Safety and efficacy of liposomal doxorubicin in a patient treated for metastatic breast cancer

Justyna Borucka, MD

Department of Chemotherapy, Lord's Transfiguration Clinical Hospital of Poznan University of Medical Sciences, Poland

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ABSTRACT

Breast cancer is the most common malignancy among women in Poland and all over the world. Despite the development of modern therapies, cytostatics still play one of the main roles in treatment of this disease. Classic anthracyclines, besides unquestionable efficacy in this disease, have a disadvantageous toxicity profile. Therefore, until now, there has been a limitation in using these drugs in patients with cardiological conditions and in patients who had previously taken anthracyclines. That was the cause for the development of a less toxic form of drug, which is liposomal doxorubicin – being as effective as classic anthracycline it has reduced cardiotoxicity. This article presents the case of a patient with metastatic breast cancer, in whom, after treatment with classic doxorubicin, liposomal form was administered which caused regression of liver metastases. Moreover, during treatment with liposomal doxorubicin, there has been no evidence of heart impairment.

KEY WORDS: metastatic breast cancer, anthracyclines, liposomal doxorubicin, cardiotoxicity

Correspondence:
Justyna Borucka, MD
Department of Chemotherapy, Lord's Transfiguration Clinical Hospital
of Poznan University of Medical Sciences
61-848 Poznań, ul. Długa 1/2
tel.: (+48) 695-108-331
e-mail: jk.borucka@gmail.com

INTRODUCTION

Breast cancer is the most frequently diagnosed female cancer in the world and its incidence continues to grow in both developed and, recently, in developing countries, including Poland. Thanks to the evolution of new treatment methods as well as the improvement of the existing ones, a progressive decrease in breast cancer-related mortality has been observed for over 20 years now. Nevertheless, following lung cancer, it presently constitutes the second cause of death among women with solid tumours in the world [1, 2].

Thanks to the advancement of screening procedures and the general patient awareness, breast cancer is now more and more frequently detected at an early stage of the disease advancement, when surgical treatment combined with radiotherapy and (depending on the biological subtype of the disease) possibly also with chemotherapy, hormonal therapy and molecular targeted therapy, permits long-term progression-free survival or even complete recovery. Nonetheless, there is a group of patients in whom the disease is only detected at the stage of systemic dissemination or when it progresses to metastatic disease after adjuvant treatment. 80% of breast cancer patients are females over the age of 50, often with a tendency to develop abdominal obesity, which indicates cardiovascular comorbidities [3]. Such a patient profile, together with the fact that anthracyclines are the cytostatic drugs with the highest confirmed efficacy in breast cancer treatment, constitutes a significant problem and a serious challenge for contemporary oncologists [4].

Balancing between the best possible therapeutic result and a safe dose of the medication proves very difficult at times. Despite numerous studies aimed at identifying cardiac injury predictors, such as the level of troponins and assessment of the heart in MRI, the determination of the ejection fraction by echocardiography remains the most common method in use [5, 6]. The method is not ideal, though. All of the above have prompted the researchers to search for safer forms of anthracyclines, such as pegylated or non-pegylated liposomal anthracyclines. Randomized clinical trials have indicated that non-pegylated liposomal doxorubicin is just as efficacious as the classical form of the drug, being safer at the same time [7, 8]. To date, its use has been limited to patients with metastatic breast cancer. However, clinical trials suggest that indications for use may be much broader, taking into consideration the fact that non-pegylated liposomal doxorubicin, compared to classical doxorubicin in adjuvant therapy, has been proven very beneficial in combination with e.g. herceptin and docetaxel [9]. Below we present a case of a patient in whom non-pegylated doxorubicin was administered for metastatic breast cancer, which allowed for significant regression of liver metastases.

CASE PRESENTATION

In February 2015, a 55-year-old female patient, treated hormonally for metastatic breast cancer, reported to the Department of Chemotherapy for imaging tests to be performed in order to assess the treatment efficacy.

