Phase II Evaluation of Liposomal Doxorubicin with Docetaxel in Patients with Metastatic Breast Cancer

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Key Words

Metastatic breast cancer · Doxil ·
Liposomal encapsulation of doxorubicin · Docetaxel

Summary

Background: Taxanes are effective in treating metastatic breast cancer. Liposomal doxorubicin (LD) is as effective as doxorubicin but less toxic. **Patients and Methods:** This phase II trial assessed the combination of LD and docetaxel (D). Between 12/2002 and 9/2005, 12 women received monthly LD (30 mg/m²) and weekly D (30 mg/m²). Cycles were continued until progression or toxicity. Primary outcome was time to progression. Secondary endpoints included response rate, time to treatment failure, duration of response, survival, and toxicity. **Results:** Median age was 49 (31–60) years. 9 (75%) patients had estrogen receptor-positive or progesterone receptor-positive tumors. 5 (41.7%) women had her-2/neu-positive tumors. 4 women stopped participation due to toxicity, and 7 due to progression. 8 (67%) participants (95% confidence interval (CI) 51.6–94.5%) had a partial response, and 2 (16.7%) had stable disease. Median time to progression was 9.6 months (95% CI 4.7–12.2). Median time to treatment failure was 6.5 months (95% CI 4.4–10.5). Median survival was 22.1 months (95% CI 9.6–40.8). Median duration of partial response was 2.7 months (95% CI 2.4–10.5). 10 (83%) women experienced grade 3/4 toxicities: neutropenia 3 (25%), infection 3 (25%), stomatitis 5 (41.7%), nausea 2 (16.7%), vomiting 1 (8.3%), dyspnea 2 (16.7%), pericardial effusion 1 (8.3%), and palmar-plantar erythrodysesthesia 1 (8.3%). **Conclusions:** LD and D resulted in an encouraging response and unacceptable toxicities.

Schlüsselwörter

Metastasiertes Mammakarzinom · Doxil ·
Liposomale Verkapselung von Doxorubicin · Docetaxel

Zusammenfassung

Hintergrund: Taxane sind wirksame Substanzen in der Behandlung des metastasierten Mammakarzinoms. Liposomales Doxorubicin (LD) ist genauso effektiv wie Doxorubicin, aber weniger toxisch. **Patienten und Methoden:** Die vorliegende Phase-II-Studie befasste sich mit der Kombination aus LD und Docetaxel (D). Zwischen Dezember 2002 und September 2005 wurden 12 Frauen mit monatlichem LD (30 mg/m²) und wöchentlichem D (30 mg/m²) behandelt. Die Behandlungszyklen wurden bis zum Auftreten von Progression oder Toxizität fortgesetzt. Das primäre Outcome war die Zeit bis zur Progression. Sekundäre Endpunkte waren Ansprechrate, Zeit bis zum Therapieversagen, Dauer des Ansprechens, Überleben und Toxizität. **Ergebnisse:** Das mittlere Alter betrug 49 (31–60) Jahre. 9 (75%) Patientinnen hatten östrogenrezeptorpositive oder progesteronrezeptorpositive Tumoren. 5 (41,7%) Frauen hatten her-2/neu-positive Tumoren. 4 Frauen beendeten die Teilnahme an der Studie auf Grund von Toxizität und 7 auf Grund von Progression. 8 (67%) Teilnehmerinnen (95% Konfidenzintervall (KI) 51,6–94,5%) zeigten ein partielles Ansprechen und 2 (16,7%) eine stabile Erkrankung. Die mittlere Zeit bis zur Progression war 9,6 Monate (95% KI 4,7–12,2). Die mittlere Zeit bis zum Therapieversagen betrug 6,5 Monate (95% KI 4,4–10,5). Das mittlere Überleben war 22,1 Monate (95% KI 9,6–40,8). Die mittlere Dauer des partiellen Ansprechens war 2,7 Monate (95% KI 2,4–10,5). 10 (83%) Frauen entwickelten Grad-3/4-Toxizitäten: Neutropenie 3 (25%), Infektion 3 (25%), Stomatitis 5 (41,7%), Übelkeit 2 (16,7%), Erbrechen 1 (8,3%), Dyspnoe 2 (16,7%), Perikarderguss 1 (8,3) und Hand-Fuß-Syndrom 1 (8,3%). **Schlussfolgerungen:** LD und D resultierten in vielversprechendem Ansprechen und inakzeptabler Toxizität.

