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Reduced Incidence of Severe Palmar-Plantar Erythrodysesthesia and Mucositis in a Prospective Multicenter Phase II Trial with Pegylated Liposomal Doxorubicin at 40 mg/m^2 Every 4 Weeks in Previously Treated Patients with Metastatic Breast Cancer

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Key Words
Mucositis · Palmar-plantar erythrodysesthesia · Pegylated liposomal doxorubicin

Abstract
Purpose: The aim of this study was to assess whether the reduction in the total dose of pegylated liposomal doxorubicin (PLD) per cycle from 50 mg/m^2 every 4 weeks to 40 mg/m^2 every 4 weeks can effectively lower the incidence of treatment-related palmar-plantar erythrodysesthesia (PPE) and mucositis. ***Methods:*** Patients received PLD 40 mg/m^2 every 4 weeks, and were evaluated for toxicity prior to each treatment and for response every 8 weeks. ***Results:*** All patients were previously treated with at least one chemotherapy regimen for metastatic disease, and 72% of the patients had a prior exposure to an anthracycline. Forty-six evaluable patients received a median of four PLD cycles, with a median dose intensity of 10 mg/m^2/week and a median cumulative dose of 160 mg/m^2. No National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or 4 PPE was observed in these patients. NCI-CTC grade 3 or 4 mucositis occurred in 4.3% of patients, only. Response rates and survival results observed here were comparable to those observed with PLD 50 mg/m^2 every 4 weeks in a matched patient population. However, patients treated with PLD 40 mg/m^2 every 4 weeks experienced less PPE and mucositis and required clearly less dose reductions and treatment delays. ***Conclusion:*** The favorable safety profile observed in this study leads us to recommend the use of PLD 40 mg/m^2 every 4 weeks for patients with advanced breast cancer.

Introduction

Anthracyclines such as doxorubicin are considered the most active agents in the treatment of breast cancer in the adjuvant and metastatic setting. However, the use of conventional anthracyclines is limited by toxicity, especially cardiac toxicity at high cumulative doses, and other side effects, including myelosuppression, alopecia, nausea, and vomiting. Encapsulation of doxorubicin by pegylated liposomes (pegylated liposomal doxorubicin; PLD) sig-

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nificantly modifies its pharmacokinetics and tissue distribution, resulting in a comparable efficacy but a distinct toxicity profile compared to free doxorubicin [1–12]. In a recent study, 509 patients with metastatic breast cancer (MBC) were randomly assigned to receive either PLD 50 mg/m^2 every 4 weeks or free doxorubicin 60 mg/m^2 every 3 weeks. Patients treated with PLD experienced significantly less cardiac toxicity, alopecia, gastrointestinal adverse events and myelosuppression [13]. However, treatment with PLD at standard doses (i.e. 50 mg/m^2 every 4 weeks or 60 mg/m^2 every 6 weeks) is associated with characteristic skin toxicity known as palmar-plantar erythrodysesthesia (PPE) in approximately half of the patients. Another dose-dependent major toxicity of PLD is mucositis. PPE, also known as hand-foot syndrome, is a dose-interval- and intensity-dependent toxicity of PLD which affects about 50% (including grade 3 PPE in 17%) of patients receiving PLD 50 mg/m^2 every 4 weeks or dose intensities $\geq$11.25 mg/m^2 per week [11, 13]. Mucositis, however, appears to be related to the dose administered per cycle and represents the dose-limiting toxicity in patients receiving single doses of PLD $\geq$60 mg/m^2 at prolonged (6 weeks) dose intervals [14]. These toxicities can be considered acceptable in patients receiving curative (adjuvant) or first-line chemotherapy but they seem less acceptable in patients at more advanced stages of metastatic disease. In these patients, severe skin or mucosal toxicity may alter the quality of life and reduce the clinical benefit of the treatment. This phase II study was designed to prospectively assess whether reducing the total dose of PLD per cycle to PLD 40 mg/m^2 every 4 weeks or the dose intensity to 10 mg/m^2 per week can effectively lower the incidence of both mucositis and PPE in patients with MBC.

Patients and Methods

Patient Eligibility

Female patients were eligible if they had histologically confirmed MBC with at least one measurable lesion, at least 1, or a maximum of 2 prior chemotherapies for metastatic disease, Karnofsky performance status $\geq$70%, age >18 years, life expectancy $\geq$3 months, no concurrent uncontrolled medical illness, no other malignancies (with the exception of squamous cell carcinoma of the skin treated by surgery), left ventricular ejection fraction $\geq$50%, and sufficient hepatic and bone marrow function. Patients were excluded from the study if they had cardiac diseases including atrial or ventricular arrhythmia, or if they were pregnant or breast-feeding. Women of childbearing age were advised to take adequate precautions to prevent pregnancy. Participants gave written informed consent before they entered the study which was approved by the ethics committees of the participating centers.

