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## Clinical report

# Liposomal doxorubicin and weekly paclitaxel in the treatment of metastatic breast cancer

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**The combination of paclitaxel and doxorubicin or epirubicin is highly active against metastatic breast cancer, yet may produce congestive heart failure. Liposome-encapsulated doxorubicin is a new formulation of doxorubicin with no dose-limiting cardiac toxicity. Twenty-one patients with metastatic breast cancer were treated with pegylated liposomal doxorubicin (20 mg/m$^2$, day 1) and paclitaxel (100 mg/m$^2$, days 1 and 8) for six cycles every 2 weeks. All patients had had relapse or progression on one to five previous chemotherapies. We observed two patients with complete and eight patients with partial remissions (48% response rate). Eight of the 10 responders had had previous therapy with epirubicin, doxorubicin or mitoxantrone. The mean remission duration was 5 months. Disease progression due to brain metastasis occurred in five cases. Severe side effects (grade 3 WHO) were alopecia (100%), skin toxicity in 29%, neuropathy in 24% and mucositis in 13%. Leukopenia (grade 4 WHO) was observed in 48%, but there was no cardiac toxicity, no death and no hospitalization. The combination of weekly paclitaxel and liposomal doxorubicin every 2 weeks is highly effective in previously treated patients. Based on the doses we administered, we recommend 15 mg/m$^2$ liposomal doxorubicin every 2 weeks and 80 mg/m$^2$ paclitaxel weekly. [© 2000 Lippincott Williams & Wilkins.]**

*Key words*: Liposomal doxorubicin, metastatic breast cancer, paclitaxel.

## Introduction

The significant antitumor activity and the lack of significant clinical cross-resistance between paclitaxel and anthracyclines in the treatment of metastatic breast cancer has produced promising results in a number of studies, and the combination is one of the most effective therapies.[1–4]

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In most of these studies paclitaxel was administered over 3 h every 3 weeks. Interesting results were obtained with weekly administration of paclitaxel at a dose of 100 mg/m$^2$ in 1 h.[5] Mitoxantrone could be added biweekly.[6] Toxicities were not severe. Overall these studies involved a real increase in dose intensity.

There has been concern about the possibility of potentiating the cardiac toxicity of doxorubicin when used in combination with paclitaxel. Gianni *et al.*[2] reported a 21% incidence of congestive heart failure after a median cumulative dose of 420 mg/m$^2$ doxorubicin. Gehl *et al.* found an incidence of 20%.[1] The combination of paclitaxel and epirubicin has also produced congestive heart failure.[7] Sparano *et al.* tried to overcome these problems by combining the doxorubicin/paclitaxel regimen with the cardioprotective agent dexrazoxane[8] or by limiting the cumulative doxorubicin dose.[4]

The study presented here is a pilot study combining paclitaxel with pegylated liposomal doxorubicin (peg-lip-DOX). In contrast to free doxorubicin (free-DOX), liposomal doxorubicin shows no dose-limiting cardiotoxicity.[9,10] The liposome formulation prolongs circulation time and enhances tumor uptake of the drug.[11] Peg-lip-DOX employs encapsulation of doxorubicin into liposomes coated with polyethylene glycol (PEG). PEG helps to evade recognition and breakdown by the immune system, thus considerably prolonging the drug's half-life in the circulation (50–66 h).

In a phase I trial involving 56 cancer patients, the main dose-limiting toxicities associated with peg-lip-DOX were mucositis and plantar–palmar erythrodysesthesia.[12] Skin toxicity appeared to be cumulative and related to the interval between cycles, but was acceptable at doses of 50 mg/m$^2$ every 3 weeks or 60 mg/m$^2$ every 4 weeks. In a phase II study in refractory ovarian cancer, peg-lip-DOX was well tolerated at doses from 40 to 50 mg/m$^2$ every 3 weeks, with 13 from 35 patients (37%) experiencing

grade 3 or 4 non-hematological skin and mucosal toxicities, either hand–foot syndrome or stomatitis.[13] Nausea, hair loss, extravasation necrosis or decreases in ejection fraction did not occur. Phase II data from 60 patients suggest that peg-lip-DOX is also active in advanced breast cancer at a dose of 45–60 mg/m$^2$ every 3–4 weeks; 16% objective responses have been reported, and, notably, nausea, vomiting and alopecia were mild or absent.[14] Skin toxicity was the major cause of treatment delays. A regimen of 45 mg/m$^2$ every 4 weeks was well tolerated. Clinical experience with peg-lip-DOX has mainly been gained in the treatment of Kaposi's sarcoma (KS).[15–18] KS patients have been treated with doses ranging from 20 to 80 mg/m$^2$ every 2–4 weeks. This prompted us to select the dose of 20 mg/m$^2$ every 2 weeks as administered in AIDS patients.[15,16]

## Patients and methods

### Patient selection

Patients with histologically proven or evaluable metastatic breast cancer failing to respond to or relapsing after previous chemotherapy were eligible. Patients were also included if they had received prior therapy with taxoids and/or anthracyclines. It was an open phase I/II trial, which was performed in two centers. Entry was restricted to bidimensionally measurable or assessable disease by clinical examination, ultrasound sonography, X-ray or computed tomography. Patients had to satisfy the following criteria: WHO performance status 0–2, life expectancy of at least 2 months, no severe uncontrolled co-morbidities, no second malignancies and written informed consent. Adequate bone marrow function (platelet count $>100\,000/\mu$l, leukocyte count $>3\,000/\mu$l and hemoglobin level $>9$ g/dl), liver function (bilirubin $<2$ mg/dl), renal function (creatinine $<2$ mg/dl) and cardiac function (no arrhythmias, no AV block) were prerequisites.

