Administration of liposomal doxorubicin in patients with metastatic breast cancer and significant concomitant cardiovascular conditions

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ABSTRACT

A frequent dilemma faced by an oncologist about to take decision on a chemotherapeutic regime for patients with metastatic breast cancer is how to maintain balance between the expected treatment efficacy and predictable adverse events. In the case of anthracyclines what is problematic is their significant cardiotoxicity, in particular with reference to patients previously treated with them as part of adjuvant therapy. A relatively new method is replacement of conventional doxorubicin with its non-pegylated form, encapsulated in liposomes, which is capable of minimizing the side effects without compromising its therapeutic index.

The present article discusses three cases of patients treated with non-pegylated liposomal doxorubicin (NPLD) as first-line chemotherapy administered for metastatic breast cancer. In all three cases considerable clinical improvement was observed, involving remission of pathological lesions and good quality of life.

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

INTRODUCTION

Treatment of metastatic breast cancer is still a challenge for oncologists, and selecting an adequate therapeutic regimen, suited to an individual case, and to the stage of disease, is never easy. Efficacy of anthracyclines, both as adjunctive treatment and as metastatic disease therapy, has been proven in clinical trials as well as in the everyday clinical settings. In metastatic breast cancer, their impact on progression free survival as well as total patient survival is unquestionable. Unfortunately, the choice of anthracyclines often involves a dilemma related to their cardiotoxicity. Some of the most serious complications of anthracycline-based chemotherapy include congestive heart failure. When the classical form of adriblastine is administered, congestive heart failure can develop already at a cumulative dose of 300 mg/m^2, and the higher the dose, the greater the risk of cardiovascular complications. Hence, re-administration of anthracycline in women who have already been exposed to it asa part of adjuvant treatment is frequently called into question. As a result of it, some of the patients are deprived of the potentially most efficacious type of chemotherapy.

A relatively new solution for patients with metastatic breast cancer is non-pegylated liposomal doxorubicin (NLPD), designed in order to reduce toxicity related to its conventional form, while maintaining the same level of efficacy. Both of the objectives have been met, as confirmed by randomized clinical trials.

The present article discusses three clinical cases of patients with metastatic breast cancer, subjected to non-pegylated liposomal doxorubicin combined with cyclophosphamide during the first metastatic attack. Therapeutic effect of the regimen has been satisfactory in all three cases, and the related toxicity has not resulted in the necessity to discontinue treatment or reduce the dose of the cytostatic drugs involved.

CASE 1

A 64-year-old woman was admitted to the Department of Chemotherapy within the Regional Oncology Centre in Lodz in July 2012, having been diagnosed with metastatic breast cancer. In June 2003, she underwent Patey's mastectomy with lymphadenectomy. Baseline histopathological examination revealed a 2.7 × 2.5 × 2 cm lesion, containing cells of invasive ductal carcinoma (G3). During the surgery, 11 lymph nodes were dissected, confirming the presence of neoplastic tissue, infiltrating the capsule and the perinodular fatty tissue, with the maximum lymph node metastasis size of 1 cm. Moreover, neoplastic cellular embolisms were observed in blood vessels. In accordance with the TNM system, the tumour was staged as pT2N3aM0 = IIIC. The cancer was defined as hormone receptor positive, without HER-2 receptor overexpression, though.

At the turn of 2003 and 2004, the patient received adjunctive chemotherapy involving 4 cycles of adriblastine (240 mg/m^2 in total) with endoxan in the AC regimen. Subsequently, sequential hormonal therapy was administered with the patient on tamoxifene for 2 years, followed by aromatase inhibitor (atrozole) for the next 2. The therapy was completed in 2008, and for the following 4 years the patient was followed up by the Oncology Clinic. In April 2012, the patient reported at the physician in charge, complaining of coughing episodes, dyspnea, fatigue, and a loss of 5 kg of body mass within the period of 2 months. Prior to the appointment, she was treated with two lines of antibiotics to no avail. One of the additional symptoms reported was moderate thoracic spine pain, which was believed to be linked to an ongoing degenerative disease.

Imaging tests were performed in order to examine the possibility of metastatic disease. Chest X-ray did not reveal any pathological lesions, whereas the CT examination revealed numerous metastatic lesions in the lungs, whose size was up to 26 mm, as well as enlarged periaortic lymph nodes. The neoplastic process did not yet involve parenchymatous organs in the abdominal cavity. Additionally, spine X-ray demonstrated numerous solid metastatic lesions, located chiefly in the thoracic segment. As the patient's pain exacerbated, thoracic spine radiotherapy was applied (Th 9–Th 11), dosed up to 30.0 Gy, as well as S1–S2 radiotherapy dosed at a maximum of 30.0 Gy. Bisphosphonate treatment was also included (intravenous infusion of pamidronate dosed at 60 mg every 21 days).

