Non-pegylated liposomal doxorubicin plus capecitabine as first-line treatment in metastatic breast cancer

Piotr Plecka, MD, PhD
Lubusz Center of Pulmonology in Torzym, Poland

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ABSTRACT

Purpose: To determine the toxicity and efficacy profile of non-pegylated liposomal doxorubicin in combination with capecitabine administered according to LipAX regimen.

Materials and methods: The analysis included 5 female patients undergoing first-line treatment for metastatic breast cancer. Patients received non-pegylated liposomal doxorubicin intravenously and oral capecitabine at usual doses used for monotherapy, until disease progression or unacceptable toxicity.

Results: Patients received a total of 26 complete treatment cycles according to LipAX regimen. During treatment, 15 toxicities occurred, including 7 adverse events with grade 3 severity. Only two haematological toxicities were observed, and the other 13 were of a non-haematological nature. Only one patient experienced no adverse events. Apart from symptomatic treatment, the capecitabine dose was reduced twice and the non-pegylated liposomal doxorubicin once.

Positive clinical outcomes were observed in 4 patients, and disease progression was reported in the case of 1 patient in the course of the treatment. The median time to disease progression was 10.4 months, and the median overall survival was 34.2 months. During the 54-month follow-up, 4 of the patients died. The surviving patient continues treatment.

Conclusions: Therapy according to the LipAX regimen was relatively well tolerated, however, since the majority of patients discontinued treatment due to adverse events, and not disease progression, an adequate reduction in the cytostatic doses should be considered. The use of the LipAX regimen may contribute to the achievement of long-term remission in some patients, a fact that encourages further studies on this form of therapy.

KEY WORDS: breast cancer, chemotherapy, new regimen, non-pegylated liposomal doxorubicin

Correspondence:
Piotr Plecka, MD, PhD
Lubusz Center of Pulmonology
66-235 Torzym, ul. Wojska Polskiego 52
e-mail: pplecka@wp.pl

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INTRODUCTION

Breast cancer is the most common cancer in women in Poland and worldwide. The number of new cases diagnosed in 2012 in the Polish population was 17 142 according to the National Cancer Register, while the number of deaths in the same period amounted to 5816 [1]. Primary metastatic breast cancer is diagnosed in ca 20% of women, while approx. 40–60% of patients experience metastasis in the natural course of the disease. At this stage the process is incurable, and the median survival is 18–24 months. This is why new drugs and therapies are investigated to effectively prolong survival or at least the disease-free survival. Completely new drugs or enhanced forms of existing cytotoxics are being introduced to clinical practice. The latter include non-pegylated liposomal doxorubicin (lipo-Dox) and capecitabine (Cap). Both drugs have been approved as first-line therapy and are reimbursed by the National Health Fund for this indication. The efficacy of these agents (measured by the response rate) as monotherapy is [2–4]:

- 26–46% for lipo-Dox,
- 50–63% for Cap.

Attempts are also made to introduce new forms of cytostatic agents into existing regimens [5–7]. The use of less cardiotoxic intravenous anthracycline in combination with an oral antimetabolite with a wide therapeutic dosing range seems to be an attractive solution in palliative care. Given the lack of reports on the use of non-pegylated liposomal doxorubicin in combination with capecitabine (LipAX regimen), it would be valuable to investigate whether the combined use of these drugs would lead to higher response rates than when used as single agents.

PURPOSE

1. To determine the toxicity of the combination regimen of non-pegylated liposomal doxorubicin and capecitabine (LipAX regimen).
2. To evaluate the efficacy of LipAX regimen.

MATERIAL AND METHODS

The analysis included 5 female patients with metastatic breast cancer, treated in an out-patient setting from July 2010 to July 2012. Three patients presented with primary metastasis, while in the case of the remaining two patients, disease metastasized following initially radical treatment (surgery, chemotherapy with doxorubicin, radiotherapy and in one case hormonal therapy). None of the patients received earlier palliative systemic treatment (including hormonal therapy).

In the beginning, the patients received non-pegylated liposomal doxorubicin at a dose of 60–75 mg/m^2 (depending on the patient's performance status) intravenously every 3 weeks in combination with capecitabine at a dose of 2500 mg/m^2/day orally for 14 days, every three weeks. The dosage of the cytostatics could, however, be modified depending on the toxicities experienced. Prior to each chemotherapy cycle, patients had a complete blood count, biochemical profile and electrocardiogram performed. An echocardiogram was performed before therapy initiation and then after 3–4 cycles. The therapy was intended to be continued until disease progression or unacceptable toxicities.

