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Myotax: A phase II trial of docetaxel plus non-pegylated liposomal doxorubicin as first-line therapy of metastatic breast cancer previously treated with adjuvant anthracyclines

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ABSTRACT

Aim: Non-pegylated liposomal doxorubicin (NPLD) has demonstrated equivalent antitumour activity to conventional doxorubicin and a significantly lower risk of cardiotoxicity when given as a single agent or in combination with cyclophosphamide. This phase II trial was performed to evaluate the efficacy and the safety of NPLD and docetaxel combination in patients with metastatic breast cancer previously exposed to adjuvant anthracyclines.

Patients and methods: Thirty-four patients received NPLD 60 mg/m^2 and docetaxel 75 mg/m^2 in a 21-day cycle as first-line therapy of metastatic breast cancer. Treatment was planned for six cycles and was continued until progression or toxicity.

Results: Objective response rate among response-assessable patients was 79% (95% CI (confidence interval), 64–94%) and 27% (95% CI, 11–43%) presented a complete response. Median progression free survival was 11.3 months (95% CI, 6.2–13.3 months) and median overall survival was 28.2 months (95% CI, 16–36.4 months). Symptomatic grade 3 cardiotoxicity occurred in 15% of cases and febrile neutropenia in 47% of the patients.

Conclusions: The combination of NPLD and docetaxel demonstrated high antitumour activity in a population of metastatic breast cancer patients exposed to adjuvant anthracyclines and showed an unexpected and unexplained 15% symptomatic left ventricular systolic dysfunction rate.

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1. Introduction

More than one million women worldwide are diagnosed with breast cancer every year.[1] Approximately 15–20% of patients treated for an early breast cancer develop metastatic disease. An increasing proportion of patients with metastatic disease have been exposed to prior adjuvant anthracyclines and/or taxanes chemotherapies. Anthracycline-containing and taxanes-containing polychemotherapy regimens have demonstrated significant improvement in disease-free survival and overall survival in the adjuvant setting.[2,3]

Anthracyclines and taxanes still remain among the most active cytotoxic drugs for metastatic breast cancer treatment.[4,5] Meta-analyses have demonstrated the superiority of anthracyclines and/or taxanes based polychemotherapies on monotherapies.[6–8] Combination regimens involving anthracyclines and taxanes are valid treatment options for patients with metastatic breast cancer, providing overall response rates ranging from 47 to 77%[9–16] and a significantly longer time to progression ranged between 6 and 10.3 months compared to other polychemotherapies. In patients pretreated at the adjuvant setting, evidence is lacking about rechallenging with anthracyclines and/or taxanes.

A prolonged use of anthracyclines is limited by cumulative, dose-related cardiotoxicity, especially in metastatic patients who have been pretreated with anthracyclines in the adjuvant setting.[17] Non-pegylated liposomal doxorubicin (NPLD) (Myocet®) results from the encapsulation of doxorubicin within a macromolecular vector, the liposome. Compared to doxorubicin, non-pegylated liposomal doxorubicin provides similar antitumour efficacy and significantly reduced cardiotoxicity, which leads to an improvement of the therapeutic index of doxorubicin.[18–21]

The rationale of the study is based on the following points: I – anthracyclines and taxanes are among the most effective cytotoxic drugs in metastatic breast cancer; II – polychemotherapies containing anthracyclines have demonstrated their superiority on anthracyclines monotherapies; III – combination regimens with doxorubicin and docetaxel are effective and usually well tolerated; IV – NPLD reduces cardiotoxicity; V – in patients treated in adjuvant (or neoadjuvant) setting with anthracyclines and/or taxanes, benefit induced by rechallenging with anthracyclines and/or taxanes is unclear.

This phase II trial, named Myotax, was designed to evaluate the efficacy and safety of the combination of NPLD and docetaxel as front line therapy for patients with locally advanced breast cancer or metastatic breast cancer pretreated in the adjuvant setting.