Chemotherapy

The initial infusion duration of PLD 40 mg/m^2 was 1 h in order to minimize the risk of infusion-related reactions. Subsequent doses were given as 30-min infusions. Cycles were repeated every 4 weeks, and treatment was continued until disease progression, unacceptable toxicity, patient refusal or physician's decision. Antiemetic prophylaxis was given according to local protocols.

Toxicity Assessment

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2). PPE was graded as (1) mild erythema, swelling or desquamation not interfering with daily activities; (2) erythema, desquamation or swelling interfering with, but not precluding, normal physical activities, including small blisters or ulcerations <2 cm in diameter; (3) blistering, ulceration or swelling interfering with walking or normal daily activities, and (4) a diffuse or local process causing infectious complications, deterioration of the performance status or hospitalization. Cardiac toxicity was based on left ventricular ejection fraction measurements and a 12-lead electrocardiogram performed at baseline and every 8 weeks. Dose modifications of PLD were permitted for hematological toxicity, increases in total bilirubin, cardiac toxicity, PPE, stomatitis and other NCI-CTC grade 3 or 4 events.

Assessment of Response

Responses were classified according to World Health Organization criteria. CT scans of measurable lesions were carried out within 4 weeks before the start of the treatment and were repeated every two cycles. Responses were to be confirmed by subsequent CT scans 4–8 weeks after the initial response documentation. Patients who discontinued the study were evaluated at least every 3 months. Patients were considered assessable for response if they had early disease progression or had received at least two cycles of treatment with at least one tumor assessment.

Statistical Analyses

The statistical analysis for response and toxicity was descriptive. The 95% confidence interval (CI) for response was calculated. Progression-free survival (PFS) was measured from the start of the treatment until disease progression or death. The overall survival (OS) was measured from the start of the treatment until death.

Results

Between October 2001 and December 2002, 46 female patients with MBC were enrolled in the study at 17 German centers. The median age was 60 years (range, 35–82 years) and the median Karnofsky performance status was 80% (range, 70–100). Patient characteristics and treatment history are listed in table 1. All patients were evaluable for efficacy and safety.

Safety

Forty-six patients received a total of 208 treatment cycles. The median number of cycles administered was four (range, 1–15 cycles). The median cumulative dose of

Table 1. Patient characteristics and treatment history

Patient characteristics	Patients (n = 46)	
	n	%
Age		
18–50 years	9	19.5
51–70 years	28	60.8
71–80 years	9	19.5
Karnofsky performance status		
100%	5	10.8
90%	16	34.7
80%	10	21.7
70%	15	32.6
Metastatic sites		
≥1 site	12	26.1
≥2 sites	18	39.1
≥3 sites	16	34.8
Estrogen or progesterone receptor positive	34	73.9
HER2 positive[a]	5	10.9
Site of the disease		
Bone only	1	2.2
Visceral and non-visceral soft tissue	45	97.8
Treatment history		
Primary surgery	46	100
Adjuvant radiation therapy	30	65.2
Hormonal therapy[b]	39	84.7
Previous adjuvant chemotherapy	21	45.6
Previous chemotherapy metastatic	46	100
1 regimen	30	65.2
2 regimens	16	34.7
Previous anthracycline-based chemotherapy		
Any[c]	33	71.7
Metastatic only	25	54.3
Previous taxane-based chemotherapy		
Any[c]	25	54.3
Metastatic only	23	50

Median age was 60 years and median Karnofsky performance status 80%.

[a] 3+ by immunohistochemistry or amplification by fluorescence in situ hybridization.

[b] Adjuvant and/or metastatic.

[c] Adjuvant or metastatic.

PLD was 160 mg/m^2 (range, 40–600 mg/m^2). The median dose intensity of PLD was 10 mg/m^2/week (range, 6.4–10 mg/m^2/week). No NCI-CTC grade 3–4 PPE was observed in 46 evaluable patients. NCI-CTC grade 1 or 2 PPE was seen in 19 of 46 patients (41.3%). NCI-CTC grade 3–4 mucositis was observed in 2 of 46 patients (4.3%). Dose reductions and treatment delays were required in 2 (4.3%) and 15 (33.3%) patients, respectively. Reasons for dose reduction were: skin toxicity in 1 patient and hematological (prolonged neutropenia) toxicity in 1 patient. Cardiotoxicity (defined as a decrease in left ventricular ejection fraction ≥15% from baseline) was not observed. No treatment-related deaths were reported. Toxicities are listed in table 2.

Tumor Response

One complete response in 46 evaluable patients (2.2%) and 5 (10.9%) partial responses were observed, adding to an overall response rate of 13% (95% CI, 3.3–22.7). Sixteen patients (34.8%; 95% CI, 20.3–47.7) had stable disease and 24 patients (52.2%) progressive disease.