When taking decision on first-line chemotherapy for metastatic breast cancer, the patient's condition was defined as moderate. She reported periodically worsening respiratory system symptoms as well as considerable fatigue. She was also diagnosed with concomitant clinically significant diseases, including hypothyroidism, in euthyroid state, second degree arterial hypertension, diabetes managed with oral medications, and *vitiligo*.

The patient was initially qualified for chemotherapy involving liposomal doxorubicin (60 mg/m^2; BSA 1.78 = 107.13 mg) with cyclophosphamide (600 mg/m^2 = 1071.72 mg). As the patient's cardiovascular competence was confirmed (normal ECG, EF of 63% under Echo, normal systolic and diastolic function of both ventricles), the consulting cardiologist didn't see any reason why the patient should not be treated with anthracycline yet again. The first cycle was administered in June 2012. No allergy reactions were observed during the infusion.

Following the second cycle, there was a severe inflammation of forearm veins accompanied by an elevated D-dimer level (4.45 μg/ml), which resulted in the administration of systemic antibiotics, anti-inflammatory and anti-thrombotic drugs. The patient was referred for arterial port-catheter implantation in order to spare her peripheral veins. In consequence, the break between the second and third cycle was prolonged by nearly 14 days.

Before the fourth cycle of chemotherapy, at the beginning of 2012, a CT examination was performed, revealing partial remission of pathological lesions. The previously described increased interstitial density in both lungs, diagnosed as lung tissue metastases, were hardly to be seen in the follow-up examination. No new *foci* were observed. As regards the skeleton, on the other hand, the test revealed disseminated calcified metastatic lesions in regression. Moreover, the patient's general condition improved, her pain was alleviated, and that in turn translated into greater mobility and self-sufficiency of the patient.

After the fourth infusion cycle (November 2012), imaging tests revealed a sustained positive response to treatment, with CT scans virtually identical to the previous ones. Due to the good treatment tolerance, and sustained normal function of the cardiac muscle (echocardiogram revealing no ejection fraction changes – EF 64%), ECG revealing no rhythm abnormalities or ischemic lesions, and no other organ toxicities (with normal liver functions, including AST, ALT and bilirubin levels, and normal kidney parameters such as urea and creatinine), it was decided that cytostatic treatment should be continued up to 10 therapeutic cycles.

In January 2013, chemotherapy was completed. The patient received a total of 600 mg/m^2 (1071.3 mg) of liposomal doxorubicin. After the completion of the above mentioned period of treatment, CT revealed small, under 5 mm large hyperdense lesions in the lungs (nearly complete remission), and calcifying bone lesions. The treatment was discontinued for safety reasons, bearing in mind the potential cardiotoxicity of high doses of anthracyclines, regardless of the liposomal form, even though based on literature data and results of clinical trials, the patient could have received twice the total dose administered (1250/m^2), without compromising her safety.

Starting in January 2013, the patient began hormonal therapy involving exemestane dosed at 25 mg daily. Infusion of pamidronate, diluted on grounds of recurrent hypocalcaemia to 60 mg every 28 days, was continued in an outpatient setting. The patient's general condition remained good, with the patient reporting no significant symptoms or pain. Her cardiovascular function was normal, with the ejection fraction within norm (60–68% depending on the date of examination), and no clinically significant ECG abnormalities. The patient remained active, and the therapy had no negative impact on her perceived quality of life.

In December 2013, nearly 12 months after the discontinuation of cytostatic infusions, the patient reported to her attending doctor with concentration and memory disturbances, period episodes of nausea, and vertigo. Motor ataxia and wide-based gait was observed. As the symptoms suggested possible CNS abnormalities, the patient was referred for head CT. The examination revealed two *foci* in cerebellum, which could be interpreted as metastases. The bigger 31 × 27 mm solid-cyst lesion was located in the right cerebellum hemisphere. Its solid component enhanced upon contrast administration. In the left cerebellum hemisphere, a smaller 12-mm large solid focus was observed, which homogenously enhanced upon contrast injection. The lesions were surround by peritumoral oedema. No lesions involving parenchymatous organs were revealed, and there was sustained remission in the lungs. The patient had not undergone prior brain imaging, as there had been no symptoms suggestive of CNS metastases.