In 2004, the patient was diagnosed with right breast cancer. The clinical stage of the disease was determined as cT2N1M0. Under immunohistochemistry, an over 75% expression of oestrogen and progesterone receptors was reported as well as the HER-2-negative status. The Ki67 proliferation index was not determined, as the test was not routinely performed. The patient underwent radical surgical treatment, including mastectomy and right-sided axillary lymph node dissection. The histopathological report included the diagnosis of G2 ductal carcinoma, today corresponding to the description of "infiltrating cancer of no special type" (NST), staged as pT2N1 in accordance with the 7th edition of the UICC classification, i.e. stage IIB breast cancer. Repeated immunochemical test confirmed the presence of oestrogen and progesterone receptors, and the HER-2-negative status. Subsequently, adjuvant chemotherapy was administered (6 courses of CMF) and a 5-year-long tamoxifen hormone therapy.

In 2010, during a regular follow-up visit, a reddened and thickened skin was observed at the post-operative scar site, which later turned out to be a local recurrence. Thanks to the chest and abdomen CT, the presence of metastatic lesions was excluded; radical resection was performed, followed by radiotherapy. The treatment was made complete with non-steroid aromatase inhibitors.

Letrozole treatment was continued until November 2012. Follow-up CT, performed at that time, revealed an enlarged (18 mm) mediastinal lymph node, and small non-measurable (up to 5 mm) liver lesions whose nature was most probably metastatic. Dissemination of neoplastic disease was diagnosed, and third-line hormonal therapy was applied, involving fulvestrant dosed at 250 mg initially, later followed by the 500 mg dose. The patient tolerated the treatment very well and the metastatic lesions stabilized, which made it possible to continue the hormonal therapy until February 2015. It was in February 2015 that the patient's general condition slightly deteriorated. Previously, her ECOG performance status had been assessed as 0, and it progressed to 1 in February. The physical examination revealed an enlarged liver

and convex lesions, most probably of neoplastic character, in the region of the post-mastectomy scar. Repeated biopsy confirmed the presence of neoplastic cells in the scar. Apart from that, no abnormalities were found. Lab test results, including haematology and biochemistry, assessing the liver and kidney functions, revealed no abnormalities either. Scintigraphy did not show any metastatic lesions within the skeleton. The Ca 15-3 marker was within the normal range. However, CT revealed a significant progression of the liver metastases, with the largest lesions, determined as the target ones, sized 46 mm and 26 mm. The patient did not give her consent to liver biopsy, which is why breast cancer dissemination progression was diagnosed, and decision was taken to start the patient on cytostatic treatment. As the patient had not been treated with anthracyclines as part of the adjuvant therapy, it was proposed that they be included as a treatment of choice. The patient consented to it and after a positive cardiac assessment (no abnormalities in ECG, with the ejection fraction of 60%), the first AC course was administered (adriamycin + cyclophosphamide). 3 weeks later, the patient reported for another course of chemotherapy. Her haematology tests revealed grade 2 neutropenia, as assessed in accordance with CTCAE 4.1, which is why after the second course of AC, the patient additionally received granulocyte colony-stimulating factors. Before the fifth course of treatment, due to intensified lower extremity oedema, and slightly compromised exertion tolerance, a follow-up Echo test was performed, proving comparable to the one performed at the outset of the treatment. Thus, cardiac and renal background of the lower limb oedema was excluded. Additionally, Doppler ultrasound did not reveal signs of deep vein thrombosis. Following the suggestion of a cardiology specialist, diuretic treatment was initiated, leading to a reduction in the intensity of the oedema. Follow-up CT was also performed, indicating partial regression of the liver lesions (lesion no. 1 – 23 mm, lesion no. 2 – 13 mm), and a non-measurable mediastinal lymph node (< 10 mm in short axis).

