Pegylated liposomal doxorubicin and gemcitabine in the front-line treatment of recurrent/metastatic breast cancer: a multicentre phase II study

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This multicentre phase II study was aimed at investigating the activity and safety of pegylated liposomal doxorubicin (PLD) and gemcitabine (GEM) as front-line therapy in a large series of chemotherapy-naïve recurrent/metastatic breast cancer patients. From June 2003 to December 2006, a total of 71 recurrent/metastatic breast cancer patients were enrolled. Median age was 63 years (range = 37–79), and 31 patients (43.7%) were ≥65 years old. Patients received PLD, 25 mg m⁻², day 1, followed by GEM, 800 mg m⁻², days 1 and 8, q21. Response was evaluable in 64 cases. Eight complete (12.5%) and 17 partial responses (26.6%) were registered, with an overall response rate of 39.1%. Thirty patients (46.9%) experienced stable disease, with an overall clinical benefit of 85.9%. Median time to progression (TTP) was 11 months, whereas median overall survival (OS) was not reached. The rate of 1- and 2-year OS was 79 and 61%, respectively. A total of 443 courses were evaluable for toxicity: grade 3 and 4 neutropaenia affected 14 patients (20.3%) and 3 patients (4.3%), respectively. Grade 3 and 4 palmar-plantar erythrodysesthesia syndrome was documented in five cases (7.2%) and one case (1.4%), whereas grade 3 and 4 mucositis occurred in six cases (8.7%) and two cases (2.9%), respectively. Grade 2 cardiac toxicity was observed in only one case. Interestingly enough, there was no difference in the percentage and severity of either haematological or non-haematological toxicity according to the age of the patients (<65 vs ≥65 years). We confirmed in a large, very homogenous study sample of chemotherapy-naïve recurrent/metastatic breast cancer patients the efficacy and safety of PLD/GEM combination, providing response rates, median TTP and OS values comparable with those achieved with more toxic combinations.

Keywords: metastatic breast cancer; pegylated liposomal doxorubicin; gemcitabine

Breast carcinoma is the most frequent cancer in women (Jemal et al., 2007). Approximately 27% of patients are initially diagnosed with already metastatic disease, and almost 30% of lymph node-negative and up to 60–70% of lymph node-positive cases will develop recurrent disease within 5 years from initial diagnosis (Paridaens, 2000; Jemal et al., 2007) In this clinical setting, the prognosis is unfavourable, with a median overall survival (OS) of 1.5–2 years (Cardoso et al., 2002). Therefore, special attention has to be paid to the issue of quality of life preservation, as prolongation of survival and palliation of symptoms remain the only realistic objectives.

Among the drugs or drug combinations currently proposed for recurrent/metastatic breast cancer, anthracyclines and taxanes are considered the most effective ones, with rates of overall response between 46 and 88% (Mavroudis et al., 2000; Morales et al., 2004; Gamucci et al., 2007; Von Minckwitz, 2007); however, the use of anthracyclines in clinical practice is limited by drug-associated toxicity, particularly myelosuppression and cardiotoxicity (Robert et al., 2004). Indeed, the replacement of doxorubicin with epirubicin or pegylated liposomal doxorubicin (PLD) has strongly improved the pattern and severity of adverse effects (Robert et al., 2004; O’Brien, 2008); moreover, the proper use of growth factor support (Morales et al., 2004) or the adoption of weekly schedules for combinations of anthracyclines/taxanes (Gamucci et al., 2007) has been proposed to overcome haematological toxicity.

Besides PLD, whose activity as a single agent in recurrent/metastatic breast cancer has been documented in several phase II studies (response rate = 31–38%) (Ranson et al., 1997; Lyass et al,
Exclusion criteria were as follows: previous or concurrent malignancies at other sites with the exception of basal or squamous cell carcinoma of the skin and cone biopsed carcinoma in situ of the uterine cervix; Brenner's and borderline ovarian tumours; symptomatic CNS metastases; and uncontrolled severe infection and/or medical problems unrelated to malignancy that would limit full compliance with the study or expose the patient to extreme risk. Additional exclusion criteria were as follows: previous chemotherapy with PLD or GEM, and administration of other investigational cytotoxic drugs within 30 days before entry into the study.