2. Patients and methods

2.1. Study design

It is a phase II multicentre, single-arm study aimed to assess the objective response rate of NPLD and docetaxel as first line treatment for locally advanced breast cancer or metastatic breast cancer.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice and the *Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Marseille*.

2.2. Eligibility

Women of age $\geqslant$18 years with histologically proven metastatic breast cancer or locally advanced breast cancer who had received adjuvant or neoadjuvant regimen with anthracyclines and/or taxanes more than 12 months before the diagnosis of locally advanced or metastatic cancer were eligible. The patients could have received a maximum cumulative anthracycline dose of 360 mg/m^2 (doxorubicin) or 600 mg/m^2 (epirubicin) in the adjuvant setting. Measurable or evaluable disease was required. Choice of chemotherapy over endocrine therapy was left to the investigator. Hormone and HER2 status were assessed locally by immunohistochemistry and/or fluorescence *in situ* hybridisation (HER2). Other eligibility criteria included a performance status of 2 or less, left ventricular ejection fraction (LVEF) $\geqslant$ 50% and adequate haematologic, renal and hepatic functions. Written, informed consent was required prior to the enrolment.

Patients with a previous chemotherapy for metastatic breast cancer or with an HER2 positive breast cancer were not eligible. Prior endocrine therapy in the metastatic setting was not allowed. Other exclusion criteria included symptomatic or progressive brain metastases, history of other prior malignancies, significant cardiac disease. Pregnant or breast-feeding women were excluded.

2.3. Treatment plan

All patients received NPLD 60 mg/m^2 as a 90-minutes intravenous infusion plus docetaxel 75 mg/m^2 as a 1-hour intravenous infusion on day 1 of a 21-day cycle. Patients received pre-medication with corticosteroids to prevent docetaxel related hypersensitivity and fluid retention.[22] Antiemetics were prescribed before each cycle. Treatment was planned for a minimum of six cycles and was continued until progression or unacceptable toxicity. Dose adjustments and treatment interruptions were planned according to adverse effects.

2.4. Tolerability and efficacy assessment

At baseline and before each cycle, vital signs and performance status were assessed. Adverse events were evaluated continuously and graded according to National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0. Serum chemistry and haematology were evaluated before each cycle. Cardiac evaluation with LVEF determination by echocardiography was performed every two cycles until sixth cycle and every cycle from the seventh cycle.

Tumour evaluation (by physical examination and imaging studies) was performed every two cycles and was assessed by investigators at the site. For measurable lesions, the response

was defined according to Response Evaluation Criteria In Solid Tumours (RECIST).

2.5. Statistical design and methodology

The primary end-point of this study was objective response rate. Response-assessable patients were defined as patients with measurable disease and with at least one cycle of chemotherapy and one tumour evaluation.

Secondary end-points included tolerability, progression free survival (PFS), duration of response (DR), time to treatment failure (TTF) and overall survival (OS). PFS was defined as the time from registration to time of first documented disease progression or death, whichever occurs first. DR was defined, for responding patients only, as the time from registration until disease progression. TTF was the time between registration and disease progression, death or withdrawal of treatment due to adverse events, withdrawn informed consent or insufficient therapeutic response, whatever occurs first. OS was calculated from the date of registration to the date of death from any cause or to the date of loss to follow-up. Survival data were computed according to Kaplan–Meier method and analyses were performed on an intent-to-treat population including all registered patients.

The study was designed to aim an estimated objective response rate of 75%, with a type I error (α) of 0.05 and a power of 80% (1-β). This hypothesis required a sample size of 32 patients.

