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ORIGINAL ARTICLE

# A phase IB dose-finding trial of liposomal doxorubicin in combination with capecitabine in patients with pretreated metastatic breast cancer

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**Abstract**
*Purpose* Anthracyclines and fluoropyrimidines are very active in breast cancer, while liposomal doxorubicin has low cardiotoxicity. We conducted a dose-finding study of the combination of liposomal doxorubicin and capecitabine in patients with pretreated metastatic breast cancer.
*Patients and methods* Patients received liposomal doxorubicin 60 mg/m$^2$ on day 1 plus capecitabine 825 mg/m$^2$ bid (level 0) or 1,000 mg/m$^2$ bid (level 1) on days 1–14 of each 21-day cycle to establish the maximum tolerated dose (MTD) and cardiac safety.
*Results* Nine patients were enrolled and a total of 52 courses were delivered (median 6 cycles per patient [range 4–7]). Grade 4 neutropenia occurred in 15% of cycles, with one episode of febrile neutropenia; most nonhematological toxicities were mild or moderate. No formal MTD was established, and the study was closed because two cardiac events were observed at dose level 1 and another at dose level 0 in patients pretreated with epirubicin $\geq$ 560 mg/m$^2$.
*Conclusions* The recommended dose for phase II studies is liposomal doxorubicin 60 mg/m$^2$ on day 1 plus capecitabine 825 mg/m$^2$/bid on days 1–14 of each 21-day cycle. Despite the lower cardiotoxicity of liposomal doxorubicin, the risk of cardiac damage persists in anthracycline-pretreated individuals and mandates close cardiac monitoring and careful evaluation of the overall cumulative dose.

**Keywords** Breast cancer · Cardiac toxicity · Capecitabine · Liposomal doxorubicin · Phase I dose-finding study

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## Introduction

Treatment of metastatic breast cancer is palliative, with multiple lines of therapy used in sequence. Although many patients receive anthracyclines in the adjuvant setting, re-challenge with an anthracycline-containing regimen is worthwhile in cases of disease relapse occurring more than 6 or 12 months after the end of adjuvant therapy [1]. Cardiotoxicity substantially limits the possibility of administering prolonged therapies with conventional anthracyclines [2].

Liposome-encapsulated doxorubicin (LD) has a longer half-life [3], lower peak plasmatic levels, and reduced distribution to normal tissues [4] than standard doxorubicin. Two phase III clinical trials demonstrated similar antitumor activity and reduced cardiotoxicity of LD compared with standard doxorubicin, both as a single agent [5] and in combination with cyclophosphamide [6] as first-line therapy in patients with advanced breast cancer.

Different triplets including conventional anthracyclines and capecitabine have been shown to be feasible and active in phase I–II clinical trials in breast cancer [7–11]. The

combination of LD with capecitabine seems appealing because of its potentially limited toxicity and the higher cumulative doses achievable. We performed a phase IB trial with this combination in patients pretreated for metastatic breast cancer to establish a recommended dose for phase II trials.

## Patients and methods

### Study population

Eligibility criteria included histologically proven metastatic breast carcinoma, pretreatment with at least one line of chemotherapy for metastatic disease, age $\geq$ 18 years, ECOG performance status >2, absolute neutrophil count (ANC) $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L, bilirubin $\leq$1.5 times the upper limits of normal (ULN), ALT $\leq$2.5 times the ULN, creatinine $\leq$1.5 times the ULN, left ventricular ejection fraction (LVEF) $\geq$ 50%, and life expectancy >12 weeks. Exclusion criteria included the presence of active brain metastases, a history of cardiac disease, and pretreatment with a cumulative dose of doxorubicin >300 mg/m$^2$ or of epirubicin >600 mg/m$^2$.

Patients were required to sign a written informed consent. The study was approved by the institutional Ethical Committee and was conducted in accordance with the principles of the Helsinki Declaration.