Introduction

Doxorubicin, an anthracycline antibiotic, is one of the most active agents used to treat metastatic breast cancer (MBC). However, the clinical utility of doxorubicin is limited by its cumulative dose-dependent propensity to cause cardiac damage. Pegylated liposomal doxorubicin (LD) is doxorubicin encapsulated in liposomes. Clinical trials have demonstrated that LD is just as effective as doxorubicin, and with less toxicity [1].

Docetaxel (D) has significant activity in both frontline and second-line therapy for advanced breast cancer [2–6]. Given the significant activity doxorubicin and D exhibit as single agents in the treatment of breast cancer, their non-overlapping side effect profiles, and their lack of clinical cross-resistance, much research has been done to assess the benefit of combining these agents to treat MBC. The doxorubicin/D doublet has been shown to be a highly active first-line treatment regimen in MBC [7–13].

Several studies have been performed to assess whether the LD/D doublet can achieve the same therapeutic response, but most have not evaluated a weekly schedule of D. When D is dosed weekly, myelosuppression is diminished but fatigue becomes the major toxicity [14–17]. A phase I trial was conducted to determine the maximum tolerated dose of D that could be administered with LD, with and without granulocyte colony-stimulating factor (G-CSF) support in 37 patients with metastatic cancer. If LD/D were given without G-CSF support, the recommended dosing was 30/60 mg/m² every 3 weeks. If the combination was given with G-CSF support, 30 mg/m² of LD and 80 mg/m² of D could be administered every 3 weeks [18]. In a phase II study, 44 women with MBC received LD 30 mg/m² and D 75 mg/m² every 3 weeks for 6 cycles. The overall response rate (ORR) was 64.3%, with 6 (14.3%) patients attaining a complete response (CR) and 21 (50%) patients attaining a partial response (PR). Median progression-free survival and overall survival (OS) were not reached. Grade 3 and 4 toxicities included neutropenia (18.4%), palmar-plantar erythrodysesthesia (PPE) (2.3%), and neurotoxicity (2.3%) [19].

Given the therapeutic efficacy of single agents in the treatment of MBC, many practitioners use single-agent therapy rather than combination therapy to avoid toxicity. However, when patients with MBC have a good performance status, extensive visceral involvement, or rapid tumor growth, they may benefit from combination therapy. Combination therapy may achieve higher response rates and longer median time to progression (TTP) and OS [20]. The antitumor efficacy of combination LD and D and the reduced cardiotoxicity in its side effect profile make this doublet a viable treatment option for women with MBC. The objective of this phase II study was to determine both the efficacy and toxicity of weekly D in combination with monthly LD as first-line therapy in patients with MBC.

Patients and Methods

Patient Population

Women aged 18–75 years with histologically confirmed MBC with measurable or evaluable disease were eligible for enrollment. Patients were recruited from NYU Medical Center and Columbia University Medical Center. Participants could have received previous hormonal or adjuvant chemotherapy. Patients who had received prior chemotherapy for metastatic disease were ineligible. Prior anthracycline exposure was permitted if the total doxorubicin dose was less than or equal to 300 mg/m² intravenous (IV) bolus or 400 mg/m² IV continuous infusion. The last dose of anthracycline must have been at least 12 months prior to study enrollment. Patients could have central nervous system (CNS) metastases only if they had completed cranial irradiation at least 3 months before study entry, were asymptomatic, and not taking corticosteroids for this condition. Inclusion criteria included: a Karnofsky performance status greater than or equal to 60%; no history of cardiac disease or clinical evidence of congestive heart failure (CHF), a left ventricle ejection fraction (LVEF) greater or equal to 50%; platelets greater than or equal to 100,000; a hemoglobin greater than or equal to 9 g/dl; an absolute neutrophil count greater than or equal to 1,500 cells/mm³; a creatinine less than or equal to 2.5 mg/dl; an aspartate aminotransferase, alanine transaminase, and alkaline phosphatase less than or equal to twice the upper limit of normal except if attributed to tumor; and a bilirubin within normal limits. Exclusion criteria included: any serious medical or psychiatric illness that might prevent informed consent or intensive treatment (e.g. serious infection), and a history of prior malignancies more than 5 years prior to study enrollment with the exception of curatively-treated basal cell or squamous carcinoma of the skin or carcinoma in situ of the cervix. Patients were expected to have a life expectancy of greater than 3 months. Patients gave written informed consent in accordance with the Declaration of Helsinki.