Treatment plan

Within 14 days from the beginning of the study treatment, patients were submitted to a complete clinical evaluation including medical history, laboratory tests with complete blood cell count, and serum chemistry, Ca 15-3 level, and urinalysis. Bone scintigraphy, CT scan, and chest X-rays were also performed. Then, PLD, 25 mg m\(^{-2}\), diluted in 250 ml of 5% dextrose, was administered on day 1 by a 60 min i.v. infusion, followed by GEM, 800 mg m\(^{-2}\), diluted in 250 ml of 0.9% saline solution, on days 1 and 8 by a 30 min i.v. infusion; cycles were repeated every 21 days, until progression of disease, unacceptable toxicity, patients’ refusal, or at physician’s discretion. All patients received dexamethasone (8 mg) and ranitidine (50 mg) before drug administration.

Response and toxicity assessment

The evaluation of response was performed every three cycles by the same clinical and imaging approach used for the baseline assessment. Clinical response was assessed according to the RECIST criteria (Therasse et al., 2000). Response rates were calculated, including 95% confidence intervals (95% CI). Clinical benefit was defined as the overall number of complete responses, partial responses, and stabilisation of disease. Patients who received at least two cycles of combination treatment were evaluable for efficacy, and patients who received at least one dose of chemotherapy were evaluable for toxicity.

Chemotherapy-induced toxicity was graded according to the common toxicity criteria of National Cancer Institute (1999). Complete blood count and PLT count were performed on a weekly basis; ECG was performed at every cycle, whereas echocardiography was performed every 2 cycles and at the end of the treatment. A multigated angiogram was planned if the echocardiography registered an LVEF reduction >10% (D’Agostino et al., 2003). A 25% dose reduction of both drugs was planned in the case of ANC <500 \(\mu l^{-1}\) and/or PLT count <25 000 \(\mu l^{-1}\) on the day of planned drug administration. A 25% dose reduction of PLD was also planned in the case of grade 1 or 2 palmar-plantar erythrodysaesthesia syndrome (PPE) or mucositis persisting for >2 weeks. In the case of ANC <1500 \(\mu l^{-1}\) and/or PLT count <100 000 \(\mu l^{-1}\) on the day of planned therapy, 1 week delay of drug administration was planned without dose adjustment. Gemcitabine administration on day 8 was omitted in the case of G4 neutropaenia, febrile neutropaenia, G3/G4 thrombocytopenia or anaemia, or G3/G4 non-haematological toxicity (excluding alopecia or nausea/vomiting).

To reliably assess the safety of PLD/GEM combination, the prophylactic use of growth factors was not allowed, and granulocyte-colony stimulating factor (G-CSF) and/or epoetin were administered in the therapeutic setting only in the case of febrile neutropaenia or grade 3–4 neutropaenia lasting >5 days, haemoglobin levels <10 g% (Rizzo et al., 2002), or at the physician’s discretion. Pyridoxine was not used as a prophylactic strategy to prevent PPE.
Criteria for treatment discontinuation

In patients who had to delay treatment for >2 weeks, treatment was discontinued. Treatment was also discontinued in the case of severe hypersensitivity reaction, grade 3 or 4 PPE or mucositis persisting for >2 weeks, reduction of LVEF >20% from baseline value, in the case of symptomatic congestive heart failure, or in any case of >G3 non-haematological toxicity (with the exception of alopecia or nausea/vomiting). Treatment was also discontinued in the case of patient’s refusal.

Statistical analysis

The sample size was calculated on the basis of the two-stage design by Simon (1989). The design tested the null hypothesis that the true response rate for this population would improve by approximately 40%, that is, from 30% to the clinically relevant alternative of 50%, using an α error of 0.05 and a β error of 0.1.

Thus, the first step will include 24 patients; if ≥8 responses are recorded, the study would enrol additional 39 patients up to a total of 63 patients. The regimen would be considered active if ≥24 responses are recorded. Considering a dropout rate of approximately 10%, at least 70 patients were planned to be enrolled.

