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ORIGINAL ARTICLE

A phase-I study evaluating the combination of pegylated liposomal doxorubicin and paclitaxel as salvage chemotherapy in metastatic breast cancer previously treated with anthracycline

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Abstract
Purpose The two main goals of this phase-I study were to determine the maximum-tolerated dose (MTD) and to characterize the toxicity of the combination of pegylated liposomal doxorubicin (PLD; Lipo-Dox) and paclitaxel (PTX) administered on a 3-week schedule in patients with metastatic breast cancer (MBC) who had previously been treated with anthracycline-based therapy.
Methods This phase-I study was performed via a two-staged dose escalation schema. The initial doses were PLD 30 mg/m^2 and PTX 150 mg/m^2, administered intravenously once every 21 days. The dose of PLD was escalated in increments of 5 mg/m^2 until the MTD was reached, at which time the PTX was then increased in increments of 10 mg/m^2 until the MTD was reached.
Results Twenty-three patients received between 1 and 13 treatment cycles. In stage I of the study, 14 patients received a fixed dose of PTX 150 mg/m^2 while PLD escalated from 30 mg/m^2. At 40 mg/m^2, PLD resulted in dose-limiting toxicities (DLT) including febrile neutropenia and palmar-plantar erythrodysesthesia that occurred in two of five patients. In stage II of the study, nine patients received fixed dose of PLD 35 mg/m^2 and escalating doses of PTX starting at 160 mg/m^2. At PTX 170 mg/m^2 and dose-limiting neutropenic fever occurred in two of five patients. Out of 19 evaluable patients, 10 (52.6%) achieved objective response (one complete response and nine partial response), and 5 had stable disease.
Conclusions The maximal tolerated doses of PLD and PTX are 35 and 160 mg/m^2, respectively, administered every 3 weeks. The combination of PLD (30–35 mg/m^2) and PTX (150–160 mg/m^2) constitutes an active regimen with mild toxicity that merits further study.

Keywords Liposomal doxorubicin · Paclitaxel · Metastatic breast cancer · Phase-I study

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Introduction

Metastatic breast cancer (MBC) is considered incurable and has a reported median survival time of only ~2 years. For MBC, anthracyclines, and taxanes are considered the most active single agents [1, 2]. In the first line treatment for MBC, paclitaxel (PTX) in combination with anthracycline achieved high response rates (46–68%) using a variety of doses and schedules [3–6]. However, the use of anthracyclines is limited by their acute toxicities (i.e., nausea and vomiting, myelotoxicity, and alopecia) as well as cardiotoxicity which reportedly occurs at cumulative doses above 400 mg/m^2 of doxorubicin [7–9].

Pegylated liposomal doxorubicin (PLD) was developed in an attempt to improve the therapeutic index of doxorubicin. PLD has a longer half-life than free doxorubicin (2–3 days vs. <10 min), and preferentially accumulates in malignant tissues [10, 11]. Compared to conventional doxorubicin, PLD is associated with a significantly lower risk of cardiac events [12–14]. Single-agent PLD studies show that PLD achieved 20–33% responses rate in patients with MBC that was either chemotherapy-naive or had one prior treatment that did not include an anthracycline [12, 15, 16].

The efficacy and less cardiotoxicity of PLD with the well-tolerated PTX make this combination an attractive alternative for the treatment of anthracycline pretreated MBC. Therefore, the primary objective of this study was to determine the maximum-tolerated dose (MTD) of the PLD/PTX combination. Secondary objectives were to assess the spectrum of toxicities associated with the use of this combination. In addition, recording objective tumoral response rates was also performed in evaluable patients.

Patients and methods

Patient selection

This multicenter phase-I study was conducted in patients with MBC who had prior chemotherapy with anthracycline-containing regimens either in an adjuvant setting or for metastatic disease. The patients included had not received treatment for a minimum of 4 weeks prior to commencing this trial. Other eligibility criteria included: bi-dimensionally measurable disease, age 18–70 years, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, left ventricular ejection fraction (LVEF) $\geq$45% with normal ventricular contractility, adequate bone marrow (white blood cells >3,500 per µl, neutrophils >1,500 per µl, and platelets >100,000 per µl), serum creatinine <1.5 mg/dl, serum bilirubin less than upper limit of normal (ULN), AST and ALT <3× ULN, and absence of clinically relevant neuropathy, psychiatric illness, pregnancy or lactation. Patients were excluded if they had brain metastases, a positive history for other types of cancer, with the exception of in situ cervical cancer radically resected and non-melanoma skin cancer. The protocol was approved by the Institutional Ethical Committee and all patients were required to provide written, informed consent to participate in the trial.