Progression-Free and Overall Survival

Forty-six patients were included in the survival analysis on an intent-to-treat basis. The median follow-up time was 14 months (up to 33 months). The median PFS was 3.3 months (95% CI, 2.8–5.4). The median OS was 10.7 months (95% CI, 6–18.3). The median response duration was 6.7 months (95% CI, 1.2–9.6). PFS and OS were assessed by Kaplan-Meier analysis as shown in figure 1.

Discussion

Safety and tolerability are major objectives in the treatment of patients with MBC. Due to its favorable safety profile, the liposomal anthracycline formulation PLD is increasingly used in the treatment of previously treated patients with MBC. However, specific side effects of PLD at standard doses such as PPE and mucositis may still severely alter the patients' quality of life. This prospective study aimed to evaluate the toxicity and efficacy of a dose modification of the monthly schedule of PLD (40 instead of 50 mg/m^2 every 4 weeks).

In the present study, 46 evaluable patients received a median of four cycles of PLD with a median dose intensity of 10 mg/m^2/week and a median cumulative dose of 160 mg/m^2. No NCI-CTC grade 3 or 4 PPE was observed in these patients, which is in contrast to the results observed in previous studies. Grade 3 or 4 PPE was documented in 54% of patients receiving 60 mg/m^2 every 3 weeks. This toxicity remained high (affecting 46% of patients) following dose reduction to 45 mg/m^2 every 3 weeks, and fell to 16% when the interval of the 45 mg/m^2 dose was prolonged to 4 weeks [10]. Reducing the dose intensity of PLD by administering higher doses at prolonged intervals (i.e. 60–70 mg/m^2 every 6 weeks) was associated with significantly less PPE but higher rates of mucositis, ranging between 53 and 100%, including grade 3 or 4 mucositis in

Table 2. Toxicities according to NCI-CTC (version 2.0)

Toxicities	Grade 1 (n = 46)		Grade 2 (n = 46)		Grade 3–4 (n = 46)		All grades (n = 46)	
	n	%	n	%	n	%	n	%
Non-hematologic								
Alopecia	9	19.6	8	17.4	1	2.2	18	39.1
Nausea	12	26.1	13	2.3	2	4.3	27	58.7
Diarrhea	6	13.0	4	8.7	2	4.3	12	26.1
Vomiting	8	17.4	6	13.0	2	4.3	16	34.8
Constipation	8	17.4	10	21.7	1	2.2	19	41.3
Fever	4	8.7	4	8.7			8	17.4
Infection	8	17.4	5	10.9	2	4.3	15	32.6
Neurosensory	14	30.4	2	4.3	1	2.2	17	36.9
PPE	10	21.7	9	19.6			19	41.3
Mucositis	9	19.6	11	23.9	2	4.3	22	47.8
Hematologic								
Neutropenia	7	15.2	8	17.4	5	10.9	20	43.5
Leukopenia	13	28.3	10	21.7	4	8.7	27	58.7
Anemia	25	54.3	10	21.7			35	76.1
Thrombopenia	11	23.9			1	2.2	12	26.1

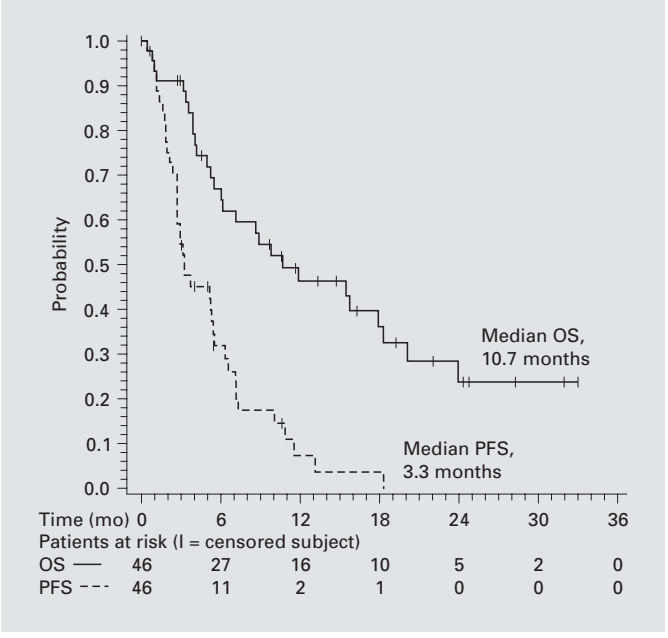

Fig. 1. Overall survival (OS) and progression-free survival (PFS).