### Study design

This open-label dose-finding study was designed to assess the safety and maximum tolerated dose (MTD) of LD in combination with capecitabine in patients with pretreated metastatic breast cancer. Cohorts of three to six patients were required to be treated at up to two different dose levels of LD (60 and 75 mg/m$^2$) and three of capecitabine (825, 1,000, and 1,200 mg/m$^2$ bid), with determination of the MTD based on dose-limiting toxicity (DLT) observed during the first cycle of treatment. For each dose level, if none of the initial three patients developed DLT, the next cohort could start one dose level higher. If one of the initial three patients developed first course DLT, a maximum of three additional patients would then be entered at the same level. The highest dose level at which less than one-third of the patients experienced first course DLT would be defined as the MTD. This cohort would then be increased to six patients if only three patients had previously received that dose. Toxicity was graded according to the Common Toxicity Criteria (CTC) Version 2.0.

DLT was defined as any of the following first cycle events: (1) neutropenia grade 4 (ANC $<0.5 \times 10^9$/L) >5 days or febrile neutropenia (fever $\geq$ 38.5°C with an ANC $<1.0 \times 10^9$/L); (2) thrombocytopenia grade 4 ($<10.0 \times 10^9$/L), or grade 3 with bleeding requiring platelet transfusion; (3) nausea/vomiting grade $\geq$ 3, notwithstanding adequate medication; (4) any grade $\geq$ 3 nonhematological toxicity (excluding alopecia); and (5) failure to re-administer treatment within 14 days of the last expected day of administration due to delayed recovery from treatment-related toxicity.

Taking into account the potential cumulative cardiotoxicity and also the fact that the target population had been mainly pretreated with anthracyclines, we assessed the cardiac safety for each dose level, waiting until all patients had completed the entire treatment before proceeding to enroll subjects for the next dose level. Left ventricular systolic dysfunction, defined as a decrease in LVEF of $\geq$20 points from baseline or a decrease $\geq$10 points from baseline to a final value <50%, or clinically manifest congestive heart failure, were considered DLTs.

Antitumor activity was assessed, as a secondary endpoint, in terms of rate of objective response according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria [12].

### Study treatment

Patients received LD 60 mg/m$^2$ on day 1 plus capecitabine 825 mg/m$^2$ bid (level 0) or 1,000 mg/m$^2$ bid (level 1) on days 1–14 every 21 days. LD was administered by intravenous infusion over 1 h after premedication with dexamethasone plus a serotonin antagonist. Oral capecitabine was taken twice daily within half an hour after eating. Treatment was continued until disease progression or unacceptable toxicity or patient refusal or for a maximum of eight cycles.

### Dose modifications

Re-treatment required ANC $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L, hemoglobin >8.0 g/dL, and recovery from all toxicities to grade $\leq$ 1 (except alopecia).

Doses of both drugs were reduced by one level in the event of any hematological result fitting the definition of DLT (at whatever cycle of therapy); the dose of capecitabine was reduced by one dose level in the event of grade $\geq$3 diarrhea or hand-foot syndrome, and doses of both drugs were reduced by one dose level if any other grade $\geq$3 nonhematological toxicity (except alopecia) occurred.

### Patient evaluation

Baseline evaluation included medical history, physical examination, performance status, hematology and blood chemistry, ECG, echocardiography, CT scan of the chest

and abdomen, and bone scintigraphy in the event of bone pain or elevated serum calcium or alkaline phosphatase, with a CT or MRI study of uptake sites. Complete blood counts were repeated weekly. Toxicity evaluation, physical examination, hematology, and blood chemistry were repeated before each cycle. CT or MRI scans for tumor evaluation and echocardiography were performed every three cycles and at the end of treatment or whenever clinically indicated.

## Results

### Patient population

From March 2006 to May 2007 nine patients were enrolled in to the study (Table 1). Median age was 58 years (range 41–74); all had good performance status, but most had visceral involvement and two or more sites of metastatic disease. All had been pretreated with at least one line (range 1–3) of chemotherapy for metastatic disease and all but one had previously received anthracyclines.

### Treatment administration

Overall, a total of 52 courses of chemotherapy were delivered, with a median of six cycles per patient (range 4–7). Three patients were treated at dose level 0 for six courses without first-cycle DLTs, significant toxicities, or LVEF changes during subsequent cycles. Three patients were treated at dose level 1 without first-cycle DLTs, but two had cardiac DLTs after six and seven cycles. Dose escalation was therefore stopped, and another three patients were enrolled at dose level 0. Although there were no first-cycle DLTs, another case of delayed cardiotoxicity was registered.