Following neurosurgical consultation, the patient was not qualified for surgery due to the location of the lesions. Palliative brain radiotherapy was proposed, involving a total dose of 30 Gy, administered in 10 fractions, 3 Gy each. After the completion of radiotherapy, the patient was expected to report at the Department of Chemotherapy in order to be qualified for another cytostatic line of treatment.

In January 2014, the patient received 6 fractions (18 Gy) of radiotherapy. During the seventh fraction, she failed to attend the visit scheduled. Multiple attempts at contacting the patient herself or her family were made, proving ineffective. Later on, it was revealed that the patient had been hospitalized in a neurology department due to impaired consciousness, and she had died there towards the end of January 2014 with symptoms of brain oedema.

When analysing the patient's course of disease, it should be observed that one cannot verify it beyond any doubt, whether the CNS metastases were already there, in asymptomatic form, during the liposomal doxorubicin treatment, or whether they only developed in the course of the hormonal therapy which followed. However, the rapidly progressing neurological symptoms, which resulted in the patient's death, might prompt one to suspect a highly aggressive clone of neoplastic cells resistant to the treatment administered.

The above presented description of a clinical case of metastatic breast cancer confirms the possibility of achieving objective response thanks to a cytotoxic regimen based on liposomal doxorubicin. The patient described was in nearly complete

16-month-long remission as regards the lung lesions, which was accompanied by stabilized bone lesions. Along with the positive response as documented in the imaging tests, the patient's general condition was significantly improved. Regression of the respiratory symptoms was observed, which previously rendered the patient's every-day life difficult, and she no longer complained about her back pain. For 12 months following the completed anthracycline treatment, in the course of the hormonal therapy, the patient remained active and self-sufficient, with no need to resort to the assistance of other people, and her quality of life considerably improved. Even if one takes into account the later fatal development of her cancer, that period of life, which the patient lived through with no substantial "sense of disease", cannot be overestimated.

CASE 2

A 56-year-old woman was admitted to the Department of Chemotherapy within the Regional Oncology Centre in Lodz in December 2013, having been diagnosed with metastatic breast cancer. In June 2010, she underwent Madden's mastectomy with lymph node dissection. Baseline histopathology revealed cells of infiltrating ductal carcinoma (G3), with the maximum lesion size of 4.5 cm. Metastases were confirmed in 2 out of the 7 lymph nodes dissected, sized up to 11 mm. According to TNM, the tumour advancement stage was pT2N1aM0 = IIB. The cancer manifested high hormone receptor expression (ER 90%, PR 90%), without HER-2 receptor overexpression.

Adjuvant treatment was administered involving chemo- and radiotherapy, followed by tamoxifen hormonal therapy. Regardless of the patient's relatively young age, 6 CMF cycles were administered as part of adjuvant treatment due to her positive cardiovascular history, as presented below.

The patient, with positive family history of cardiovascular diseases, and exposed to significant stress levels due to her profession, was diagnosed with unstable arterial hypertension and severe complex type IIb hyperlipidaemia at the age of 35. In 1998, at the age of 41, the patient was urgently hospitalized at the Cardiology Clinic for stenocardiac symptoms, defined as CCS class III/IV. The coronarography procedure performed at the time revealed a critical LAD stenosis, and a 30% RCA stenosis with a tendency for spasms. The patient underwent PTCA, whose outcome was satisfactory, and additionally adequate pharmacological treatment was administered, including, inter alia, calcium channel blockers.

The patient remained under observation. When decisions were taken as to the choice of adjuvant chemotherapy, the Echo test revealed a minor hypokinesis of the infero-posterior wall, with EF of 57%. Upon cardiovascular consultation, it was decided that the administered chemotherapeutic regimen would not include anthracyclines. During the CMF chemotherapy period (August–December 2014), subjective exacerbation of stenocardiac symptoms was reported as well as two episodes of syncope immediately after the intake of nitroglycerine, followed by short-term hospitalization at the Hospital Emergency Department.

Cardiac ultrasound, performed after treatment completion, revealed the ejection fraction that had gone down to 50%. In the period of January 2011–September 2013, the patient was on tamoxifen as adjuvant hormonal therapy. The treatment involved no complications, and the patient remained under continuous cardiovascular follow-up.

In August 2013, the patient reported new lumbosacral pain, associated with fatigue. The symptoms had intensified over the previous 3 months, but the patient would link them to excessive physical activity. Scintigraphy revealed a remarkably increased tracer uptake in thoracolumbar spine as well as in the pelvis, and discreet lesions in the parietotemporal region, *scapulas*, and sternoclavicular joints. The lesions were radiologically confirmed and defined as of mixed, osteolytic and osteosclerotic character. The CT examination additionally revealed two focal lesions in the liver, whose sizes were 20 × 15 mm and 10 × 15 mm, but no lesions involving other parenchymatous organs. Due to the patient's intensified pain, RT was applied in the lumbosacral spine area, bringing about relative improvement.