3. Results

3.1. Patients

Between 16th April 2004 and 26th June 2007, 37 patients were enrolled across nine centres in France. Three patients who did not receive any prior anthracycline therapy had been enrolled. Because they did not meet a major inclusion criterion, they were eliminated from analysis. Then, all subsequent analyses are performed in a population of 34 patients pretreated with anthracyclines at the adjuvant setting. Patient demographic characteristics and baseline disease characteristics were representative of a population with metastatic breast cancer treated as first-line therapy (Table 1). The median age was 56 years (range, 36–75). Patients had significant baseline disease: 62% of patients had liver metastases, 35% had lung metastases and 59% presented with at least two metastatic sites. Thirty-one patients (91%) had measurable disease according to RECIST criteria and two of these patients were lost to follow-up. Consequently, a total of 29 patients (85%) had response-assessable disease. Seven patients (21%) had triple-negative metastatic breast cancer. All patients included in the analysis had received prior adjuvant (32 patients) or neoadjuvant (two patients) anthracycline-containing chemotherapy. Ten of them (29%) were also exposed to a taxane as part of their adjuvant regimen. The median disease free interval was 48 months (range 17–258).

Table 1 – Baseline patient demographics and clinical characteristics (n = 34).

Age, years	
Median	56
Range	36–75
WHO performance status	
0	23 (68%)
1	10 (29%)
2	1 (3%)
Menopausal status	
Non-menopausal	8 (24%)
Menopausal	26 (76%)
No. of metastatic sites	
1	14 (41%)
2	15 (44%)
3	5 (15%)
Disease site	
Liver	21 (62%)
Lung	12 (35%)
Bone	16 (47%)
Lymph nodes	5 (15%)
Skin/soft tissues	5 (15%)
Carcinomatosis	2 (6%)
Hormone receptors status	
ER+, PgR+	17 (50%)
ER+, PgR–	9 (26%)
ER–, PgR+	0 (0%)
ER–, PgR–	7 (21%)
Unknown	1 (3%)
Disease free interval	
$\leqslant$2 years	7 (21%)
>2 years	26 (76%)
Unknown	1 (3%)
Neoadjuvant/adjuvant treatment	
Anthracyclines	34 (100%)
Epirubicin	27 (79%)
Taxanes	10 (29%)
Endocrine treatment	27 (79%)

3.2. Dosing

A total of 214 cycles were administered throughout the study. Patients received a median of six cycles (range, 2–12) and 82% of patients received at least six cycles. One hundred eighty one cycles (85%) were administered at the planned dose and a total of 25 cycles (12%) were delayed. Treatment was discontinued before 6th cycle due to disease progression in three patients (9%). Seven patients (21%) withdrew of treatment due to adverse events treatment. The median relative dose intensity was 95% of the theory dose exposure for both NPLD and docetaxel.

3.3. Safety

3.3.1. Haematologic toxicity (Table 2)

Most common grade 3/4 adverse events were neutropenia occurring in 15% of the cycles. Sixteen patients (47%) experienced at least one febrile neutropenia and febrile neutropenia was observed in 13% of the cycles administered without prophylaxis with granulocyte colony-stimulating factors (G-CSF). Seventeen patients (50%) received prophylaxis with granulocyte colony-stimulating factors (G-CSF); it was a secondary prophylaxis in the majority of cases. Grade 3/4 anaemia and

Table 2 – Toxicity *per* patients (n = 34) according to NCI CTC version 2.0.

	Grade 1	Grade 2	Grade 3	Grade 4
Haematologic toxicity				
Neutropenia	NE	NE	7 (21%)	19 (56%)
Febrile neutropenia	–	–	8 (23,5%)	8 (23,5%)
Anaemia	NE	NE	1 (3%)	2 (6%)
Thrombocytopenia	NE	NE	1 (3%)	2 (6%)
Non-cardiac, non-haematologic toxicity				
Nausea	2 (6%)	2 (6%)	1(3%)	0
Vomiting	1 (3%)	0	0	0
Diarrhoea	2 (6%)	3 (9%)	1 (3%)	0
Oedema	0	1 (3%)	1 (3%)	0
Neurotoxicity	0	1 (3%)	0	0
Hypersensitivity	0	2 (6%)	0	0
Stomatitis/mucositis	1 (3%)	1 (3%)	0	0
Oesophagitis	1 (3%)	1 (3%)	0	0
Stomach ulcer	0	1 (3%)	0	0
Tracheitis	0	1 (3%)	0	0
Headache	1 (3%)	0	0	0
Infection (except febrile neutropenia)	0	1 (3%)	2 (6%)	0
PPE	0	0	0	0
Total	8 (24%)	14 (42%)	5 (15%)	0
Cardiac toxicity				
LVSD	5 (15%)	3 (9%)	5 (15%)	0