Due to a very good therapeutic effect, further anthracycline treatment was offered to the patient, but in the form of non-pegylated liposomal doxorubicin this time. Following 4 treatment courses, the levels of transaminases were slightly elevated – ALT 80 U/l, AST 75 U/l – corresponding to a grade 1 increase according to CTCAE v. 4.03. Abdominal CT was performed at that point, revealing further regression of the liver metastases (the target lesions were assessed as non-measurable, and additionally there was complete regression of some of the neoplastic foci). Ornithin aspartate was administered as adjunctive treatment, combined with a liver-protective diet, resulting in the normalization of the transaminases during the 6th course of chemotherapy.

Presently, the patient has undergone 6 courses of chemotherapy (total anthracycline dose of 600 mg/m^2), with good treatment tolerance, normal results of the Echo test performed every 3 weeks, no abnormalities in laboratory tests, and no skin reactions associated with the pegylated form of doxorubicin. During the therapy, it was not necessary to administer G-CSF. Doxorubicin therapy will now be continued to reach the total dose of 1260 mg/m^2, with cardiac assessment and an Echo test performed with every administration of the drug.

DISCUSSION

The case described above involves a breast cancer patient, in whom dissemination of neoplastic disease occurred 8 years after primary treatment. Due to the high expression of oestrogen and progesterone receptors, and no symptomatic or massive metastases in the parenchymal organs, hormonal therapy was successfully continued for 3 years. Afterwards, disease progression (involving the liver) exhausted the possibilities of hormonal therapy, and as everolimus could not be used [10, 11], the patient was started on cytostatics. There are no unequivocal indications as to the type of chemotherapy that should be administered for metastatic disease in the first and consecutive lines of the treatment. It goes without saying, though, that when selecting an individual cytostatic, one should take into consideration the patient's general condition, organ competence, prior treatment, and patient preferences [11]. Anthracyclines are one of the high-activity drugs in breast cancer, and as such should be considered for first-line chemotherapy [11, 12]. As there were no contraindications in our patient, no cardiovascular conditions, and anthracyclines had not been previously administered as part of the adjuvant chemotherapy, it was decided to include them at a further stage of treatment. Initially, the classical form of doxorubicin was administered in combination with cyclophosphamide, reaching a relatively safe dose of 240 mg/m^2. The good therapeutic outcome along with the risk of cardiotoxicity resulted in the continuation of anthracycline treatment in the form of non-pegylated liposomal doxorubicin. The non-pegylated form of liposomal doxorubicin shows a comparable therapeutic effect while its cardiotoxicity is lower [13].

Liposomal doxorubicin makes it possible to prolong the treatment and receive the best possible response. The total dose of liposomal doxorubicin, including the previously administered anthracyclines, amounts to 1260 mg/m^2 [14]. Thus, with good general treatment tolerance, good systolic heart function, and good response confirmed by imaging tests, this form of treatment can be continued for around a year. To date, the patient has received 600 mg/m^2 of doxorubicin, which allows her to continue

the therapy, providing her condition is followed up on closely. The patient has tolerated the treatment well so far. There have been no episodes of neutropenia, like the ones reported during the previous treatment regimes. One should pay attention to the elevated liver enzymes, though, following the 4th course of treatment. We should bear in mind that the drug is metabolized by the liver, and that apart from cardiac assessment, performed before every consecutive treatment course, liver function should also be closely monitored once the total dose of 550 mg/m^2 has been reached. In summary, liposomal doxorubicin made it possible for the patient to continue the treatment with a class of drugs whose efficacy is undebatable, with a hope to improve the overall effectiveness of further therapy.

CONCLUSIONS

1. Liposomal doxorubicin is a possible therapeutic option for first-line treatment of metastatic breast cancer.
2. Due to the fact that liposomal doxorubicin does not penetrate the walls of healthy capillaries and only the abnormally functioning vessels feeding the tumour, its affinity to the neoplasm is much higher than to the healthy tissue, including cardiomyocytes. Hence, its cardiotoxicity profile is more favourable than of the classical form of the drug.
3. When administering liposomal doxorubicin, cardiac competence should be closely monitored.
4. When administering liposomal doxorubicin, one should remember that the drug is metabolized by the liver, whose function should thus be monitored, with the dose of the drug reduced in case of liver insufficiency.

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