12.5–82% of patients [14]. The rate of severe skin toxicity in our study is also lower than that observed using the FDA-recommended dose schedule of PLD (50 mg/m^2 every 4 weeks), which is associated with an overall rate of PPE of approximately 50% and grade 3 PPE of 17% [13]. NCI-CTC grade 3 or 4 mucositis was also less common in our study than in previous studies (4.3 vs. 20% with the 50 mg/m^2 every 4 weeks schedule in ovarian cancer [15] or 12.5% with the 60 mg/m^2 every 6 weeks schedule in breast cancer [14]). Other toxicities such as neutropenia, thrombocytopenia, alopecia and gastrointestinal toxicity were similar to those previously reported.

Many factors may limit the comparability of our results to the historical data mentioned above. Side effects in patients receiving PLD as a second- and third-line treatment (our patients), for example, may differ from those receiving PLD at early stages of disease, and different methods may have been used by investigators for grading PPE. Therefore, we analyzed our results in contrast to those of a matched patient population (comparator population) generated from a secondary analysis of an identically designed phase II study of our group using PLD 50 mg/m^2 every 4 weeks for patients with MBC [Al-Batran et al., submitted for publication]. This analysis (table 3) shows that patients treated with PLD 40 mg/m^2 every 4 weeks experienced less PPE and clearly required less dose reductions and treatment delays as compared to patients treated with PLD 50 mg/m^2 every 4 weeks. On the other hand, there were no remarkable differences in response rates or survival results between both dose groups (table 3). The efficacy results observed here are, furthermore, consistent with those reported from recent clinical trials using PLD or other active drugs, e.g. vinorel-

Table 3. Toxicity and efficacy of PLD 40 mg/m^2 every 4 weeks compared to that of PLD 50 mg/m^2 every 4 weeks

	PLD 40 mg/m^2 (n = 46)	PLD 50 mg/m^2 (n = 69)
Patient characteristics		
Median age, years	60	62
Median Karnofsky performance status, %	80	90
1 previous regimen (metastatic), %	65	59
2 previous regimens (metastatic), %	35	40
Anthracycline-based previous treatment, %	72	72
Taxane-based previous treatment, %	54	45
Median dose intensity, mg/m^2/week	10	12
Toxicity (PPE and mucositis)		
PPE, all grades, %	41.3	52.1
PPE, grade 3 or 4, %	–	8.6
Mucositis, all grades, %	47.8	43.4
Mucositis, grade 3 or 4, %	4.3	17.3
Dose reductions, % of patients	4.3	21.7
Treatment delays, % of patients	30.4	47.8
Efficacy		
Complete and partial responses, %	13	11.5
95% CI	3.3–22.7	3.6–18.4
Stable disease, %	34.8	33.3
95% CI	20.3–47.7	21.9–44
Progressive disease, %	52.2	53.6
Median PFS, months	3.3	3.7
95% CI	2.8–5.4	2.8–5.8
Median OS, months	10.7	13.8
95% CI	6–18.3	9.2–18.3

A matched patient population (comparator population) was generated from a secondary analysis of an identically designed phase II study of our group using PLD 50 mg/m^2 every 4 weeks for patients with MBC [Al-Batran et al., submitted for publication].

bine and capecitabine, in pretreated MBC patients [16–19]. An overall response rate of 13% was achieved with an additional 35% of patients having stable disease. The median PFS was 3.3 months, and the median OS was 10.7 months in a population with a relatively poor prognosis (72% of patients had received prior anthracycline and 54% prior taxane therapy, 35% of patients had received 2 prior chemotherapy regimens in the metastatic setting and most had visceral disease). The efficacy results are also in concordance with those reported by Keller et al. [16] using PLD at 50 mg/m^2 in taxane- and anthracycline-pretreated patients with MBC (response rate: 10%; median PFS and OS: , 2.9 and 11 months, respectively), and with a recent report on PLD at a dose of 45 mg/m^2 as a second-line treatment in MBC patients (median PFS and OS were 4 and 12 months, respectively) [17]. Therefore, the dose reduction in PLD in our study does not appear to affect its efficacy, at least in this patient population.

To date, the evidence that reduced dose intensity of PLD provides comparable efficacy and fewer side effects derives from retrospective observations in which clinicians have empirically reduced the dose of PLD in their clinical practice to 40 mg/m^2 every 4 weeks [20–23]. Our study represents the first prospective trial investigating this issue. Our results support the hypothesis that the reduction in the dose intensity of PLD to 10 mg/m^2 per week (i.e. 40 mg/m^2 every 4 weeks) leads to similar efficacy and better tolerability compared with the standard regimen (i.e. 12.5 mg/m^2 per week; 50 mg/m^2 every 4 weeks). The favorable safety profile seen in this study leads us to recommend the use of PLD 40 mg/m^2 every 4 weeks for patients with advanced breast cancer.

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