Treatment Schedule and Dose Adjustments

Patients received both D (30 mg/m²) IV and LD (30 mg/m²) IV on day 1, week 1. Participants received D (30 mg/m²) IV on day 8, week 2, and day 15, week 3. Chemotherapy was held on day 22, week 4. Patients were to receive antiemetics and other supportive treatment, i.e. colony-stimulating factors, at the discretion of the treating physician. Cycles were repeated every 28 days until one of the following took place: patients had received a cumulative anthracycline dose of 550 mg/m²; patients had disease progression on therapy; unacceptable toxicities (as determined by the physician) developed; clinical or laboratory adverse events occurred; LVEF fell to less than 45% or fell 20% from baseline; or participants did not comply with protocol requirements.

The National Cancer Institute (NCI) Common Toxicity Criteria were utilized for toxicity grading. If a patient developed prolonged grade 4 neutropenia or thrombocytopenia, treatment was withheld until both resolved to grade 1. Treatment could be resumed with a 25% reduction in doses for both drugs. If neutropenia persisted without significant thrombocytopenia, colony-stimulating factor could be given with the next course of therapy, without any dose modification. For patients exhibiting grade 3 or 4 PPE or stomatitis, treatment was held for 2 weeks or until the toxicity resolved to grade 0–1. The dose of LD was reduced by 25%. If there was no resolution after 2 weeks, LD was discontinued. If the total bilirubin rose to greater than 1.2 but less than or equal to 3.0 mg/dl, then the dose of LD was reduced by 25%. If the bilirubin increased to greater than 3 mg/dl and was unrelated to treatment with LD, the dose was reduced by 50%. If the elevation of bilirubin to greater than 3 mg/dl was thought to be secondary to LD, the patient was withdrawn from the study. For all other grade 3 or 4 non-hematologic events, a 25% reduction of the LD and D dose was recommended until the toxicity resolved to less than or equal to grade 2.

Baseline LVEF was performed on all patients prior to enrollment. After the patient received a cumulative anthracycline dose of greater than 350 mg/m², a MUGA or 2-d echo was obtained every 3 cycles. If during treatment the LVEF fell to less than 45% or fell 20% from the baseline level, LD was discontinued.

Treatment Evaluation

Initial evaluation included a thorough history, physical examination, hematology, and serum biochemistry tests, tumor markers (CEA, and CA27.29), computed tomography scans of the chest, abdomen, and pelvis, and bone scan. Radiologic assessment of response was performed every 2 cycles.

Statistical Analysis

This was a non-comparative phase II trial designed to examine the efficacy and toxicity of combination D and LD when utilized as first-line therapy in patients with MBC. TTP was the primary endpoint and was calculated from date on study to date of progression or death (any cause), whichever occurred first. A patient who was alive and progression-free at the end of study was censored. The planned sample size of 40 would provide 80% power to detect an increase of 60% in TTP from 5 to 8 months. The Kaplan-Meier method was used to plot the TTP curve and estimate the median TTP with a 95% confidence interval (CI). Secondary endpoints included: time to treatment failure (TTF), OS, ORR, duration of response, and toxicity. TTF was calculated from the date on study to date of disease progression, death (any cause), or toxicity, whichever occurred first. A patient who was alive and progression-free with no toxicity at the end of study was censored. The Kaplan-Meier method was used to estimate the median TTF with a 95% CI. OS was calculated from the date on study to date of death (any cause). A patient who was alive at the end of study was censored. The Kaplan-Meier method was used to estimate the median OS time with a 95% CI. ORR was defined as the proportion of patients with a CR or PR. A 95% CI was calculated for the response rate. The duration of response for any patient with either CR or PR was calculated from the first documentation of response to the date of disease progression or death (any cause), whichever occurred first. A patient who was alive and progression-free at the end of study was censored. The Kaplan-Meier method was used to plot the response duration curve and estimate the median response duration with a 95% CI. All calculations used SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Between December 2002 and September 2005, 12 women received treatment. The median age was 49 (range 31–60) years. Ten women had an ECOG performance status of 1, and 2 women had an ECOG performance status of 2. Nine (75%) participants had tumors that were estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+). Five (41.7%) women had malignancies that overexpressed her-2/neu. Information about tumor grade was available for 9 participants. Three women had grade III invasive ductal cancer, and 6 women had grade II invasive ductal cancer. At the time of enrollment, bone, lung, liver, skin, and lymph node metastases were reported in 58.3, 58.3, 41.7, 25, and 16.7% of the patients, respectively. Seven women had received prior adjuvant chemotherapy. Four participants had received anthracycline-based therapy. Seven women had received prior hormonal therapy. All women with hormone-positive disease had received hormonal therapy in the adjuvant setting. Six patients with metastatic hormonal responsive disease had received a median number of 2 lines of antihormonal therapy prior to inclusion into the trial, with a range of 1 to 2 lines of therapy (table 1).

