

Efficacy and safety of liposomal doxorubicin in a patient treated for metastatic breast cancer

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ABSTRACT

Liposomal doxorubicin is a newer form of chemotherapeutic agents that, due to its own special properties, preferably accumulates in cancer tissue. On the other hand, it shows lower affinity to cardiomyocytes and in this way is less cardiotoxic. As a result of that, there is the possibility to use liposomal form of doxorubicin until disease progression or chemotherapy intolerance in palliative setting, without treatment cessation after reaching the maximum cumulative dose of conventional doxorubicin.

In this article we describe the case of a female patient diagnosed with breast cancer who was primary treated with adjuvant treatment, including chemotherapy and in whom a disease recurrence occurred after seven years of observation. As a primary palliative treatment the patient received chemotherapy based on liposomal doxorubicin and cyclophosphamide with a very good tolerance. The initial response was partial remission in lungs and in mediastinal lymph nodes. During the whole course of therapy there were no pathological changes in electrocardiogram, no signs and no symptoms of congestive heart failure, and the left ventricular ejection fraction was within normal limits.

KEY WORDS: breast cancer, liposomal doxorubicin, cardiotoxicity

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INTRODUCTION

Breast cancer is one of the most frequent types of malignant solid tumours in women [1]. Incidence of breast cancer is growing in Poland, however the mortality rate has been decreasing since 1990s. Currently, over three-fourths of women with breast cancer experience a five-year survival [2]. The last decades have seen a tremendous progress in breast cancer therapy owing to the introduction of monoclonal antibodies (trastuzumab and pertuzumab) [3, 4], tyrosine kinase inhibitors (lapatinib) [5] and mTOR pathway inhibitors (everolimus) [6] to clinical practice. However, chemotherapy is still the basic treatment for a significant number of breast cancer patients in early and advanced stages [7–9]. Anthracyclines are the golden standard of systemic therapy, provided there are no cardiac contraindications [10, 11]. However, the use of anthracyclines is largely limited due to their significant potential cardiotoxicity [12]. For this reason, therapy is continued only until the prescribed cumulative dose is reached. In the case of patients who have received previous radiation in the chest area or are planned to receive postoperative radiotherapy, the maximum allowable dose of adriamycin or epirubicin is even smaller. The problem of toxicity limiting effectiveness of therapy could be resolved by a cytostatic drug showing similar efficacy to that of anthracyclines and not posing a risk of damage to the heart. The first attempts to create a new chemotherapeutic drug showing such properties were made already in the 1990s [13]. Those efforts resulted in developing new forms of doxorubicin whose molecules were encapsulated in liposomes made of phosphatidylcholine and cholesterol. Their modified structure extended the half-life of the drugs and led to preferential accumulation of the drug in cancerous tissue [14, 15], thus significantly reducing the risk of cardiotoxicity. However, as a result of the modification, other adverse events increased (e.g. mucositis) or new ones occurred, such as the palmar-plantar erythrodysesthesia that has been seen in patients receiving pegylated liposomal adriamycin [16]. In any case, modified anthracyclines retained their efficacy against tumours [17].

To date, three forms of liposome-encapsulated anthracyclines have been developed, including liposomal daunorubicin, and pegylated and non-pegylated liposomal doxorubicin. Non-pegylated liposomal doxorubicin (D-99) has been registered in the European Union and Canada for a combined therapy of metastatic breast cancer (in combination with cyclophosphamide) [18]. Due to its additive cardiotoxicity, anthracycline-based chemotherapy has not been broadly used in combination with anti-HER2 therapy outside of clinical settings despite reports on its superior efficacy [19]. Development of adriamycin associated

with a lower risk of myocardial damage opened up new possibilities to use more effective drug combinations.

In 2011, the findings of phase 2 clinical trials were published, which evaluated the efficacy and safety profile of a tri-drug neo-adjuvant therapy, based on a combination of liposomal doxorubicin with trastuzumab and docetaxel. The clinical response rate was high at 86%, while the cardiac toxicity profile was favourable [20].

In addition, in case of patients initially treated with radical methods who later develop a metastatic disease, liposomal doxorubicin gives an opportunity to repeat anthracycline-based therapy despite its high cytostatic activity.

In Poland, liposomal doxorubicin may be used in breast cancer therapy only at the stage of metastatic disease. This provides an opportunity to improve the prognosis for patients without exposing them to excessive cardiovascular risk.