### Treatment compliance

The dose of LD was reduced to 80% and then 60% for four cycles in one patient because of neutropenia, while capecitabine was decreased to 80% for one cycle in another patient because of persistent nausea. Capecitabine was also suspended in advance in one patient for two cycles because of neutropenia and nausea, and in a second patient because of insomnia. Treatment was delayed 1 week in 23 cases and 2 weeks in 5 cases due to hematological toxicity.

### Safety

Most nonhematological toxicities (Table 2) were mild or moderate, with only one case of grade 3 diarrhea. Among grade 1–2 side effects, alopecia was reported in seven patients (78%), nausea in 15 cycles (29%), vomiting in seven cycles (13%), and fatigue in 21 cycles (40%). Of the 52 cycles administered, there were eight episodes of grade 4 neutropenia (15%), with one case of febrile neutropenia, and 27 episodes of grade 3 neutropenia (52%). None of the patients received granulocyte colony-stimulating factors as prophylaxis.

**Table 1** Patient characteristics

| Variable | Patients ($n$ = 9) | |
|---|---|---|
| | No. | % |
| Median age in years (range) | 58 (41–74) | |
| Performance status (ECOG) | | |
| 0 | 8 | 89 |
| 1 | 1 | 11 |
| Menopausal status | | |
| Premenopausal | 0 | 0 |
| Postmenopausal | 9 | 100 |
| Histology | | |
| Invasive ductal carcinoma | 9 | 100 |
| Hormone receptors | | |
| Estrogen | | |
| Positive | 9 | 100 |
| Negative | 0 | 0 |
| Progesterone | | |
| Positive | 5 | 56 |
| Negative | 4 | 44 |
| Her2 status | | |
| Negative | 4 | 44 |
| Not evaluated | 5 | 56 |
| Prior chemotherapy for metastatic disease: | | |
| 1 line | 5 | 56 |
| 2 lines | 3 | 33 |
| 3 lines | 1 | 11 |
| With anthracyclines, without taxanes | 1 | 11 |
| With taxanes, without anthracyclines | 4 | 44 |
| With anthracyclines and taxanes | 4 | 44 |
| With fluoropyrimidines | 8 | 89 |
| Other | 2 | 22 |
| Prior adjuvant therapy | | |
| With anthracyclines | 3 | 33 |
| Without anthracyclines | 3 | 33 |
| Number of metastatic sites | | |
| 1 | 2 | 22 |
| 2 | 6 | 67 |
| >2 | 1 | 11 |
| Site of metastatic disease | | |
| Skin, lymph nodes, effusions | 5 | 56 |
| Bone | 5 | 56 |
| Visceral | 8 | 89 |

**Table 2** Toxicity according to the Common Toxicity Criteria Version 2.0

| | Grade | | | |
|---|---|---|---|---|
| | 1 *n* (%) | 2 *n* (%) | 3 *n* (%) | 4 *n* (%) |
| Dose level 0 (34 cycles) | | | | |
| Leucopenia | 9 (26) | 6 (18) | 8 (24) | 0 |
| Neutropenia | 4 (12) | 5 (15) | 13 (38) | 7 (1 febrile) (21) |
| Thrombocytopenia | 0 | 0 | 0 | 0 |
| Anemia | 18 (53) | 3 (9) | 0 | 0 |
| Nausea | 3 (9) | 6 (18) | 0 | 0 |
| Vomiting | 4 (12) | 3 (9) | 0 | 0 |
| Fatigue | 4 (12) | 8 (24) | 0 | 0 |
| Diarrhea | 3 (9) | 2 (6) | 1 (3) | 0 |
| Fever | 2 (6) | 0 | 0 | 0 |
| Dyspepsia | 0 | 1 (3) | 0 | 0 |
| Muscular pain | 0 | 1 (3) | 0 | 0 |
| Sore throat | 0 | 1 (3) | 0 | 0 |
| Insomnia | 0 | 4 (12) | 0 | 0 |
| Headache | 0 | 1 (3) | 0 | 0 |
| Hand-foot syndrome | 0 | 1 (3) | 0 | 0 |
| Alopecia[a] | 1 (17) | 4 (67) | 0 | 0 |
| Dose level 1 (18 cycles) | | | | |
| Leucopenia | 5 (28) | 7 (39) | 0 | 0 |
| Neutropenia | 4 (22) | 4 (22) | 6 (33) | 1 (6) |
| Thrombocytopenia | 0 | 0 | 0 | 0 |
| Anemia | 2 (11) | 0 | 0 | 0 |
| Nausea | 4 (22) | 2 (11) | 0 | 0 |
| Vomiting | 0 | 0 | 0 | 0 |
| Fatigue | 8 (44) | 1 (6) | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 |
| Fever | 0 | 0 | 0 | 0 |
| Dyspepsia | 0 | 0 | 0 | 0 |
| Muscular pain | 0 | 0 | 0 | 0 |
| Sore throat | 0 | 0 | 0 | 0 |
| Insomnia | 0 | 0 | 0 | 0 |
| Headache | 0 | 0 | 0 | 0 |
| Hand-foot syndrome | 0 | 0 | 0 | 0 |
| Alopecia[a] | 0 | 2 (67) | 0 | 0 |