RESULTS

Patient characteristics

From June 2003 to December 2006, a total of 71 recurrent/metastatic breast cancer patients were enrolled into this phase II multicentre clinical trial.

Patient characteristics at study entry are given in Table 1. Median age was 63 years (range = 37 – 79), and 31 patients (43.7%) were ≥65 years old.

Forty-one (57.7%) patients had been treated with adjuvant radiotherapy, 41 patients had received adjuvant hormone therapy, and 49 (69.0%) had been administered neoadjuvant/adjuvant chemotherapy: overall, at the time of study entry, 29 (40.8%) had already been treated with anthracycline-containing regimens. The vast majority of cases (n = 62, 87.3%) had visceral localisation of recurrent/metastatic disease, including 6 cases of liver metastasis, 7 cases of lung metastasis, and 49 cases with multiple sites of disease. The expression of ER, PR, and erbB2/neu was available in 67 cases: ER or PR positivity was documented in 43 (64.2%) and 37 (55.2%) cases, respectively, whereas 35 patients (52.2%) had erbB2/neu-overexpressing (2+/3+ score) tumours (see Table 1).

Response to treatment and clinical outcome

Evaluation of response according to the intent-to-treat analysis and assessable population is summarised in Table 2. Seven patients were not considered evaluable for response due to early discontinuation.

Table 1: Patient characteristics at study entry

| Characteristics | No. (%) |
|-----------------|---------|
| Patients enrolled | 71 |
| Age (years) (median (range)) | 63 (37–79) |
| ECOG performance status 0/1/2 | 53/16/2 |
| Site of recurrence | |
| Liver | 6 (8.4%) |
| Lung | 7 (9.8%) |
| Mixed | 49 (69.0%) |
| Bone | 5 (7.0%) |
| Axilla | 4 (5.6%) |
| Previous treatment | |
| Adjuvant RT | 41 (57.7%) |
| Adjuvant HT | 41 (57.7%) |
| Adjuvant/neoadjuvant CT | 49 (69.0%) |
| Anthracycline-based CT | 29 (40.8%) |
| ER status (by immunohistochemistry) | |
| Positive | 44 (61.9%) |
| Unknown | 4 (5.6%) |
| PR status (by immunohistochemistry) | |
| Positive | 37 (52.1%) |
| Unknown | 4 (5.6%) |
| ErbB2/neu status (by immunohistochemistry) | |
| Negative or 1+ | 32 (45.1%) |
| 2+ | 14 (19.7%) |
| 3+ | 21 (29.6) |
| Unknown | 4 (5.6%) |
| ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy; HT = hormone therapy; CT = chemotherapy. a Ten out of 14 erbB2/neu 2+ cases showed DNA amplification at FISH. |

Table 2: Clinical response in the overall series

| Intention to treat (n=71) | Assessable (n=64) |
|--------------------------|------------------|
| No. | % (95% CI) | No. | % (95% CI) |
| Complete (CR) | 8 | 11.3 (4.1, 18.5) | 8 | 12.5 (4.4, 20.6) |
| Partial (PR) | 17 | 23.9 (14.0, 33.8) | 17 | 26.6 (15.7, 37.3) |
| Overall response | 25 | 35.2 (2.4, 46.3) | 25 | 39.1 (27.1, 50.9) |
| Stable disease (SD) | 30 | 42.2 (30.9, 53.5) | 30 | 46.9 (34.7, 59.1) |
| Progression (PD) | 9 | 12.7 (5.1, 20.3) | 9 | 14.1 (5.6, 22.6) |
| Not available | 7 | 9.9 — — | — | — |
| Clinical benefit (CR, PR, SD) | 55 | 77.5 (67.8, 87.2) | 55 | 85.9 (77.4, 94.4) |
| Time to response (months) (median (range)) | 3.0 (2.0–7.0) | 3.0 (2.0–7.0) |
| Duration of response (months) (median (range)) | 4.7 (2.0–8.0) | 4.7 (2.0–8.0) |
| Duration of SD (months) (median (range)) | 2.5 (1.5–5.2) | 2.5 (1.5–5.2) |
| Duration of clinical benefit (months) (median (range)) | 4 (2–11) | 4 (2–11) |
progression ($n = 2$), death from non-cancer-related causes ($n = 2$), severe allergic reaction during the first administration of PLD ($n = 2$), and patient refusal ($n = 1$). Therefore, at the time of analysis, response was evaluable in 64 cases: 8 complete responses (12.5%) and 17 partial responses (26.6%) have been registered, with an overall response rate of 39.1%. The median duration of response was 4.7 months (range = 2.0 – 8.0), and among the responders, 6 had response lasting more than 6 months. Thirty patients (46.9%) experienced stabilisation of disease, with a rate of overall clinical benefit (complete responses, partial responses, and stabilisation of disease) of 85.9%. The median duration of stable disease and clinical benefit was 2.5 months (range = 1.5 – 5.2) and 4 months (range = 2 – 11), respectively.