CASE PRESENTATION

A female patient, 53 years old, was under on-going care of a Breast Outpatient Clinic due to mastopathic changes. In April 2004, the patient underwent a routine screening mammography scan which revealed a possibly cancerous lesion assessed as BI-RADS category 5. An irregularly shaped mass measuring 12 × 15 mm was found at the junction of outer quadrants of the left breast, along with pathological microcalcifications and a smudge in the adjacent tissue parenchyma. No focal lesions were found in the right breast. The patient was referred for further diagnostic tests. An ultrasound-guided core-needle biopsy was performed. The histopathological exam revealed ductal carcinoma, not otherwise specified. In May 2004, the patient underwent a breast-conserving surgery involving left axillary lymphadenectomy. According to the histopathological exam report, the patient had a grade G3 ductal breast carcinoma, determined as triple negative (oestrogen receptor [ER] – negative, progesterone receptor [PR] – negative and human epidermal growth factor receptor 2 [HER-2] – negative) and pathological stage pT1cN0. The patient received 6 cycles of adjuvant CMF chemotherapy (based on cyclophosphamide, methotrexate and 5-fluorouracil) and adjuvant radiotherapy targeting left breast with a total dose of 50 Gy given in 25 fractions of 2 Gy each, followed by a boost on the tumour bed up to a total radiation dose of 60 Gy. The X-ray exam did not show any potentially cancerous lesions and no material abnormalities were identified in a follow-up abdominal ultrasound scan.

The patient had been previously treated for hypertension and hypercholesterolemia. She had been receiving perindopril in combination with metoprolol and statin for several years. An ECG exam showed a sinus tachycardia which persisted throughout chemotherapy. Other possible causes of tachycardia, including a co-existing hyperthyroidism, were ruled out. Following the scheduled adjuvant treatment, the patient remained under the regular care of a cardiologist and oncologist.

In late September 2011, a routine screening ultrasound scan was performed which showed an enlarged lymph node in the left armpit measuring 20 mm in diameter. In order to obtain a more accurate image, a chest CT scan was performed which revealed multiple bilateral pulmonary metastases and enlarged packages of paratracheal lymph nodes measuring up to 25 mm. In the left armpit, a suspicious lymph node was identified with an irregular outline and a diameter of 27 mm. A lymph node with a 13 mm diameter was found in the right armpit. An abdominal ultrasound scan did not show any potential cancerous lesions. The histopathology exam of the tissue sample removed from the left axillary lymph nodes during a biopsy confirmed a metastasized breast cancer with similar characteristics to those established in the initial histopathology exam, with no change in glicocorticosteroid receptor status and HER-2 status. The patient was scheduled for palliative treatment with 60 mg/m² liposomal doxorubicin combined with 600 mg/m² cyclophosphamide. In the initial echocardiogram, the left ventricular ejection fraction was 65%. The patient continued receiving a β -blocker and angiotensin II converting enzyme inhibitor to manage hypertension, and statins to manage hypercholesterolemia. The patient also underwent three series of chemotherapy and showed a very strong tolerance for treatment. According to the echocardiogram, the ejection fraction remained unchanged.

A follow-up CT scan of the chest showed a partial regression of pulmonary metastases and a reduction in size of the enlarged mediastinal lymph nodes. According to an abdominal ultrasound scan, no potentially cancerous lesions were found in parenchymal organs. The patient continued chemotherapy with good direct tolerance. The patient did not experience serious ailments during her systemic treatment while results of biochemical tests did not significantly differ from normal values. Another imaging scan was made after completion of 6 chemotherapy cycles. It showed that the pulmonary metastases remained stable but the cancer progressed to the bones where metastatic foci were found. A sclerotic lesion was identified in the Th3 vertebral body as well visible sclerotic foci in the

Th7, Th10 and Th11 vertebral bodies. The patient was referred for a scintigraphy which confirmed presence of bone metastasis. The patient was initiated on bisphosphonates. In March 2012, chemotherapy was completed and the patient continued receiving bisphosphonates. On account of progression of the disease to parenchymal organs, the patient had to undergo another line of chemotherapy.

The patient did not experience any significant cardiovascular symptoms and her blood pressure was not elevated. According to a follow-up echocardiogram performed 6 months after completion of chemotherapy, the patient's left ventricular ejection fraction was within a normal range at 60%. The patient did not report any symptoms which could be attributed to myocardial failure.

DISCUSSION

A metastatic breast cancer patient, previously treated for hypertension and hypercholesterolemia for several years, received liposomal doxorubicin in combination with cyclophosphamide as the first line of treatment. As a result, a partial regression of metastases in lungs and lymph nodes was achieved, with no resulting cardiovascular complications. Systemic tolerance of the treatment was good. No Grade 3 or 4 adverse events were identified based on the CTCAE v4.03 assessment. The patient received a total of 600 mg of liposomal doxorubicin. The patient would not have been able to receive the same amount of conventional doxorubicin because in her case exceeding the threshold amount would dramatically increase the risk of cardiotoxicity.

CONCLUSION

Introduction of new forms of doxorubicin associated with a lower risk of myocardial damage created an opportunity for metastatic breast cancer patients to receive effective treatment. Such patients may continue therapy until a response is elicited with no severe adverse events involved. Treatment with the liposome-encapsulated cytostatic drug does not need to be interrupted when the maximum lifetime dose is reached, which improves the efficacy of treatment for some patients without exposing them to cardiac complications. This marks a major breakthrough in the therapy of metastatic breast cancer.

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Authors' contributions:

Both authors equally contributed to idea & design of the article, clinical data collection, analysis of the data and writing the manuscript.