The patients' performance status according to the Karnofsky scale was generally good; three patients had a score of 80–100, and the remaining two a score of 70. All patients were post-menopausal, aged 47–71 years (median age 57 years), standard deviation (SD) 9.407. Before treatment each patient had cardiovascular system assessed using echocardiography, ECG and blood pressure measurements – no abnormalities were detected. During follow-up, two patients died due to central nervous system (CNS) metastases and two due to metastases outside the CNS. One patient is still alive. This data is summarised in table 1.

Four patients were diagnosed with ductal carcinoma. The histological tumour grade was determined only in two patients and described as G3. Four patients were hormone-receptor positive – three were estrogen-positive and four were progesterone-positive. One patient was HER-2 positive, and in one patient no hormone receptors were present. All three patients diagnosed with primary metastatic disease had breast ulcerations (T4). The remaining 2 patients underwent radical treatment for stage III disease, and one of them presenting with T3 breast cancer underwent induction chemotherapy. There are different numbers of metastatic sites at baseline and upon initiation of LipAX therapy. At baseline, lung metastases was discovered in two patients, bones metastases in three patients and liver metastases in one patient. Prior to treatment, lung metastases was determined in three patients, liver metastases in two patients, bone metastases in three patients, CNS metastases in one patient and skin metastases in one patient. A similar change in the number of organs involved was observed in one patient. At baseline, two patients had metastases in one organ and one patient had metastases in three organs. Before treatment initiation, two patients had metastases in one organ, one patient had metastases in two organs and the remaining two in three organs. Those data are collected in table 2.

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TABLE 1.
Patient demographics.

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	50	57	47	71	60
Postmenopausal	yes	yes	yes	yes	yes
Previous treatments: • chemotherapy • anthracyclines • radiotherapy • hormonal therapy	no - - - -	yes yes yes yes yes	yes yes yes yes no	no - - - -	no - - - -
Performance status acc. to Karnofsky: • 100 • 90 • 80 • 70	 yes - - -	 - yes - -	 - - - yes	 - - yes -	 - - - yes
Ejection fraction by echocardiography – normal	yes	yes	yes	yes	yes
ECG recordings – normal	yes	yes	yes	yes	yes
Blood pressure – normal	yes	yes	yes	yes	yes
Death	no	yes	yes	yes	yes
Cause of death: central nervous system metastasis	-	-	yes	-	yes
Metastasis outside the central nervous system	-	yes	-	yes	-

TABLE 2.
Tumour characteristics.

Tumour characteristics	Number of patients (n = 5)	(%)
Histology • Ductal carcinoma • Unknown	 4 1	 80 20
Histological tumour grade • III • Unknown	 2 3	 40 60
Receptor status • E-positive • P-positive • HER-positive • E-, P- and HER-negative	 3 4 1 1	 60 80 20 20
Baseline disease stage • IV st. • III st.	 3 2	 60 40
Baseline local state • Ulceration • T3 • T2	 3 1 1	 60 20 20
Baseline site of metastases (3 patients) • Lungs • Liver • Bones	 2 1 2	 67 33 67

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Site of metastases at therapy initiation		
• Lungs	3	60
• Liver	2	40
• Bones	3	60
• CNS	1	20
• Skin	1	20
Baseline number of metastatic organs (3 patients)		
• 1	2	67
• 2	0	00
• 3	1	33
Number of metastatic organs at therapy initiation		
• 1	2	40
• 2	1	20
• 3	2	40

RESULTS

A total of 26 complete LipAX cycles (mean 5.2, range 3–8) was administered, including 28 cycles of LipoDoxorubicine, mean 5.6, range 3–8 (2 cycles without Capecytabine) and 34 cycles of capecitabine, mean 6.8, range 3–12 (8 cycles without LipoDoxorubicyne).

Favourable clinical outcome was observed in four patients, two with a partial response to treatment (RECIST version 1.1), and the other two with the stable disease. Disease progression during therapy was observed in one patient only.

The median time to progression (time from therapy initiation to disease progression) was 10.4 months, with the range 2–27 months and SD 10.03. During a follow-up period of 54 months, 4 deaths were reported, and one patient is still alive. The median survival (measured from the start of treatment to death from any cause) was 34.2 months, with the range was 4–83 months and SD 29.97.