Table 1. Patient characteristics

Median age, years (range)	49 (31–60)
Patients, n (%)	
Patients entered	12
ECOG performance status	
1	10 (83.3)
2	2 (16.7)
ER+/PR+/both	9 (75)
Her-2/neu-positive	5 (41.7)
Tumor grade ^a	
II	6 (50)
III	3 (25)
Site of metastasis	
Bone	7 (58.3)
Lung	7 (58.3)
Liver	5 (41.7)
Skin	3 (25)
Lymph nodes	2 (16.7)
Prior treatments	
Adjuvant chemotherapy	7 (58.3)
Anthracycline-based	4 (33.3)
Hormonal therapy	7 (58.3)

^aInformation available for 9 participants.
ER = Estrogen receptor; PR = progesterone receptor.

Treatment Administration

A total of 64.5 cycles of chemotherapy were administered, with a median number of 4 (range 1–12) cycles per patient. Toxicity caused a delay in treatment for 7 patients. Side effects led to dose reduction of LD by 25% in 5 patients. Toxicity led to dose reduction of D by 25% in 1 patient. Toxicity led to the removal of 4 participants from the protocol.

Efficacy

The median follow-up time for the 12 women was 14.7 (range 0.9–40.8) months. Eleven of 12 women were taken off study because of disease progression or toxicity. One woman was taken off study for administrative reasons. Out of the 11 women, 7 have died, 3 remain alive with disease, and 1 was lost to follow-up. The woman lost to follow-up was censored at date off treatment due to toxicity. The estimated median TTP was 9.6 months (95% CI 4.7–12.2) (fig. 1, table 2). The estimated median TTF was 6.5 months (95% CI 4.4–10.5) (fig. 2, table 2). The estimated median OS was 22.1 months (95% CI 9.6–40.8) (fig. 3, table 2). Eight (67%) participants (95% CI 51.6–94.5%) had a PR to chemotherapy, and 2 (16.7%) had stable disease. For the 8 women who had a PR to chemotherapy, the estimated median duration of response was 2.7 months (95% CI 2.4–10.5) (fig. 4). All patients with her-2/neu-positive metastatic disease went on to receive trastuzumab-based chemotherapy regimens.

Toxicity

Seven of 12 women were taken off study because of disease progression. One woman developed a grade 3 infection and

Table 2. Estimated medians and confidence intervals (95% CI) for outcomes (n = 12)

	Estimated median, months	95% CI
TTP	9.6	4.7–12.2
TTF	6.5	4.4–10.5
OS	22.1	9.6–40.8

TTP = Time to progression; TTF = time to treatment failure; OS = overall survival.