Treatment plan

Pegylated liposomal doxorubicin was diluted in 250 ml of 5% dextrose/water and was infused intravenously over 1 h, followed by PTX diluted in 500 ml of 0.9% saline infused intravenously over 3 h. Treatment courses were repeated once every 21 days. Routine anti-allergy medication was always given prior to each treatment. This consisted of a triplet of 20 mg dexamethasone, 30 mg diphenhydramine, and 200 mg cimetidine administered intravenously 30 min prior to initiation of treatment.

The protocol treatment was continued until the maximal response was achieved (provided that treatment was more than six courses), until the time of disease progression, or until intolerable toxicity occurred. In the case of a patient experiencing dose-limiting toxicities (DLT) and further treatment being considered beneficial, therapy could be continued off-protocol at the lower doses, based on the clinical judgment of the treating physician.

Evaluation of toxicity and definition of dose-limiting toxicity (DLT)

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC Version 2). Complete blood count, biochemical analysis, and clinical toxicity assessment were performed weekly during all treatment courses. DLT was defined as grade 4 neutropenia lasting more than 7 days, febrile neutropenia (fever >38°C with grade 3 or grade 4 neutropenia), grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding disorders, and any grade 3 or grade 4 non-hematological toxicity except alopecia, nausea or vomiting. Dose escalation and determination of DLT were determined based on the toxicity that occurred during the first two cycles of chemotherapy.

Dose escalation schema

A dual-dose escalation scheme was adopted to comprehensively evaluate the PLD/PTX regimen. In stage I of the study, the initial dose levels were PTX 150 mg/m^2 and PLD 30 mg/m^2. The PLD dose was increased by 5 mg/m^2. Cohorts of three to six patients were treated at a given dose level. There was no intra-patient dose escalation. Instead, escalation to the next higher dose level took place only after all three patients had completed the first two treatment cycles without evidence of DLT. If there was one DLT among the initial three patients, an additional three patients were treated at the same dose level. If two or less patients out of six experienced DLT, the dose was escalated to the next level. If more than two patients out of three experienced DLT, the dose was not escalated to the next level, and the MTD_1 was defined as the next lower dose level.

In stage II of the study, the initial dose levels were PTX 160 mg/m^2 and the MTD_1 level for PLD. The PTX dose was escalated by 10 mg/m^2 for each dose level. The dose

escalation schema was similar to that described in stage I until MTD_2 was identified.

Treatment modification

Chemotherapy was only given in the presence of appropriate hematological reserves (WBC >3,000 per μl with ANC >1,000 per μl, platelet count >75,000 per μl) and recovery of significant non-hematological toxicity. If these criteria were not met, treatment was delayed for a maximum of 4 weeks. Hematopoietic growth factors were only allowed for the management of complicated febrile neutropenia. Prophylactic therapy with ciprofloxacin 500 mg orally twice daily and fluconazole 50 mg once daily were administered until recovery from grade 4 neutropenia.

Evaluation of response

Patients completing at least two cycles of treatment with at least one follow-up tumor assessment were considered evaluable for response. An initial tumor assessment for all patients was performed within 4 weeks prior to treatment initiation. While on study, patients were evaluated every two cycles and every 2 months thereafter until the progression of disease. Chest X-rays, computed tomography scans, ultrasound imaging studies, and clinical measurements, were employed to evaluate patient response.

In terms of response criteria, the size of measurable lesions was reported as the product of the longest diameter and its perpendicular. Standard response criteria were applied [17]. For characterization of complete response (CR), total disappearance of all measurable and assessable disease was required; for partial response (PR) a >50% reduction in the size of all lesions as measured by the product of the greatest length and width of measurable lesions was required. Confirmation of objective responses was required in all cases at a minimum time interval of 4 weeks.

Results

Patient characteristics

From November 1998 to March 2003, a total of 23 patients were enrolled in this multicenter study in Taiwan. Patient characteristics recorded at the beginning of the study are provided in Table 1. The median patient age was 50 years; 17 (74%) patients had an ECOG performance status of 0 or 1; 11 (48%) were postmenopausal and 18 (78%) were hormone receptor positive. The lung was the most common site of metastasis in 15 (65%) patients, followed by liver in 13 (57%) and soft tissue or lymph node in 13 (57%) patients. Eighteen (78%) patients had two or more sites of metastases.