[a] Percentages calculated on the number of patients

Cardiac function changes and cardiac adverse events are summarized in Table 3, together with cumulative doses of previous anthracyclines and LD. All three patients treated at dose level 1 had cardiac problems. The first, a 74-year-old woman not pretreated with anthracyclines, underwent echocardiography which showed a normal LVEF but an increase in the diastolic diameter of the left ventricle from 50 mm at baseline to 63 mm after 4 months. Treatment was suspended after five cycles. The second, a 58-year-old woman with hypertensive cardiopathy, pretreated with epirubicin 600 mg/m$^2$ plus radiotherapy of the left thoracic wall, showed a decrease in the LVEF (61 to 49%) after six cycles. The third, a 58-year-old woman with supraventricular arrhythmia, pretreated with epirubicin 600 mg/m$^2$, had a reduction in the LVEF (59 to 36%) after seven courses. Among the six patients treated at the lower dose level, a 49-year-old woman without significant comorbidities, pretreated with epirubicin 560 mg/m$^2$ and radiotherapy of the left breast, developed symptomatic heart failure after six cycles. A second patient, pretreated with 240 mg/m$^2$ of doxorubicin, had an asymptomatic decrease in LVEF (71 to 56%). Overall, three patients stopped therapy because of cardiac toxicity, and one developed congestive heart failure a few weeks after the end of treatment. No treatment-related deaths occurred.

### Antitumor activity

Two patients had a partial response and five had disease stabilization >6 months (range 7–13), while one patient showed stable disease of shorter duration and one had disease progression. Median progression-free survival was 7 months.

## Discussion

Although the combination of LD and capecitabine showed a modest acute toxicity profile and produced an encouraging clinical benefit rate in patients pretreated for metastatic breast cancer, cardiac toxicity was significant in individuals previously exposed to higher doses of anthracyclines.

Two large randomized clinical trials were carried out comparing LD with conventional doxorubicin in patients who had been pretreated with up to 300 mg/m$^2$ of doxorubicin [5, 6]. Results showed significant lower rates of cardiac-related events for the experimental arms than for the standard arms. In monotherapy, LD produced a cardiac event rate of 13 vs. 29% in the conventional doxorubicin arm, and the probability of a cardiac event on the basis of the lifetime cumulative dose was significantly higher with conventional doxorubicin than with LD [5]. The combination of LD and cyclophosphamide produced a cardiac event rate of 6%, significantly lower than the 21% reported in the arm receiving conventional doxorubicin and cyclophosphamide [6]. Moreover, the median cumulative doxorubicin dose at the onset of cardiac toxicity was >2,200 mg/m$^2$ in patients treated with LD plus cyclophosphamide vs. only 480 mg/m$^2$ for conventional doxorubicin plus cyclophosphamide. Taking into account the results from these two large trials, selection criteria for our study permitted pretreatment with a maximum cumulative dose of doxorubicin $\leq$ 300 mg/m$^2$ or epirubicin $\leq$ 600 mg/m$^2$. In

