1.0) and 1.0 (range 0.85–1.0), respectively.

Treatment efficacy

Of the 34 patients, two were not available for response assessment; one case was due to death after the first cycle of chemotherapy from underlying heart failure that was not related to the chemotherapy, and the other was removed from the study because of development of idiopathic thrombocytopenic purpura after the first cycle of chemotherapy. The RR was 23.5% (8 PRs, no CR) under the intent-to-treat analysis with a median response duration of 14.0 months [95% confidence interval (CI) 4.5–23.5]. The disease control rate (DCR) was 70.6%. The RR and DCR were not different according to the number of metastatic organs (1–2 vs. $\geq$3 sites), liver metastasis (absent vs. present), and number of prior chemotherapy for metastasis (0–1 vs. $\geq$2 sets of chemotherapy) (data not shown). At a median follow-up period of 7.6 months (range 1.2–29.1), 21 of the 34 patients experienced disease progression. The median PFS was 5.9 months (95% CI 3.4–5.4). Of twenty-two patients who died, 19 patients died from cancer progression and three died from non-cancer-related causes (one congestive heart failure, one hepatic encephalopathy, one seizure of unknown origin). The median OS was 8.5 months (95% CI 6.8–10.3).

Subgroup analyses regarding treatment efficacy were performed according to prior docetaxel or anthracycline resistance (Table 3). Eight responders had previously been treated with docetaxel as neo-/adjuvant therapy ($n = 4$) or for metastatic disease ($n = 4$). Three of eight responders had previously been treated with anthracyclines as neo-/adjuvant therapy and five with anthracycline for metastatic disease. The RRs by category of docetaxel or anthracycline resistance (primary or secondary) were not different. But the secondary anthracycline-resistance group (94.4%) had a higher DCR than the primary resistance group (63.3%) with a borderline significance ($P = 0.054$). The PFS and OS durations were not different between the primary and secondary resistance groups of docetaxel or anthracycline.

Toxicity profiles

The dominating toxicity was neutropenia, of which grade III/IV was 46.6% (81 of 174 cycles). However, febrile neutropenia was only 1.7% (three of 174 cycles). The most common grade III/IV non-hematological toxicities were peripheral neuropathy (17.6%; 6 of 34), followed by infection (11.8%; 4 of 34 patients), liver enzyme elevation (2.9%; 1 of 34 patients), nausea/vomiting (2.9%; 1 of 34 patients) and fatigue (2.9%; 1 of 34 patients). Three of six patients with grade 3 peripheral neuropathy were removed from the study treatment after three, six, and seven cycles of chemotherapy, respectively. Other non-hematological toxicities were mild. There were no treatment-related deaths (Table 4).

Discussion

The current study evaluated the efficacy and tolerability of paclitaxel in combination with ifosfamide in the treatment of anthracycline-/docetaxel-pretreated breast cancer. This combination showed activity with a RR of 23.5% and a durable response duration of 14 months. Activity was seen even in patients with poor prognostic factors, including those with liver metastasis (RR 19%, DCR 76.2%), extensive metastases of $\geq$3 organs (RR 21.4%, DCR 78.5%), or

Table 4 Toxicity profiles

Toxicity	NCI-CTC grade				
	G1	G2	G3	G4	G ≥ 3 (%)
Hematological (by cycle)					
Neutropenia	6	16	38	43	81(46.6)
Febrile neutropenia	0	0	0	3	3(1.7)
Anemia	8	43	4	0	4(2.3)
Thrombocytopenia	8	6	7	5	12(6.9)
Non-hematological (by patient)					
Peripheral neuropathy	1	3	6	0	6(17.6)
Infection	0	3	2	2	4(11.8)
Nausea/vomiting	1	3	1	0	1(2.9)
AST/ALT elevation	1	3	1	0	1(2.9)
Fatigue	1	1	1	0	1(2.9)
Hemorrhagic cystitis	5	5	0	0	0
Myalgia	1	4	0	0	0
Anorexia	0	2	0	0	0
Abdominal pain	1	1	0	0	0

NCI-CTC National Cancer Institute's Common Terminology Criteria, *G* grade, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

extensive prior chemotherapy with ≥2 sets (RR 15.4%, DCR 76.9%). Furthermore, 88% of our patients had visceral metastases.