Table 1 Patients characteristics

Clinical parameter	*N*	%
Median age in years (range)	50 (35–69)	
ECOG performance status		
0	2	9
1	15	65
2	6	26
Menopause status		
Premenopausal	12	52
Postmenopausal	11	48
Receptor status		
ER or PR positive	18	78
ER and PR negative	5	22
Prior surgery		
Biopsy only	3	13
Simple mastectomy	1	4
Radical mastectomy	1	4
Modified radical mastectomy	18	78
Prior hormone therapy		
Tamoxifen	17	74
Medroxyprogesterone acetate	8	35
Anastrozole	4	17
None	5	22
Prior radiotherapy		
Adjuvant	11	48
For metastatic disease	3	13
Prior chemotherapy		
Adjuvant		
Anthracycline containing regimens	15	65
CMF	7	30
Docetaxel	1	4
For metastatic disease		
Anthracycline containing regimens	11	48
CMF	3	13
Prior cumulative dose of anthracycline		
<240 mg/m^2	6	26
>240 mg/m^2	17	74
Site of metastatic disease		
Liver	13	57
Lung	15	65
Bone	9	39
Skin	7	30
Soft tissue or lymph node	13	57

ER estrogen receptor, *PR* progesterone receptor, *CMF* cyclophosphamide plus methotrexate plus 5-fluorouracil

Eighteen (78%) patients received prior adjuvant chemotherapy including 15 (65%) who received anthracycline-

containing regimens. In particular, 11 patients received CEF (cyclophosphamide plus epirubicin plus 5-fluorouracil), three patients received CAF (cyclophosphamide plus doxorubicin plus 5-fluorouracil) and one patient was treated with AC (doxorubicin plus cyclophosphamide).

Thirteen (57%) patients received prior chemotherapy for metastatic diseases, 11 (48%) of whom received anthracycline-containing regimens. Seven patients received CEF, three patients received CAF and one patient received CE (cyclophosphamide plus epirubicin). Seventeen (74%) patients received chemotherapy with cumulative anthracycline dose ≥240 mg/m^2.

DLT and MTD

Table 2 summarizes the results of the dose escalations and DLTs trials. In stage I of the study, the median number of treatment cycles was 5 (range 1–13). Two of five patients developed DLTs at PTX 150 mg/m^2 and PLD 40 mg/m^2. The MTD_1 was PTX 150 mg/m^2 and PLD 35 mg/m^2.

In stage II of this study, the median number of treatment cycles was 3 (range 1–8). Two of five patients developed DLTs at PTX 170 mg/m^2 and PLD 35 mg/m^2; thus, the MTD_2 was PTX 160 mg/m^2 and PLD 35 mg/m^2. Overall, a total of five DLTs occurred including four febrile neutropenic events and one palmar-plantar erythrodysesthesia (grade 3). Each of the four febrile neutropenic events developed in cycle 1. The palmar-plantar erythrodysesthesia developed in the second cycle.

Overall toxicities

A total of 114 treatment cycles were completed, including 95 on-protocol treatment cycles and an additional 19 off-protocol treatment cycles. Five patients who developed DLT and two patients who requested dose reduction after completion of three treatment cycles were taken off study, but continued to receive the PTX and PLD combination at reduced doses ranging from PTX 140 to 170 mg/m^2 and PLD 30 to 35 mg/m^2.

The hematologic toxicity per dose level during the first two cycles and the overall hematologic toxicity in the 114 treatment cycles are summarized in Tables 3 and 4, respectively. The most common grade 3 and grade 4 hematologic toxicity was neutropenia. Grade 3 and grade 4 neutropenia occurred in 39 (34%) treatment cycles, with 6 (5%) cases of hospitalization for febrile neutropenia. Grade 3 anemia and thrombocytopenia occurred only in 2 (2%) and 5 (4%) treatment cycles, respectively. Grade 4 anemia or thrombocytopenia was not reported.

Table 3 Hematological toxicity recorded in first two cycles (total cycles = 42)

PLD (mg/m^2)	30	35	40	35	35	Total (%)
PTX (mg/m^2)	150	150	150	160	170	
Anemia						
Grade 1	0	0	1	1	0	2 (5)
Grade 2	2	2	4	3	1	12 (29)
Grade 3	0	0	0	0	2	2 (5)
Grade 4	0	0	0	0	0	0
Neutropenia						
Grade 1	1	0	0	0	1	2 (5)
Grade 2	1	0	1	2	1	5 (12)
Grade 3 (no DLT)	2	3	1	2	1	9 (21)
Grade 3 (DLT)	0	0	1	0	1	2 (5)
Grade 4 (no DLT)	1	0	1	0	0	2 (5)
Grade 4 (DLT)	1	0	1	0	1	3 (7)
Thrombocytopenia						
Grade 1	0	0	3	1	1	5 (12)
Grade 2	0	0	0	0	0	0
Grade 3	2	2	0	0	1	5 (12)
Grade 4	0	0	0	0	0	0