**Table 3** Cardiac toxicity

| Patient initials | Age (years) | Risk factors | Previous anthracycline | Previous cumulative dose (mg/m$^2$) | LD cumulative dose (mg/m$^2$) | Baseline LVEF (%) | Lower LVEF (%) | Cardiac toxicity (grade)[a] | DLT | Therapy stopped due to cardiac toxicity |
|---|---|---|---|---|---|---|---|---|---|---|
| M.I. | 58 | None | Doxo | 300 | 300 | 59 | 67 | 0 | No | No |
| B.P. | 53 | None | Doxo | 240 | 360 | 71 | 56 | 1 | No | No |
| C.A. | 73 | LBRT, hypert | Doxo | 240 | 360 | 78 | 65 | 0 | No | No |
| D.P.E. | 74 | Obesity | None | – | 300 | 57 | 61 | 0 | No | Yes[b] |
| R.L. | 58 | hypert, LPMRT | Epi | 600 | 360 | 61 | 49 | 2 | Yes | Yes |
| B.C. | 58 | None | Epi | 600 | 420 | 59 | 36 | 3 | Yes | Yes |
| T.R. | 41 | LBRT, med. RT | Epi | 360 | 360 | 62 | 55 | 0 | No | No |
| A.A. | 50 | None | Epi | 360 | 360 | 70 | 70 | 0 | No | No |
| N.L. | 49 | LBRT | Epi | 560 | 360 | 51 | 35 | 3 | Yes | No |

*LVEF* left ventricular ejection fraction, *DLT* dose-limiting toxicity, *LBRT* left breast radiotherapy (after conservative surgery), *hypert* arterial hypertension, *LPMRT* left post-mastectomy radiotherapy, *med. RT* mediastinal radiotherapy, *Doxo* doxorubicin, *Epi* epirubicin, *LD* liposomal doxorubicin

[a] According to the Common Toxicity Criteria Version 2.0 (CTC)

[b] The echocardiography showed an increase in the diastolic diameter of the left ventricle

our study, grade 3 cardiotoxicity developed in two patients at cumulative anthracycline doses of 1,020 and 920 mg/m$^2$, well below the median cumulative dose for a cardiac event reported in the study by Batist et al. [6], but comparable with that observed in the study by Harris et al. [5]. It must, however, be pointed out that patients in the latter study were pretreated with conventional doxorubicin and not with epirubicin, which should, in theory, allow an even higher cumulative dose to be administered safely. Although a capecitabine-induced cardiac ischemic insult could hypothetically contribute to worsening the cardiac damage caused by anthracyclines, this has never been proven, and cardiac failure has only anecdotically been reported with capecitabine [13]. On the other hand, the risk of developing epirubicin-related cardiotoxicity was recently assessed in relation to the competing risks of death from breast cancer and from other causes, leading to a recommendation of lower lifetime cumulative doses than those previously assumed as safe [14]. Apart from cardiac toxicity and alopecia, tolerability in our study was quite good, and the regimen produced an encouraging clinical benefit rate.

Our study was closed because of two delayed cardiac DLTs at dose level 1 and before a formal MTD was identified. Although dose level 0 had the same dosage of LD as level 1, we proceeded by expanding the starting level cohort because we could not rule out the possibility that the combination of the two drugs, at higher doses of capecitabine, would increase the risk of cardiotoxicity with respect to what could be expected from LD alone. We were not interested in further escalating the doses of capecitabine, which has not proven to result in superior delivered dose intensity [8].

The recommended dose for phase II studies is LD 60 mg/m$^2$ on day 1 plus capecitabine 825 mg/m$^2$ bid on days 1–14 of each 21-day cycle. However, the potential for cardiac toxicity casts some doubts about the clinical value of this combination in advanced breast cancer patients heavily pretreated with anthracyclines. In these individuals, despite the relatively lower cardiac toxicity of LD, a real risk of decline in cardiac function remains. We therefore recommend careful selection of patients to be submitted to this treatment, with evaluation of the total (conventional ± liposomal) anthracycline cumulative dose administered and close cardiac monitoring. These same measures would likely be appropriate when LD is used either in combination or as monotherapy.

The risk of cardiac toxicity suggests the potential advantage of using LD with respect to conventional anthracyclines, or of adding a cardioprotector, from the very first lines of treatment, i.e., in adjuvant and neoadjuvant settings. This would be more feasible if predictors of response, such as topoisomerase II, were to prove useful in selecting patients who could benefit from these drugs. A more rational use of anthracyclines could also be achieved by identifying reliable markers of early cardiac damage [2].

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