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Pegylated Liposomal Doxorubicin as Adjuvant Therapy for Stage I-III Operable Breast Cancer

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Abstract. *Background: Conventional anthracyclines play an essential role for the treatment of breast cancer and have potent cytotoxic activity, but are associated with severe toxicity. In metastatic breast cancer, pegylated liposomal doxorubicin (PLD) is a formulation with efficacy similar to conventional doxorubicin but with reduced toxicity. This multicenter study evaluated the efficacy and safety of PLD-based adjuvant chemotherapy for women with stage I-III operable breast cancer. Patients and Methods: One hundred and eighty women with stage I-III breast cancer who received PLD-based adjuvant chemotherapy at six different Institutions in Taiwan from February 2002 to March 2008 were included and followed-up until April 2015. Treatment efficacy was determined by disease-free survival (DFS) rate and safety was evaluated by adverse events. Results: The 5- and 10-year DFS rates were 76.3 and 72.6%, respectively. Univariate analysis revealed that tumor size >5 cm (p=0.045; hazard ratio=3.31) and stage III (hazard ratio=3.54; p=0.019) were each associated with shorter DFS. Only stage III (hazard ratio=5.60; p=0.018) retained statistical significance with regard to DFS in the multivariate analysis. Grade 3/4 hematological toxicity was neutropenia (n=13; 7.2%). The women receiving PLD had low-grade 3 or 4 nausea/vomiting, mucositis, and alopecia. Grade 3 hand–foot syndrome occurred in three patients (1.7%). Conclusion: PLD could be considered an effective and safe alternative to conventional anthracyclines in the treatment of stage I-III operable breast cancer.*

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Breast cancer, the most common cancer diagnosed in women and the second most common cancer overall, being a major threat to global public health (1). In spite of significant improvement in the outcome of treatment, which can be attributed to better diagnostic tools and an array of available therapeutic agents, it is still a leading cause of cancer death. The improvement in survival rate for patients with breast cancer benefiting from the use of more powerful chemotherapy agents has resulted in a proportionate increase in toxicities or side-effects. Anthracycline-based adjuvant chemotherapy is the standard therapy for early-stage breast cancer. However, this therapy can provoke a toxic host response, such as nausea, vomiting, and leukopenia that sometimes makes treatment unfeasible (2). In addition, elderly patients and those who receive multiple courses of anthracycline-based chemotherapy are at risk for cardiac toxicity, which can lead to heart failure (3, 4).

Incorporation of doxorubicin into polyethylene glycol-coated (pegylated) liposomes reduces the toxicity profile of classic anthracyclines while maintaining their efficacy (5). Pegylated liposomal doxorubicin (PLD) treatment has similar efficacy to conventional doxorubicin and is

associated with a lower incidence of nausea/vomiting and cardiotoxicity in metastatic breast cancer (6). The aim of the current study was to evaluate the efficacy and toxicity profile of PLD as adjuvant chemotherapy for stage I-III operable breast cancer.

Patients and Methods

Patient population. One hundred and eighty women with operable stage I, II, or III invasive breast cancer who had received PLD-based adjuvant chemotherapy from February 2002 to March 2008 at the following six Institutions in Taiwan were included in the analysis: China Medical University Hospital, Taiwan Adventist Hospital, Kaohsiung Medical University Hospital, National Taiwan University Hospital, Changhua Christian Hospital, and Chia-Yi Christian Hospital. Clinical and demographic inclusion criteria were age between 28 and 76 years, a Karnofsky performance score ≥80%, and no evidence of metastatic disease. Data on the pathological characteristics of tumors and history of treatments were extracted from clinical charts. The following pre-chemotherapy laboratory values were also inclusion criteria: absolute neutrophil count ≥1,400/μl, platelet count ≥100,000/μl, hemoglobin ≥9 g/dl, direct bilirubin ≤1.5 mg/dl, serum creatinine <1.5 mg/dl, and aspartate transaminase (AST) ≤2.5×the upper limit of normal. Exclusion criteria were evidence of serious infection or an underlying medical condition, history of prior chemotherapy or hormonal therapy, pregnancy, and lactation. This study was approved by the Institutional Review Board of Chia-Yi Christian Hospital, Taiwan (CYCH-IRB No. 099014).