Table 2 Dose escalation and DLTs per cohort

	Dose (mg/m^2)		Number of patients	Number of cycles	DLTs	
	PLD	PTX			Number of events	Description
Stage I						
1	30	150	6	37	1	FN, cycle 1
2	35	150	3	17	0	
3	40	150	5	12	2	FN, cycle 1; PPE (grade 3), cycle 2
Stage II						
	35	160	4	19	0	
1	35	170	5	10	2	FN, cycle 1; FN, cycle 1
Total			23	95		

PLD pegylated liposomal doxorubicin, *PTX* paclitaxel, *DLT* dose-limiting toxicity, *FN* febrile neutropenia, *PPE* palmar-plantar erythrodysesthesia

Table 4 Hematological toxicity recorded in 114 treatment cycles

	Overall (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	78 (68)	32 (28)	7 (6)
Febrile neutropenia	6 (5)	5 (4)	1 (1)
Anemia	47 (41)	2 (2)	0
Thrombocytopenia	20 (18)	5 (4)	0

Table 5 Non-hematological toxicity recorded in 114 treatment cycles

	Overall (%)	Grade 3 (%)
Nausea	43 (38)	1 (1)
Vomiting	26 (23)	1 (1)
Diarrhea	3 (3)	1 (1)
Stomatitis	33 (29)	1 (1)
Palmar-plantar erythrodysesthesia	38 (33)	1 (1)
Sensory neuropathy	43 (38)	0
Asthenia	23 (20)	0
AST/ALT elevation	11 (10)	1 (1)
Edema	8 (7)	0
Allergic reaction	4 (4)	0

Observed non-hematologic toxicities are summarized in Table 5. The most common non-hematological adverse events observed in this patient population were stomatitis, nausea/vomiting, neurotoxicity, palmar-plantar erythrodysesthesia, and fatigue. The majority of these events were mild and manageable. Grade 3 gastrointestinal toxicity (nausea, vomiting, diarrhea, and stomatitis) occurred in only 4 (4%) treatment cycles. One patient experienced grade 3 palmar-plantar erythrodysesthesia at cycle 2, which defined the DLT. One patient with liver metastases at baseline had grade 3 hepatic enzyme elevation at cycle 5. Imaging studies documented disease progression and the patient died of hepatic failure 6 months later, off study. The hepatic enzyme elevation was possibly associated with disease progression instead of treatment-related toxicity. There was no grade 4 non-hematologic toxicities reported.

Response and survival

Nineteen of the 23 patients were evaluable for tumor response. Among the 19 evaluable patients, one (5%) CR and nine (47%) PRs were documented. Another five patients had disease stabilization while four patients exhibited progressive disease. As illustrated in Table 6, objective responses occurred at almost all dose levels, whereas patients treated at lowest dose (PTX 150 mg/m^2 plus PLD 30 mg/m^2) derived the greatest response rate.

Table 6 Response rates in 19 evaluable patients

	Dose (mg/m^2)		Number of patients	Response	
	PLD	PTX		CR	PR
Stage I					
1	30	150	5	0	4
2	35	150	3	0	1
3	40	150	4	1	0
Stage II					
1	35	160	4	0	2
2	35	170	3	0	2
Total			19	1 (5%)	9 (47%)

PLD pegylated liposomal doxorubicin, *PTX* paclitaxel, *CR* complete response, *PR* partial response

The time to disease progression and overall survival in the 23 patients was 7.9 months [95% confidence interval (CI) 4.7–11.0 months] and 26.2 months (95% CI 15.6–36.8 months), respectively.

Discussion

In the present phase-I multicenter study, the MTD of the PLD/PTX combination was 35/160 mg/m^2. Dose escalation was limited primarily due to development of febrile neutropenia which occurred in four patients at cycle 1. Grade 3 and grade 4 neutropenia occurred in 34% of treatment cycles. Another dose-limiting toxicity was grade 3 palmar-plantar erythrodysesthesia, which occurred in one patient at cycle 2. Other grade 3 or grade 4 non-hematological toxicities were rare and manageable and no clinical significant cardiotoxicity was observed in this study.

To date, this is the first phase-I trial involving PLD/PTX combination therapy administered on a 3-week schedule, although there have been three phase-I trials in which PTX was administered weekly (summarized in Table 7) and four phase-II trials based on a 3-week schedule (Table 8). In one of the phase-I studies, Briasoulis et al. [18] reported that the clearance of PLD was reduced by PTX, resulting in a significant increase in systemic tissue exposure; the mechanism of the observed drug-to-drug interaction is not known. Therefore, a phase-I study with a 3-week administration schedule should be mandatory for further phase-II testing.