Table 3. Patient toxicity

	Toxicity, n (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	4 (33.3)	0	3 (25)	0
Anemia	9 (75)	0	0	0
Thrombocytopenia	4 (33.3)	0	0	0
Infection	1 (8.3)	0	3 (25)	0
Nausea	4 (33.3)	3 (25)	2 (16.7)	0
Emesis	3 (25)	2 (16.7)	1 (8.3)	0
Stomatitis	0	3 (25)	5 (41.7)	0
Dyspnea	0	0	1 (8.3)	1 (8.3)
Palmar-plantar erythrodygia	1 (8.3)	0	1 (8.3)	0
Pericardial effusion	0	0	1 (8.3)	0
Constipation	1 (8.3)	7 (58.3)	0	0
Diarrhea	0	1 (8.3)	0	0
Fatigue	5 (41.7)	6 (50)	0	0
Edema	1 (8.3)	1 (8.3)	0	0
Elevated liver function tests	0	1 (8.3)	0	0
Neuropathy	5 (41.7)	1 (8.3)	0	0
Myalgias	4 (33.3)	3 (25)	0	0
Hyperlacrimation	1 (8.3)	1 (8.3)	0	0
Hot flashes	1 (8.3)	1 (8.3)	0	0
Nail changes	2 (16.7)	1 (8.3)	0	0
Anorexia	2 (16.7)	2 (16.7)	0	0
Alopecia	1 (8.3)	1 (8.3)	0	0
Mucositis	1 (8.3)	2 (16.7)	0	0

grade 4 dyspnea after 1 cycle of chemotherapy. She was found to have gram-positive cocci septicemia and died. Three patients asked to be removed from the study because of side effects. Three women experienced grade 3 neutropenia. None of the participants developed neutropenic fever. Three women experienced a grade 3 infection. Non-hematologic grade 3 and 4 toxicities included grade 3 nausea (16.7%), grade 3 emesis (8.3%), grade 3 stomatitis (41.7), grade 3 and 4 dyspnea (16.7%), grade 3 PPE (8.3%), and grade 3 pericardial effusion (8.3%). No women developed signs and symptoms of CHF while on study (table 3).

Discussion

Side effects associated with the combination of D and doxorubicin include febrile neutropenia, nausea, and stomatitis. These toxicities are amenable to therapeutic intervention.

However, a commonly recognized adverse event that occurs in conjunction with anthracycline use is a reduction in LVEF and the development of CHF [9, 12, 13].

In a phase II trial conducted by Alexopoulos et al. [19], 44 patients received LD 30 mg/m² (day 1) and D 75 mg/m² (day 2) every 3 weeks. A small percentage (18.4) of patients developed grade 3–4 neutropenia. Neutropenia led to the removal of 1 patient from their cohort. These results are similar to results reported in our clinical trial. In the present study, 3 women experienced grade 3 non-febrile neutropenia, and neutropenia led to the reduction of the LD dose for 1 patient and the delay of chemotherapy for 2 patients. The frequency of grade 3 and 4 adverse events was higher in our phase II trial when compared to the trial conducted by Alexopoulos et al. [19]. The total dose of D given over 3 weeks in our trial was 90 mg/m², while the total dose of D given every 3 weeks in the Alexopoulos et al. [19] study was 75 mg/m². In fact, most phase II and phase III trials that have incorporated D into an anthracycline-based treatment regimen have done so at doses ranging from 60 to 75 mg/m². The higher doses of D given to our study cohort may have led to the development of more grade 3 and 4 adverse events. Surprisingly, the incidence of PPE in our trial and the Alexopoulos et al. [19] study was quite low. This result could be attributed to the smaller dose of LD 30 mg/m² utilized in both studies. As expected, no patient in the present study developed a reduction in her LVEF. The diminution of cardiac risk conferred by the use of LD has been substantiated in several other clinical trials [1, 19, 21].

Conclusions

Since this protocol was established, the use of taxanes in the adjuvant setting and the use of biologic agents in combination with chemotherapeutic agents in the adjuvant and metastatic settings have become standard of care. This may explain why there was a small number of patients recruited to participate in this trial. The combination of LD and D was highly active as a first-line treatment regimen in patients with MBC. The rate of grade 3 and 4 toxicity was unacceptably high. The combination may warrant further evaluation with prophylactic growth factors or altered dose schedules.

Supplemental Figures

Fig. 1. Kaplan-Meier progression-free survival curve.

Fig. 2. Kaplan-Meier failure-free survival curve.

Fig. 3. Kaplan-Meier overall survival curve.

Fig. 4. Kaplan-Meier response duration curve.

To access the figures please refer to www.karger.com/DOI/10.1159/000272119.

Conflict of Interest Statement

Dr. Amy Tiersten is on the speakers' bureau for Sanofi Aventis and has received honoraria from Aventis. The other authors have no conflicts of interest to disclose. Orthobiotech supplied research funding.

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