Treatment. None of the patients received neoadjuvant chemotherapy. Before PLD treatment, a definitive breast surgery of the primary tumor was performed. The adjuvant cytotoxic regimens used at the six Institutions during the study period included intravenous 600 mg/m^2 cyclophosphamide plus 25-35 mg/m^2 PLD with 600 mg/m^2 5-fluorouracil in 112 patients, intravenous 600 mg/m^2 cyclophosphamide plus 25-35 mg/m2 PLD in 57 patients, and intravenous 25-35 mg/m^2 PLD alone in eight patients (Table I). Therapeutic radiation therapy was performed and hormone therapy was administered after the completion of chemotherapy for appropriate patients. None of the patients received trastuzumab adjuvant chemotherapy because the treatment period predated the coverage of trastuzumab in the adjuvant setting by the National Health Insurance of Taiwan in Jan 2011. Pre-medication with antiemetic agents (5-hydroxytryptamine receptor antagonists, metoclopramide, and dexamethasone) was prescribed routinely before each cycle of chemotherapy.

Assessments. Baseline data included vital signs, height and weight, Eastern Cooperative Oncology Group (ECOG) performance status, complete blood count with differential and platelet count, disease assessment, and laboratory tests (total bilirubin, serum creatinine, AST, and alanine transaminase). Toxicity was assessed at each follow-up visit and for 30 days after the last dose for each patient. Disease status was assessed based on computed tomography, ultrasound, routine X-rays, and bone scan findings. The left ventricular ejection fraction was quantified using echocardiogram or multinucleated gated angiography when clinically indicated during the study. Patients were followed at 3-month intervals for 5 years and annually thereafter until April 2015. At each follow-up examination, laboratory findings, annual chest X-rays, mammograms (if indicated), and health status were evaluated. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (7). Study-related unacceptable toxicities were defined as greater than grade 3 non-hematological toxicity (excluding nausea and vomiting), grade 4 vomiting despite use of antiemetics and grade 4 hematological toxicity. No prophylactic growth factors were used. Oral prophylactic antibiotics were administered to some of the patients at the discretion of the treating physician.

Statistical analysis. Disease-free survival (DFS) was defined as the time between the start date of treatment and the date of disease progression or death. Patients still alive without their disease progressing at the end of the study were censored at the date of their last follow-up. DFS was assessed using the Kaplan–Meier method, and log-rank tests were used to compare differences between the resulting curves. Multivariate survival by Cox regression model incorporated age, menstruation status, tumor size, stage, hormone and human epidermal growth factor receptor 2 (HER2) positivity. Overexpression of HER2 was defined as a score of 2+ or 3+. Treatment-related toxicities were reported and summarized by the highest grade per patient. All statistical tests were two-sided and a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using STATA version 11 (STATA Corp., College Station, TX, USA).

Results

Outcome. A total of 180 patients from six medical centers were included in the analysis. Patients' characteristics are shown in Table I. Six cycles of PLD-based chemotherapy were given to 148 (82.8%) patients, and the rest received four to five courses (17.2%), with 3 weeks between each cycle. The mean dose of PLD was 33.12 mg/m^2. The 5- and 10-year DFS rates were 76.3 and 72.6%, respectively. (Figure 1). Parameters in the multivariate survival analysis by Cox regression model included age, menstruation status, tumor size, stage, hormone and HER2 receptor positivity.

Univariate analysis showed that tumor size greater than 5 cm [hazard ratio (HR)=3.31, 95% confidence interval (CI)=1.03-10.69; p=0.045] and stage III (HR=3.54, 95% CI=1.23-10.22; p=0.019) were each associated with shorter DFS. Of these, only stage III was independently associated with DFS in the multivariate analysis (HR=5.60, 95% CI=1.34-23.43; p=0.018) (Table II).