A series of tests were performed aimed at evaluating the cardiovascular system competence, including ECG, Echo, and the stress test. As the patient's cardiovascular situation was proven to be stable, with EF of 56%, the consulting cardiologist saw no absolute contraindications to anthracycline-based chemotherapy. Once the available patient files have been examined, it was decided that she should be included in a trial of first-line metastatic breast cancer treatment with the use of liposomal doxorubicin, dosed at 60 mg/m^2 (BSA – 1.84 m^2; the patient's calculated dose = 110.78 mg), combined with endoxan dosed at 600 mg/m^2 (1107.78 mg) administered every 21 days. Moreover, therapy oriented on bone lesions was included as part of treatment (60 mg of pamidronate every 21 days). Chemotherapy and bisphosphonate infusions were started in October 2013. No allergy reactions were observed during the drug infusion, but before the first infusion, the patient was prophylactically given antihistamine medications and dexamethasone.

On the date of her third cycle, the patient reported to the attending physician with a fever nearing 38°C, lasting for several days, without symptoms of cough, *rhinitis* or any other signs of infec-

tion. Under auscultation, no signs of active inflammation were revealed over the bronchial tree. Complete blood count revealed 2nd degree neutropenia (WBC – 2.1 × 1000/µl, neutrocytes 1.1 × 1000/µl).

Cardiac activity was regular, with normocardia (HR of 85/min), normotension (RR 140/85), and no clinical signs of circulatory insufficiency or stasis in peripheral blood vessels. Oral antibiotic therapy was included (500 mg ciprofloxacin every 12 hours for 5 days) in outpatient setting, and the chemotherapy cycle was delayed by 7 days. Neutropenic incidents did not recur during the therapy that followed, and there was no need to reduce the dose of cytostatics.

After the fourth cycle (January 2014), follow-up CT revealed complete remission of the liver lesions. The patient's condition was largely improved, and the pain subsided.

The Echo examination did not demonstrate a significant decrease in the ejection fraction (EF 52%), but only minor incompetence of the heart valves, which had previously been identified. ECG revealed no cardiac rhythm abnormalities or new ischaemic lesions. Liver function tests (AST, ALT, bilirubin) and kidney parameters (*urea*, creatinine) were within norm. Therefore, it was decided to continue treatment up to 6 cycles.

Tests performed upon the completion of liposomal doxorubicin treatment (March 2014) revealed sustained remission of the abdominal parenchymatous lesions, with the bone lesions identified under scintigraphy demonstrating a comparable tracer uptake, and without any new disease *foci*. Results of the Echo and ECG examinations were comparable to the prior ones.

The patient was qualified to second line hormonal therapy involving aromatase inhibitor (atrozole). Bisphosphonate infusions were continued, with pamidronate replaced with zoledronate dosed at 4 mg every 28 days for reimbursement reasons.

The patient continues the treatment to this day (September 2014). No objective signs of disease progression have been reported. According to the imaging tests, the previously achieved positive therapeutic result has been sustained, and the patient has not reported any complaints related to the advanced neoplastic process or the concomitant cardiovascular diseases. She remains under follow-up of the oncology and cardiology clinics. The patient leads an active lifestyle, and has returned to professional activity, which she had to interrupt for the period of cytostatic treatment.

To sum up the above clinical case, it should be emphasised that the patient, regardless of the positive cardiovascular history, has safely completed chemotherapy based on liposomal doxorubicin. Hence, she had the opportunity to undergo adequate first -line treatment for metastatic breast cancer, whose efficacy has been confirmed in randomized clinical trials. It is all the more important, taking into consideration the fact that suboptimum adjunctive treatment, which was initially administered for fear of the potential adverse effects stemming from standard therapy involving "classical" anthracycline, might have contributed to further neoplastic dissemination.

Thanks to the administration of liposomal doxorubicin, remission of the liver lesions was observed, and the bone lesions stabilized. Positive response to treatment has lasted for around 5 months now. Moreover, the treatment had no negative impact on the patient's perceived quality of life. Quite to the contrary, her subjective quality of life has clearly improved, which is reflected in the follow-up tests performed at the oncology centre.

CASE 3

A 65-year-old patient reported at the Oncology Clinic of the Regional Oncology Centre in May 2013 due to reddening and localised pain in the quadrantectomy scar. Physical examination revealed swollen, hard and painful remaining breast parenchyma, whose colour was changed. It was tender on palpation. Judging by the look of it, the lesion resembled inflammatory breast cancer.