The results of our study are supported by preclinical evidence that docetaxel and paclitaxel have only partial cross-resistance. Although these two taxanes share major parts of their structures and mechanisms of action, the relative differences in potency and efficacy may play a role in the absence of complete cross-resistance between them. For example, docetaxel and paclitaxel have a different affinity for the tubulin-binding site [19], a different microtubule polymerization pattern [19], different intracellular retention times and concentrations in target cells [20], and different potencies in the induction of bcl-2 phosphorylation and apoptosis [21]. These mechanistic evidences for incomplete cross-resistance between the two taxanes parallel clinical evidence that there is no complete cross-resistance in breast cancer as follows; weekly paclitaxel after progression on docetaxel was reported to be active in phase II trials, showing a RR of 17–32% [11–13]. In contrast, docetaxel activity was also reported in some small trials of paclitaxel-resistant MBC (RR 18–25%) [8, 22]. In this study, it should also be considered that docetaxel resistance may have been overcome with potential synergism between paclitaxel and ifosfamide or just with the activity of ifosfamide.

We chose ifosfamide to combine with paclitaxel as a chemotherapeutic to exploit the additive effect due to the different mechanisms of action. Furthermore, there are preclinical [23] and clinical data [24] on the potential synergistic interaction between paclitaxel and oxazophosphorine cytotoxics (cyclophosphamide or ifosfamide), as well as other alkylating agents. Some researchers previously investigated the efficacy and tolerability of combined paclitaxel and ifosfamide treatment in phase II trials of MBC progressing after prior anthracycline treatment [25, 26]. In these two trials, the RRs and DCRs were 43–48% and 70–86%, respectively. In terms of tolerabilities, neutropenia and peripheral neuropathy were the main toxicities, but they were acceptable. Previously, these phase II trials with a combination of paclitaxel and ifosfamide were performed in MBC that had been pretreated with anthracycline, but not with docetaxel, whereas our patients had been pretreated with both anthracycline and docetaxel. This difference might explain the relatively lower RR (23.5%) in our trial.

Our dosages and dosing schedules for both drugs were inferred from two prior phase I trials of paclitaxel/ifosfamide in various solid tumors [24, 27]. With indicated doses and schedules, most of the patients well tolerated the treatment with a median six cycles of chemotherapy delivered and median RDIs of 1.0 for both drugs. Although grade III/IV neutropenia occurred in a considerable number of cycles (47%), the duration of neutropenia was short (2–3 days) and febrile neutropenia only occurred in 1.7% of cycles. Peripheral neuropathy was a relatively common non-hematologic toxicity (29.4% of patients).

If targeted therapy is not considered, capecitabine is a generally accepted salvage treatment in the anthracyclines and taxanes-resistant breast cancer [28, 29]. However, the objective RR in these phase II studies was only 15–20% and the median time to progression was only 3–3.5 months [28, 29]. Recently, ixabepilone, a novel class of antitubulin agent has emerged as the reference drug, in combination with capecitabine, with proven activity in a phase III study of anthracyline- and taxane-resistant MBC [30]. The RR of combined ixabepilone and capecitabine was 35% and the median PFS was 5.8 months. However, the issue with quality of life has been raised in the use of this regimen. Furthermore, financial costs now limit the availability of this novel drug. Although our study has a small number of patients, the RR (23.5%) and PFS (5.9 months) were comparable to currently approved salvage therapies in this setting of disease. Twenty-nine percent of our patients had already received capecitabine and activity (RR 10%, DCR 60%) was observed even in patients with prior capecitabine treatment. Furthermore, as mentioned earlier, our patients tolerated this combination. Based on these results, our report suggests that paclitaxel combined with ifosfamide can be a reasonable treatment option in this clinical situation.

Anthracycline- or taxane resistance in breast cancer is less strictly defined, but has been used in several studies for

disease that progressed or recurred after a chemotherapy-free interval of 6–12 months [13, 15, 30]. Of particular interest is the observation of equivalent antitumor activity of combined paclitaxel and ifosfamide treatment in patients with primary resistance to docetaxel when compared with those who had secondary resistance to docetaxel, which was in agreement with the previous report by Taguchi and colleagues [13]. In contrast, Yonemori and colleagues [11] reported that paclitaxel was only effective in patients with secondary docetaxel resistance. Based on our study of administering paclitaxel in combination with ifosfamide, the activity independence of prior docetaxel resistance needs to be further evaluated.

In conclusion, paclitaxel combined with ifosfamide is an effective and tolerable treatment for anthracycline- and docetaxel-pretreated MBC. Overcoming docetaxel resistance by using paclitaxel in combination with ifosfamide needs to be addressed through further investigation.

Conflict of interest statement There is no conflict of interest for any listed authors.

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