Toxicity. The clinically significant toxicities are listed in Table III. Thirteen patients (7.2%) developed grade 3/4 neutropenia, while 14 (7.8%) reported grade 1 thrombocytopenia. Grade 3 nausea, vomiting, and mucositis each developed in only one patient (0.6%). PLD-related hand-foot syndrome occurred in 50 patients; among these patients, 47 had grade 1/2, and three had grade 3. Alopecia occurred in four patients (2.2%), who were all grade 1. None of the patients in this study developed congestive heart failure, leukemia, or myelodysplasia.

Table I. *Patients' demographics and characteristics.*

Demographic characteristic	n=180
Median age, years (range)	50 (28-76)
ECOG performance status (%)	
0	176 (97.8)
1	4 (2.2)
Menopausal status (%)	
Premenopause	99 (55)
Postmenopause	81 (45)
Location of breast cancer (%)	
Right	86 (47.8)
Left	91 (50.6)
Both	3 (1.7)
Surgery (%)	
Breast conservative surgery	66 (36.7)
Modified radical mastectomy	114 (63.3)
Pathological confirmation (%)	
Ductal carcinoma	171 (95.0)
Lobular carcinoma	5 (2.8)
Other	4 (2.2)
Stage at diagnosis (%)	
I	44 (24.4)
IIa	79 (43.9)
IIb	36 (20.0)
IIIa	17 (9.4)
IIIb	1 (0.5)
IIIc	3 (1.7)
Estrogen receptor (%)	
Positive	105 (58.3)
Negative	72 (40.0)
Unknown	3 (1.7)
Progesterone receptor (%)	
Positive	109 (60.6)
Negative	68 (37.8)
Unknown	3 (1.7)
HER-2 (%)	
Negative	61 (33.9)
+	40 (22.2)
2+	38 (21.1)
3+	38 (21.1)
Unknown	3 (1.7)
Adjuvant regimen (%)	
PLD/cyclophosphamide	57 (31.7)
Fluorouracil/PLD/cyclophosphamide	112 (62.2)
PLD alone	8 (5.0)
PLD/others	3 (1.7)
Radiotherapy (%)	
Yes	96 (53.3)
No	83 (46.1)
Hormone therapy (%)	
Yes	122 (67.8)
No	57 (31.7)

PLD: Pegylated liposomal doxorubicin; HER2: human epidermal growth factor receptor 2.

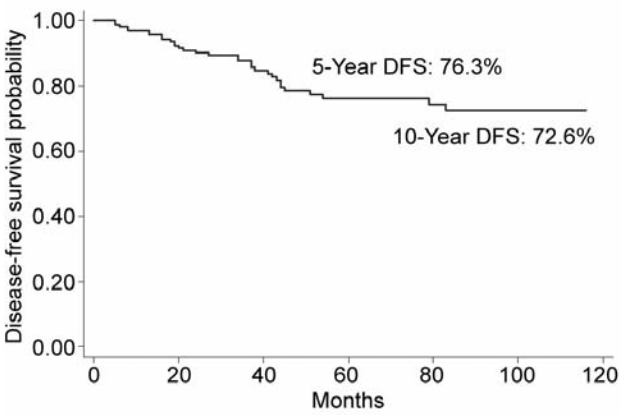

Figure 1. *Disease-free survival (DFS) of patients with breast cancer treated with pegylated liposomal doxorubicin-based adjuvant chemotherapy.*

Discussion

PLD has been shown to have a cytotoxic effect in metastatic breast cancer and other types of cancer (8). It has been suggested that toxicity is less pronounced in PLD-based regimens (9). In addition to the lower frequency of cardiomyopathic toxicity, nausea/vomiting discomfort, the low incidence of alopecia makes PLD a practical agent for treatment of breast cancer (10).