The proportion of responders according to the site (visceral vs not visceral localisation) of disease was not statistically significant (60.0% vs 75.0%, $P$-value = 0.6). In addition, there was no difference in the rate of overall response in patients who had already been treated with anthracyclines vs anthracyline patients (38.5% vs 42.4%, $P$-value = 0.7).

The percentage of cases achieving complete or partial response to treatment was significantly higher in cases showing immunohistochemically assessed overexpression of erbB2/neu than in cases that do not express or express $1 +$ erbB2/neu (51.4% vs 24.1%, $P$-value = 0.039). On the other hand, no difference in the response rate according to ER and PR status was documented (data not shown).

Follow-up data were available for all patients. As of November 2007, median follow-up duration was 15 months (range = 1 – 44). During the follow-up period, progression and death of disease were observed in 35 and 23 cases, respectively. Median TTP was 11 months, whereas the median OS was not reached (Figure 1). The rate of 1- and 2-year OS was 79 and 61%, respectively.

**Toxicity**

A total of 443 courses were evaluable for toxicity, with a median number of 6 cycles (range = 1 – 17) administered per patient (Table 3); 17 patients (24.6%) received >8 cycles of treatment.

The data on toxicity were available in 69 patients, as in 2 cases chemotherapy administration had to be discontinued early owing to the occurrence of severe allergic reaction to PLD during the administration of the first treatment course. In particular, both patients experienced sudden occurrence of cutaneous erythema (face and hands), arterial hypertension, dyspnea, and tachycardia after a few minutes since the beginning of PLD; the infusion was stopped and the patients were treated with steroids and H2-antihistamines with the regression of the described symptoms. Both patients refused to continue the treatment.

The median cumulative dose of PLD per patient was 227 mg $m^{-2}$ (range = 36 – 630 mg $m^{-2}$), whereas the median cumulative dose of GEM per patient was 13 600 mg $m^{-2}$ (range = 1200 – 36 800 mg $m^{-2}$) (Table 3). The delivered dose of PLD and GEM was 94 and 85% of the projected dose, respectively.

In 10 patients (14.5%), dose reduction was required, mostly because of haematological toxicity; 1 week delay was necessary in 10 patients (14.5%). There were six patients discontinuing treatment because of chemotherapy toxicity, including five cases of grade 3 PPE and one case of grade 2 cardiotoxicity.

As far as haematological toxicity is concerned (Table 4), myelosuppression was usually brief and manageable with dose adjustments or treatment delay. Grade 3 and 4 neutropenia affected 14 (20.3%) and 3 (4.3%) patients; only 1 (1.4%) case of febrile neutropenia was registered. Eight (11.6%) required administration of G-CSF.

Grade 3 anaemia and grade 3 thrombocytopenia were documented in only three cases (4.3%) and one case (1.4%), respectively. Recombinant human erythropoietin (rHu-Epo) was administered to six patients (8.7%) As far as non-haematological toxicity is concerned, grade 3 asthenia was registered in only four patients (5.8%) and nausea/vomiting (grade 3) occurred in one patient.

Hepatotoxicity was infrequent and mild (grade 1 or 2 = 10.1%). Moderate and severe PPE was documented in five cases (7.2%) and 1 case (1.4%), respectively, whereas grade 3 and 4 mucositis occurred in six cases (8.7%) and two cases (2.9%), respectively. Complete alopecia was documented in only one case.