### Treatment plan

Peg-lip-Dox (Caelyx®; Essex-Pharma/Schering Plough, Munich, Germany) was administered i.v. at a dose of 20 mg/m$^2$ in 5% dextrose over 30 min on day 1 followed by paclitaxel (Taxol®; Bristol-Myers Squibb, Munich, Germany) 100 mg/m$^2$ over 1 h on days 1 and 8. Chemotherapy cycles were repeated on day 15. The premedication given prior to peg-lip-DOX and paclitaxel was dexamethasone 16 mg i.v., cimetidine 300 mg or ranitidine 56 mg i.v., clemastine hydrogen fumarate 2 mg or dimetinden 4 mg i.v. and ondansetron 8 mg or tropisetron 5 mg i.v.

After three cycles (6 weeks) patients were examined again during a 2-week drug holiday and patients with progressive disease were switched to another chemotherapy regimen. Patients with response or no change received three additional courses. The treatment plan consisted of six cycles and lasted 14 weeks altogether (12 weeks of therapy and 2 weeks of rest). During this time patients were scheduled to receive 120 mg peg-lip-DOX/m$^2$ (8.6 mg/m$^2$/week) and 1200 mg paclitaxel/m$^2$ (86 mg/m$^2$/week).

Therapy was continued in the presence of a leukocyte count $>1500/\mu$l, platelets $>75\,000/\mu$l and no grade 3 or 4 toxicities except the hematological ones mentioned. Tumor response was assessed according to the WHO criteria[19] and toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

## Results

Twenty-one patients with previously treated metastatic breast cancer entered the trial. Patient characteristics are shown in Table 1. The mean number of previous chemotherapies therapies per patient was 2 (range 1–5), adjuvant therapies included. Fourteen patients (67%) had received prior anthracyclines (doxorubicin or epirubicin) or mitoxantrone.

**Table 1.** Patient characteristics

| | All patients ($n=21$) | Responders ($n=10$) |
|---|---|---|
| Median age (years) | 59 | 56 |
| range (years) | 44–74 | 51–74 |
| Median performance status | 1 | 1 |
| range | 0–1 | 0–2 |
| Dominant metastatic site | | |
| liver | 5 | 3 |
| lung/pleura | 5 | 3 |
| bone | 8 | 5 |
| skin/soft tissue | 7 | 4 |
| lymph nodes | 3 | 1 |
| Prior chemotherapy | | |
| CMF | 13 | 9 |
| epirubicin/cyclophosphamide | 6 | 4 |
| mitoxantrone | 4 | 3 |
| gemcitabine | 4 | 3 |
| vinorelbine | 4 | 2 |
| docetaxel | 3 | 1 |
| epirubicin/ifosfamide | 2 | 2 |
| doxorubicin/cyclophosphamide | 1 | 1 |
| epirubicin/fluorouracil/cyclo | 1 | 1 |
| high-dose fluorouracil | 1 | 1 |
| mitomycin | 1 | 0 |
| capecitabinum | 1 | 1 |
| trastuzumab | 1 | 1 |

### Response data

The overall response rate as assessed by physical, X-ray, computed tomography or ultrasound investigation was 48%. Complete responses (CR) occurred in two patients (9.5%) and partial responses (PR) in eight patients (38%). One patient had stable disease on therapy (5%) and 10 patients had progressive disease (52%). Disease progression during chemotherapy was due to brain metastasis in two of the 10 cases. The visceral metastases outside the brain responded in these cases.

The characteristics of the responders are shown in Table 1. Eight of the 10 patients with remission had had previous therapy with anthracyclines (doxorubicin/epirubicin) or mitoxantrone, but none of them had a documented disease progression during this kind of therapy. Remissions were seen at all kinds of metastatic sites. The mean duration of remission was 5 months, with intervals from 2 to 12 months. Disease progression or relapse was again due to brain metastasis in three cases.

A median survival time of greater than 12 months is achieved in responders, for eight of the 10 responders are still alive. The median survival time is greater than 10 months in all patients and it is 9 months in non-responders.

### Dose intensity

Twenty-one patients received a total of 238 weeks of chemotherapy. In comparison to the treatment plan (see Patients and methods), the average delivered dose of peg-lip-DOX and paclitaxel was 0.92 (7.9 mg/m$^2$/week) and 0.88 (76 mg/m$^2$/week), respectively. Nine patients completed six cycles of the combination in 12–16 weeks.