Abbreviations: PPE = palmo-plantar erythrodysesthesia syndrome, NE = non-evaluated.
LVSD = left ventricular systolic dysfunction, NCI CTC = national cancer institute common toxicity criteria.

thrombocytopenia both occurred in three patients and five transfusions were needed. Eight patients (24%) received erythropoietin.

3.3.2. *Cardiac toxicity (Table 2)*

Five (15%) patients experienced congestive heart failure symptoms requiring chemotherapy discontinuation. Median time of occurrence of grade 3 cardiotoxicity was 18.2 weeks. One of these patients died of cardiac complication two years later. All patients with grade 3 cardiotoxicity received epirubicin at the adjuvant setting. Epirubicin cumulative dose (600 mg/m^2 or less) was no different in the sub-group with grade 3 cardiac toxicity and in the sub-group without cardiac toxicity (p = 0.82). Similarly, doxorubicin cumulative dose received in the metastatic setting did not explain cardiotoxicity. One patient discontinued therapy as a result of grade 2 cardiac toxicity. Four patients (12%) had non-assessable cardiac ejection fraction. They were asymptomatic for congestive heart failure.

3.3.3. *Non-haematologic non-cardiac toxicity (Table 2)*

Severe adverse events were infrequent. Two grade 3 infections without neutropenia (6%) were observed and required intravenous antibiotics. Grade 1 and 2 adverse events were observed in 66% of the patients, mainly related to gastrointestinal toxicity. No patient experienced palmo-plantar erythrodysesthesia syndrome.

3.4. *Efficacy*

Objective response rate (ORR) among response-assessable patients was 79% (95% CI (confidence interval), 64–94%). Eight of the 29 assessed patients (27% (95% CI, 11–43%)) presented a complete response. Three patients (10% (95% CI, 0–21%)) had stable disease and three patients (10% (95% CI, 0–21%)) experienced a progression under therapy (Table 3).

Tumour responses were durable, with a median duration of 12.8 months (95% CI, 7–16.2 months). Median progression free survival was 11.3 months (95% CI, 6.2–13.3 months) with a median time to treatment failure of 6.9 months (95% CI, 4.7–11.3 months). Median overall survival was 28.2 months (95% CI, 16–36.4 months) (fig. 1).

4. Discussion

This phase II trial was designed to evaluate the efficacy and the safety of a docetaxel and NPLD combination in metastatic breast cancer pretreated with adjuvant anthracyclines and/or taxanes.

This chemotherapy combination showed high activity in a small population of patients exposed to anthracyclines in the adjuvant setting. All patients included in the analysis had experienced anthracyclines re-challenge and 29% had experienced re-challenge to both taxanes and anthracyclines. The overall response rate was notably high in response-assessable patients (79%) with a median duration of response exceeding one year. Patients with assessable disease were eligible for this trial even if their disease did not meet RECIST criteria. It explains that response rate was assessed according to the stringent RECIST criteria in only 29 patients. With a median progression free survival of 11.3 months and a median overall survival of 28.2 months, the study's regimen demonstrated an encouraging efficacy regarding to survival data. These results are similar to those reported in trials assessing anthracycline

Table 3 – Best response in response-assessable patient population (n = 29).