Compared with the three other phase-I trials involving weekly PTX [18–20], the present study demonstrated similar DLTs, including febrile neutropenia and palmar-plantar erythrodysesthesia (Table 7). In the three phase-II trials conducted on a 3-week schedule (PLD/PTX at 30/150 mg/m^2), the results of toxicity profiles were conflicting. One phase-II study reported a good toxicity profile [25], while another study reported a high incidence of febrile

Table 7 Phase I clinical trials of paclitaxel in combination with pegylated liposomal doxorubicin

Trial	*N*	MTD[a]		Days/cycle	DLT
		PTX (mg/m^2)	PLD (mg/m^2)		
Lortholary et al. [19]	16	80, days 1 and 8	22.5[b], day 1	14	No
Bourgeois et al. [20]	30	80, day 1; 90, days 8 and 15	35, day 1	28	FN, cycle 1; FN, cycle 1
Briasoulis et al. [18]	27	80, days 1, 8, and 15	30, day 1	28	Treatment delay, cycle 2; DVT, cycle 1
	17	70, days 1, 8, and 15	35, day 1	28	PPE, cycle 4; treatment delay, cycle 2

DVT deep venous thrombosis

[a] Maximal-tolerated dose, defined as the next lower dose at which DLTs occurred in at least one-third of a six-patient cohort

[b] At a PLD dose of 22.5 mg/m^2 , three patients received only one cycle and none had a DLT

Table 8 Clinical trials of paclitaxel in combination with liposomal doxorubicin in metastatic breast cancer

Trial	*N*	Phases	Prior chemo[a]/prior doxorubicin	PTX (mg/m^2)	LD (mg/m^2)	Days/cycle	ORR (%)	TTP (m)	OS (m)
PLD									
Lortholary et al. [19]	16	I	Yes/NS	80, days 1, 8	12.5–22.5, day 1	14	31	NA	NA
Bourgeois et al. [20]	30	I–II	No/NS	70–100, days 1, 8, and 15	30–35, day 1	28	60	12	25
Schwonzen et al. [21]	21	II	Yes/NS	100, days 1, 8	20, day 1	14	48	5	>10
Jones et al. [22]	17	II	No/NS	80, days 1,8, 15	45, day 1	28	75	NA	NA
Fulfaro et al. [23]	11	II	No/Yes	70, days 1, 8, 15	30, day 1	28	56	NA	NA
Moore et al. [24]	13	II	No/NS	200, day 1	30 day 1	21	70	NA	NA
Vorobiof et al. [25]	34	II	No/NS	175, day 1	30, day 1	21	73	10	>16
Rigatos et al. [26]	23	II	No/NS	175, day 1	30, day 1	21	70	6	10
Woll et al. [27]	43	II	No/NS	175, day 1	30, day 1	21	40	7	14
NPLD									
Miller et al. [28]	19	I–II	NS/NS	135–175, day 1	50–60, day 1	21	62	NA	NA

NS not specified in eligibility criteria, *NA* not available *LD* liposomal doxorubicin, *NPLD* non-pegylated liposomal doxorubicin

[a] Prior systemic chemotherapy for metastatic breast cancer

neutropenia and palmar-plantar erythrodysesthesia and the other study was terminated early because of frequent hand-foot adverse reactions. Our study demonstrated that patients tolerated the lower dose (PLD/PTX at 30/150, 35/150, or 35/160 mg/m^2) better than the higher dose (PLD/PTX at 40/150 or 35/170 mg/m^2; Table 3).

Although the primary objective of this phase-I trial was not to define the response rate for this combination, it is certainly an important issue to address. In this study, the objective response rate was 52%. This is a promising rate in MBC patients who had prior chemotherapy with anthracycline-containing regimens either in an adjuvant setting or for metastatic disease. Compared to other trials using various combinations of liposomal doxorubicin and PTX in MBC patients (summarized in the Table 8), our eligibility criteria could demonstrate the effectiveness of this combination more clearly in this particular population of patients.

The objective response of 52%occurred at nearly all dose levels and the greatest response rate observed in the present study (80%) was identified in patients treated at the lowest dose level (Table 6), although the sample size was not adequately powered for efficacy analysis. Our study also demonstrated that patients treated at the lower dose level received more treatment cycles (median 6.2 cycles at lowest dose level compared to 2.0 cycles at the highest dose level). As such, PLD (30–35 mg/m^2) in combination with PTX (150–160 mg/m^2) is recommended for phase-II testing.

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