In this study, the most common adverse event from PLD-based regimen was neutropenia. Grade 3 and 4 toxicity occurred in only 7.2% of the study population, and all cases were manageable. The hematological toxicity ratio was lower compared to other clinical trials, such as CALGB5841, CALGB9344, and CALGB9741, in which the grade 4 neutropenia rate was around 15% (11). About one-fourth of the patients experienced grade 1/2 nausea and vomiting, and only 0.6% of the patients developing grade 3/4 toxicity, which is much lower than the previously reported incidence rates of as high as 10% grade 4 nausea and vomiting for classic anthracyclines (12, 13). The incidence of alopecia was also low (2.2%). For many women, the breast symbolizes femininity, and the psychological impact and distress on body image can be profound after breast surgery, and may be further aggravated by chemotherapy-induced alopecia (14, 15). Thus, PLD that minimizes the incidence of alopecia, appears to be a promising adjuvant chemotherapy agent for the treatment of breast cancer in women.

Palmar-plantar erythrodysesthesia (hand–foot syndrome) is a PLD-specific adverse effect (16). The clinical features usually begin with dysesthesia and tingling in the hands and feet, which may progress to desquamation, crusting, and ulceration. This condition can be managed with non-pharmacological methods or the use of topical ointment. Hand–foot syndrome occurred in 50 patients (27.8%) in this

Table II. *Univariate and multivariate Cox regression model for disease-free survival.*

Variable	Univariate			Multivariate		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (years)						
<45	1.00			1.00		
45-65	0.91	0.40-2.05	0.814	0.55	0.19-1.61	0.272
>65	0.85	0.18-4.02	0.841	0.33	0.05-2.09	0.240
Menopausal status						
Premenopause	1.00			1.00		
Postmenopause	1.42	0.70-2.88	0.330	1.54	0.55-4.32	0.415
Tumor size (cm)						
<2	1.00			1.00		
2-5	1.07	0.49-2.31	0.865	0.59	0.21-1.61	0.301
>5	3.31	1.03-10.69	0.045	1.24	0.30-5.16	0.769
Stage						
I	1.00			1.00		
II	1.59	0.63-4.04	0.329	2.60	0.80-8.41	0.112
III	3.54	1.23-10.22	0.019	5.60	1.34-23.43	0.018
Estrogen receptor						
Positive	1.00			1.00		
Negative	1.05	0.52-2.15	0.888	0.68	0.26-1.82	0.445
Progesterone receptor						
Positive	1.00				1.00	
Negative	1.92	0.94-3.89	0.072	2.66	0.98-7.18	0.054
HER2						
Negative	1.00				1.00	
Positive	1.40	0.69-2.85	0.347	1.28	0.59-2.75	0.529

CI: Confidence interval; HR: hazard ratio; HER2: human epidermal growth factor receptor 2.

Table III. *Patients' toxicity profiles.*

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%
Neutropenia	61	33.9	50	27.7	12	6.7	1	0.6
Thrombocytopenia	14	7.8	0	0.0	0	0.0	0	0.0
Nausea	24	13.3	31	17.2	1	0.6	0	0.0
Vomiting	17	9.4	31	17.2	1	0.6	0	0.0
Mucositis	17	9.4	31	17.2	1	0.6	0	0.0
Hand–foot syndrome	31	17.2	16	8.9	3	1.7	–	
Alopecia	4	2.2	0	0.0	–		–	

study and only three cases (1.7 %) reached grade 3 toxicity. Although this adverse effect is reversible and manageable, patients should be informed about this common drug-related adverse effect before receiving PLD.

The DFS findings showed that the efficacy of PLD-based adjuvant chemotherapy was comparable to that of conventional anthracycline. Multivariate analysis of DFS in this study revealed that only disease stage was an independent prognostic factor.

In conclusion, for women with operable stage I to III invasive breast cancer, PLD appeared to be a safely and efficacious option as an adjuvant agent, as the toxicities associated with the treatment were mostly manageable. One major strength of the present study is the long follow-up duration, which is necessary to monitor the incidence of heart failure, leukemia, or myelodysplasia events (17). The limitations of this study included its retrospective design and its relatively small sample size of 180 patients. Although

these patients were treated at six different Institutions in Taiwan, a larger patient population and prospective randomization could provide more convincing results. Moreover, because comparison with classic anthracycline was not included in the present study. Further research to directly compare the efficacy of PLD with classic anthracycline agents may be an attractive prospective study for the future.

Conflicts of Interest

The Authors state that they have no conflicts of interest.

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