	Patients	%	95% CI
CR	8	27	11–43
PR	15	52	34–70
ORR	23	79	64–94
SD	3	10	0–21
PD	3	10	0–21

CR: complete response, PR: partial response, ORR: objective response rate.
SD: stable disease, PD: progressive disease.

and taxane combinations in first-line therapy for metastatic disease.[9–16] Interestingly, previous exposure to anthracycline-based regimen did not seem to impair treatment efficacy.[23] Furthermore, response rate was similar in patients with prior adjuvant taxane exposure (p = 0.76).

In the present study, haematologic toxicity was common, with a febrile neutropenia occurrence in 47% of patients. In the dose-finding study of docetaxel plus doxorubicin, neutropenia and its complications were the dose-limiting toxicities.[24] The present trial used slightly higher dose of doxorubicin-equivalent (60 mg/m^2), which can explain the high rate of febrile neutropenia. Other haematologic and non-haematologic non-cardiac adverse events occurred at expected rates, similar to those observed in conventional doxorubicin plus docetaxel combination. Palmo-plantar erythrodysesthesia, which is a dose-limiting toxicity with pegylated liposomal doxorubicin, was not observed despite the addition of docetaxel. A high rate of cardiac toxicity was highlighted. Five patients (15%; 95% CI, 3–27%) experienced durable grade 3 symptomatic congestive heart failure. The mechanisms involved in the five patients who developed cardiotoxicity are unclear. Different factors such as cumulative dose of anthracyclines, age, pre-existing cardiac dysfunction, long-standing hypertension and cardiotoxic therapies are known to increase the risk of cardiotoxicity.[17] The best predictor of cardiotoxicity is the total cumulative dose of anthracyclines. In this trial, prior anthracyclines cumulative-dose exposure fails to explain cardiac toxicity. No significant difference in cumulative doses between patients with or without cardiotoxicity was reported. All patients had initial cardiac functions within normal limits, but one patient with left ventricular ejection fraction ranged between 50% and 55%. Furthermore, the addition of a taxane to doxorubicin does not seem to increase cardiotoxicity.[25,26] In total, there is no explanation of such rate of cardiotoxicity. Definitively if liposomal doxorubicin appears less cardiotoxic than standard anthracyclines, their toxicity is not null. This signal should be taken into account for the routine use of liposomal doxorubicin in terms of treatment duration, cardiac follow-up and in the development of association with high cardiac potential toxicity.

Four previous phase II[27–30] trials assessing liposomal doxorubicin and taxane combinations have been published and