Although our series included 29 cases (40.8%) who had been previously treated with anthracyclines and 13 cases who were >65 years old and had received previous radiotherapy to the chest, grade 2 cardiac toxicity was observed in only one case: in particular, this patient was 70 years old and had already received radiation to the left chest wall and previous treatment with anthracyclines. A reduction of 20% of LVEF from baseline value was registered after three cycles of PLD treatment (cumulative PLD

![Figure 1](image)

**Figure 1** Time to progression and OS curves in the whole population.

| Table 3 | Study drug administration details |
|---------|----------------------------------|
| Total cycles administered | 443 |
| Number of cycles per patient (median (range)) | 6 (1 – 17) |
| Cumulative PLD dose (mg $m^{-2}$) (median (range)) | 227 (36 – 630) |
| Cumulative GEM dose (mg $m^{-2}$) (median (range)) | 13 600 (1200 – 36 800) |
| Patients with dose reduction (no. (%) | 10 (14.5%) |
| Patients with treatment delay (no. (%) | 10 (14.5%) |
| Patients discontinuing treatment owing to toxicity (no. (%)) | 6 (8.7%) |

GEM = gemcitabine; PLD = pegylated liposomal doxorubicin.

| Table 4 | Overall toxicity (per patient) ($n = 69$) |
|---------|----------------------------------------|
| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Leukopenia | 4 | 5.8 | 16 | 23.2 | 12 | 17.4 | 1 | 1.4 |
| Neutropenia | 5 | 7.2 | 19 | 27.5 | 14 | 20.3 | 3 | 4.3 |
| Anaemia | 17 | 24.6 | 10 | 14.5 | 3 | 4.3 | 0 | — |
| Thrombocytopenia | 5 | 7.2 | 4 | 5.8 | 1 | 1.4 | 0 | — |
| Fatigue | 12 | 17.4 | 9 | 13.0 | 4 | 5.8 | 0 | — |
| Nausea/vomiting | 12 | 17.4 | 8 | 11.6 | 1 | 1.4 | 0 | — |
| Liver | 4 | 5.8 | 3 | 4.3 | 0 | — | 0 | — |
| PPE | 4 | 5.8 | 8 | 11.6 | 5 | 7.2 | 1 | 1.4 |
| Mucositis | 6 | 8.7 | 11 | 15.9 | 6 | 8.7 | 2 | 2.9 |

PPE = palmar-plantar erythrodysesthesia syndrome.
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Blackstein M, Vogel CL, Ambinder R, Cowan J, Iglesias J, Melemed A (2002) non-haematological toxicity according to the age of the patients in the percentage and severity of either haematological or of patient’s refusal. Interestingly enough, there was no difference in the haematological toxicity nor in the non-haematological toxicity in patients aged ≥ 65 years compared with younger ones: this is a very relevant clinical issue considering that no standard chemotherapy has been established for elderly patients with recurrent/metastatic breast cancer, and efforts are constantly made to maintain the drug combination approach (Cianfrocca and Gradishar, 2007), but not at the expense of safety.

Finally, also alopecia, a treatment-related side effect hardly tolerable in patients also required to cope with the distress of disease relapse, has been reported as complete in only one case, and this is expected to contribute to preserve patient’s quality of life, as shown by Fabi et al (2006).

In conclusion, we showed that PLD/GEM combination is active in recurrent/metastatic breast cancer patients, providing response rates, and above all median TTP and OS values comparable with those achieved with more toxic combinations (Von Minckwitz, 2007). In particular, the very low incidence of cardiac toxicity even in older patients already irradiated and treated with anthracyclines allows one to propose to a larger subset of patients a re-challenge with this class of agents, which remain the most active drugs in the management of this disease.

Finally, the possibility to take advantage of the assessment of erbB2/neu and topoisomerase IIa expression to select the patients most likely to benefit from PLD/GEM combination, and possibly from the addition of trastuzumab in erbB2/neu-positive cases, emphasises the need to administer chemotherapy on a patient by patient basis, an issue that becomes clinically crucial in the subset of salvage treatment.

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