In the course of treatment, a total of 15 toxicities occurred with 7 which were severe (WHO version 3.0). No toxicities were reported for one patient. Two patients with the longest duration of LipAX therapy experienced only 4 adverse events. No grade 4 toxicities were observed, while grade 3 skin reactions were reported in one patient, phlebitis of the lower extremity veins in two patients and asthenia in two patients, leucopenia in one patient and thrombocytopenia in one patient. Grade 2 skin reactions occurred in two patients, stomatitis in two patients, and alopecia and asthenia in one patient each. Grade 2 stomatitis was observed in one patient and diarrhoea in one patient. Table 3 presents a summary of the toxicities.

TABLE 3.
Adverse events.

Type of adverse event	Severity			
	Grade 1	Grade 2	Grade 3	Grade 4
Skin reactions	0	2	1	0
Deep vein phlebitis	0	0	2	0
Stomatitis	1	2	0	0
Alopecia	0	1	0	0
Diarrhoea	1	0	0	0
Asthenia	0	1	2	0
Leucopenia	0	0	1	0
Thrombocytopenia	0	0	1	0

Toxicities were treated symptomatically. In two cases it was necessary to delay the next cycle of treatment, but in the case of three patients adverse reactions were the direct cause of early discontinuation (after 12, 11 and 6 chemotherapy cycles) because asthenia in case of two patients and skin reactions in one patient. The patient with the largest number of toxicities had 6 adverse events, followed by patients with 4, 3 and 2 events. One patient had no adverse events reported.

DISCUSSION

The study presents the results of LipAX regimen treatment, consisting of non-pegylated liposomal doxorubicin and capecitabine. According to the data presented in the first part of the study, the patients and tumour characteristics are quite typical for this kind of population [3, 6]. Interesingly, all three patients presenting initially with metastatic disease had primary lesions in the form of breast ulcerations and were estrogen – positive

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and progesterone-positive which can indicate a possibility of potentially good therapeutic response. But on the other hand, metastases in more than one organ in more than three patients suggest rather an unfavourable prognosis.

The relatively high number of LipAX cycles administered (mean 5.2) in the treatment of metastatic breast cancer may be a result of good qualification for treatment (first-line therapy, normal cardiac ejection fraction) and/or of a relatively low toxicity.

The administration of a high number of LipAX cycles when combined with its good tolerance can lead to high therapeutic efficacy, evidenced by: time to progression – 10.4 months and median survival – 34.2 months [8, 9].

With the occurrence of a total of 15 toxicities, there were an average of 3 adverse events per patient and 0.6 toxicities per one LipAX chemotherapy cycle. Moreover, no grade 4 adverse events were identified and only 7 grade 3 adverse events were reported (47% of toxicities). The grade 1 and 2 toxicities were more prevalent (53% of total toxicities). Given the toxicity profile of both cytotoxic agents used as monotherapy, capecitabine alone could account for 5 toxicities (skin reactions, diarrhoea and thrombocytopenia) and Lipo-Dox for 6 toxicities (deep vein phlebitis, alopecia and asthenia), and the remaining 4 may be the result of their combined effect [7, 8]. It should be noted that no adverse events occurred in the case of 1 patient (she received 3 LipAX cycles) whose treatment was discontinued because of CNS metastases; the remaining 4 patients discontinued therapy due to toxicities, with asthenia being the most common cause occurring in 2 patients, which gives a significantly higher percentage than in other reports [3, 6].

Because of toxicity, capecitabine doses were reduced twice in both patients with the longest retreatment duration. Lipo-Dox doses were not modified. However, based on the results achieved, similarly to other reports, this had no significant effect on the time to disease progression and overall survival [4, 10].

Glucocorticosteroids were given several times because of general health conditions, and, at least in one case, they could account for phlebitis. Granulocyte-colony stimulating factor (G-CSF) was used only once and seemed to have no relation to the toxicities. It should be noted, that compared to other studies, the incidence of neutropenia and the associated requirement to administer granulocyte-colony stimulating factors was markedly lower, despite the use of two cytotoxic agents at full or nearly full doses.

No negative cardiovascular effect of this therapy regimen was observed. No abnormalities were found in the routinely performed electrocardiograms and echocardiograms, which coincide with the findings of other researchers [11].

CONCLUSIONS

1. The occurrence of a small number of toxicities with majority of which were not life threatening, indicates an acceptable toxicity profile of the LipAX regimen. However, because most patients discontinued therapy due to adverse events rather than disease progression, more optimal doses of both cytostatics should be sought.
2. The use of the LipAX regimen resulted in a good therapeutic effect measured by the time to progression and overall survival, and the achievement of long-term remissions in some patients suggests the need to continue investigations on the introduction of this regimen into regular clinical practice.

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