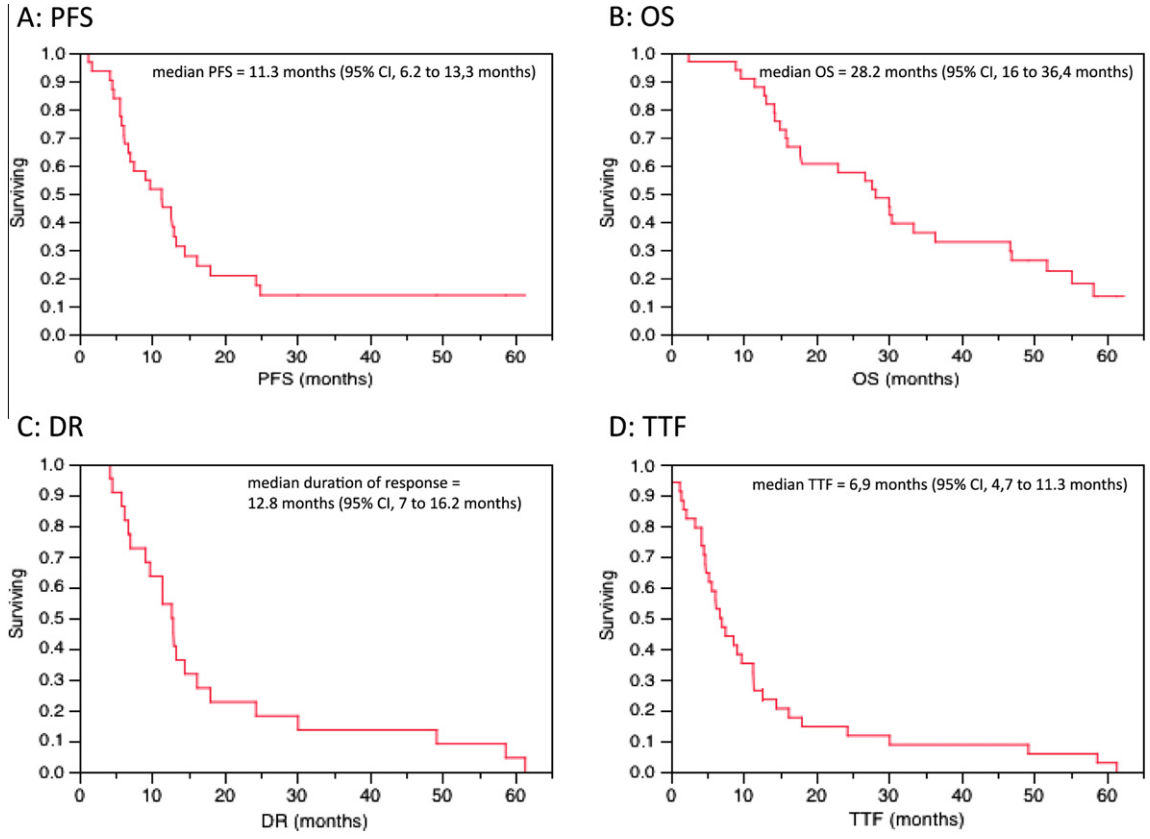

Fig. 1 – A: progression free survival (PFS); B: overall survival (OS); C: duration of response (DR); D: time to treatment failure (TTF).

two of them assessed a combination of a taxane with NPLD. In these two trials,[27,28] the combination therapy demonstrated a high activity with a modest toxicity profile. The results of the Myotax trial are concordant with the data of the literature concerning the efficacy of the chemotherapy combination but are discordant regarding the toxicity profile. It is the first time to the best of our knowledge that a trial assessing liposomal anthracycline and taxane combination highlights congestive heart failure in 15% of the patients. Classic predictive factors of toxicity fail to explain this side-effect. Other trials have evaluated liposomal doxorubicin as first-line therapy in the metastatic setting as a single agent or in combination with cyclophosphamide or taxane.[18–20,27–33] They also included patients previously exposed to anthracyclines[18,19,27–33] and did not highlight an increased cardiotoxicity. In phase III trials, the number of patients previously exposed to anthracyclines was small, below 20%, but a retrospective analysis of two of these trials showed that treatment based on NPLD significantly reduced the risk of cardiotoxicity in patients pretreated with adjuvant doxorubicin.[34]

Efficacy and toxicity have to be balanced to offer the patients the best treatment able both to prolong life and to maintain quality of life. Combinations therapies allow a high antitumour efficacy while monotherapies and sequential treatments offer a better quality of life. This trial showed an unfavourable toxicity profile. To improve the safety, the schedule doses of the combination of non-pegylated liposomal doxorubicin and docetaxel could be adapted.[24,28] Despite the advent of targeted therapies, the best first-line therapy in metastatic breast cancer is still not defined and warrants further trials to optimise and to identify the best regimens. A trial comparing an adapted combination of NPLD–docetaxel to conventional doxorubicin–docetaxel could be interesting to assess the interest of liposomal anthracyclines in first-line treatment of metastatic breast cancer.

Conflict of interest statement

E. Curtit, P. Nouyrigat, N. Dohollou, E. Levy, A. Lortholary, J. Gligorov, T. Facchini, D. Jaubert and N. Maille have declared no conflicts of interest. X. Pivot and L. Cals perceived Honorarium from Cephalon SA. There is however no conflict of interest in regard to the content of this contribution. V. Grangé has declared conflict of interest as follows: 'Cephalon employee in the medical affairs department'.

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