### Toxicity

Neutropenia was observed in all patients, with 13 (62%) experiencing grade 3 and 4 episodes (Table 2). Febrile neutropenia requiring i.v. antibiotics and/or hospitalization did not occur. No patient received prophylactic or therapeutic granulocyte colony stimulating factor. Severe thrombocytopenia or bleeding was not seen.

Three patients experienced grade 3 (no grade 4) mucositis (14%). Examination revealed painful superficial ulcerations in the oropharynx requiring analgesics, but parenteral nutrition was not necessary. The mucositis produced treatment delays ranging from 2 to 4 weeks.

Peripheral sensoral neuropathy was observed in eight patients (38%), grade 2 in three cases (14%) and grade 3 in five cases (24%), which necessitated reducing the dose or stopping paclitaxel. The neuropathy, manifested by numbness and paresthesias in a glove and stocking distribution, was slow to subside.

**Table 2.** Incidence of toxicities in 21 patients (worst grade)

| | Grade (WHO) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Neutropenia | 3 (14) | 2 (10) | 10 (48) | 3 (14) |
| Thrombocytopenia | 4 (19) | | | |
| Mucositis | 2 (10) | | 3 (14) | |
| Neurotoxicity | 2 (19) | 3 (14) | 5 (24) | |
| Skin | 2 (10) | 3 (14) | 6 (29) | |

Percentages in parentheses. Toxicity graded according to the NCI-CTC.

Palmar–plantar skin eruptions characterized by swelling, pain, erythema and desquamation of the skin of the hands, feet and other sites was observed in six patients (29%). All surface areas could be involved by an exanthem or rash, sometimes it was not symmetric. The reactions were reversible but severe and debilitating enough to require delaying treatment for 1–3 weeks. Peg-lip-DOX treatment was continued in all patients displaying signs of toxicity. The dose was reduced to 60% in 12 cycles in five patients.

Reversible alopecia was observed in all patients; nausea and vomiting were minimal. No cardiac event or congestive heart failure was recorded, no patient was hospitalized during chemotherapy and there were no treatment-related deaths.

One patient exhibited acute skin flushing and head and back pain 20 min after starting the first infusion of peg-lip-DOX. The symptoms vanished quickly and the drug was continued at a lower infusion rate after 1 h with no further events.

## Discussion

A weekly paclitaxel schedule provides a dose-dense treatment that might be of benefit to patients. The weekly schedule at doses of 100 mg/m$^2$ in 1 h described in this paper delivers more drug than the standard schedule and causes less bone marrow suppression.[5] Neurotoxicity was appreciable, however, with 38% of patients experiencing symptomatic grade 2 and 3 paresthesias, although we reduced the dose or discontinued paclitaxel (Table 2).

A look at combination versus single-agent therapy shows that combination therapy with paclitaxel and free doxorubicin (free-DOX) improves response rates, but this combination produces a significant risk (20%)

of cardiotoxicity.[1,2] The new formulation of doxorubicin in pegylated liposomes (peg-lip-DOX) shows quite different toxicities than free-DOX, notably a clear reduction in cardiac toxicity.[20] Accordingly, interest in combining peg-lip-DOX with paclitaxel prompted a phase I/II study.

The most important toxicity was related to the skin in the form of palmar–plantar erythrodysesthesia and/or macular rash (43%, grade 2 and 3). This skin toxicity developed frequently after more than two courses of treatment at a 20 mg/m$^2$ dose every 2 weeks, which is the recommended dose in KS.[15,16]

Pharmacokinetic studies have shown major interactions between paclitaxel administered before free-DOX; it results in slower elimination of the latter and a higher incidence of cardiac failure.[1,2] It might therefore be supposed that paclitaxel also prolongs the duration of peg-lip-DOX in the circulation, peg-lip-DOX has a long half-life of 50–65 h.

Despite the toxicities, the response rate (48%) in the heavily pretreated patient population was high. The disease severity in these patients is shown by the number of previous treatments (Table 1) and by the 24% patients experiencing disease progression due to brain metastases during chemotherapy or relapsing after chemotherapy while metastases in other visceral organs had responded. Therefore, in addition to the options for controlling the systemic disease outside the brain, there might be a need for cytotoxic drugs that pass the blood–brain barrier.

Considering the short therapy time of 14 weeks, the response rates are very similar to those obtained with a combination of free-DOX and paclitaxel in patients with no prior chemotherapy for metastases and no prior taxane or anthracycline therapy. Importantly, peg-lip-DOX seems to be an ideal anthracycline in patients at risk of congestive heart failure, i.e. patients with previous anthracycline therapy. Eighty percent of our responding patients had had prior epirubicin, doxorubicin or mitoxantrone. Based on the average doses of peg-lip-DOX (7.9 mg/m$^2$/week) and paclitaxel (81 mg/m$^2$/week) administered, we recommend a combination schedule consisting of peg-lip-DOX 15 mg/m$^2$ every 2 weeks and paclitaxel 80 mg/m$^2$ every week.

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