The patient consulted specialists at the surgery clinic several time, with attempts made at verifying the nature of the lesion. Fine needle biopsy was performed, revealing no neoplastic cells in the aspired material. Hence, the decision was made to harvest a surgical specimen. The histopathological examination revealed an inflammatory infiltration with numerous lymphocytes and adipose cells. The neoplastic character of the lesion was not confirmed. The patient was additionally consulted by a radiotherapist, and the lesion was interpreted as a reaction to prior irradiation.

The patient's oncological case history was analysed. In July 2009, she was diagnosed with right breast ductal cancer. The tumour, located in the superior internal quadrant, was detected during a screening mammography test. Ultrasound-guided fine needle aspiration biopsy of a 23 × 15 mm lesion (BIRADS 4) revealed the presence of neoplastic cells. The patient was offered quadrantectomy with sentinel node biopsy, followed by lymph node dissection due to the positive result of the biopsy.

Histopathological examination determined the stage of disease advancement as G3, according to TNM: pT2N1bMO = IIB (3 involved lymph nodes, metastasis size of around 1 cm). Hormone receptors were positive, with no HER-2 receptor overexpression. The proposed treatment was AC adjuvant chemotherapy. 6 cycles were administered, involving the combined dose of 360 mg/m^2 of adriblastin. Radiotherapy followed.

Adjuvant treatment was completed without major complications. The suspicious breast lesion appeared in the third year of tamoxifen hormonal therapy.

Imaging diagnostics was performed, as metastatic disease was suspected. Chest CT revealed a pathological 65 × 33 mm mass in the mediastinum. Abdominal and pelvic ultrasound as well as bone scintigraphy revealed no other suspicious *foci*. In order to verify the results, and to be able to offer the patient adequate treatment, mediastinoscopy was performed (suspicion of another primary neoplastic process, with the image suggestive of small-cell lung cancer, among others). Adenocarcinoma cells were revealed, which were most probably metastatic and secondary to the breast cancer. The subsequently ordered immunophenotypic profiling unequivocally pointed to breast cancer as the origin of the neoplastic tissue in question.

The patient was qualified for first-line metastatic disease treatment involving liposomal doxorubicin combined with endoxan. The choice of such a combination of cytostatics was possible thanks to the patient's good cardiovascular profile. She did not take any cardiovascular medications, was not treated for arterial hypertension, her ECG revealed no clinically significant abnormalities, and the left ventricle ejection fraction was nearly 70% on Echo examination.

The patient began her chemotherapy in July 2013. She tolerated infusions of both cytostatics very well throughout the treatment, with no signs of hypersensitivity, nausea or emesis, and with all the laboratory parameters within norm. The therapeutic regimen was adhered to, with no need to delay cycles or reduce the dose of the cytostatics. Following the third cycle, chest CT revealed partial remission according to RECIST. The size of the lesion went down by over 50% to 25 × 14 mm. No new metastatic lesions were detected. The breast tissue infiltration seemed softer, even though there was no distinct difference in appearance. The patient's general condition was good. She reported no coughing, haemoptysis or dyspnea episodes, and no compromised exercise tolerance, but even before the treatment, there were no clinically significant symptoms involving the patient's respiratory system.

Cytostatic therapy was continued, and in December 2013, following the fifth cycle of myocet with endoxan, a considerable change was noted in physical examination with reference to the breast under observation. The infiltration subsided, with the reddening and oedema nearly completely gone, the skin temperature normal, and breast parechyma soft on palpation, comparable to the contralateral healthy breast. For lack of significant cardiovascular symptoms, and because of a clearly beneficial therapeutic effect, it was decided that the patient continue cytostatic treatment.

The patient kept receiving liposomal doxorubicin and endoxan infusions until April 2014, with 10 cycles altogether. A CT examination performed after the tenth cycle revealed minor fibroses in the right lung, most probably a result of prior radiotherapy, and a lack of pathological tissue mass in the mediastinum and hila, with no adenopathy. No neoplastic *foci* were observed within the abdominal cavity or the retroperitoneal space. There were no changes in lumbar and sacral spine X-ray examination either. Thus, one can claim that the result of the treatment administered has been complete remission of the local and mediastinal pathological lesions.

In May 2014, upon the completion of first line metastatic disease chemotherapy, the patient was qualified for aromatase inhibitor (atrozole) hormonal therapy. The patient's general condition has been very good, without significant symptoms of cancer disease, and with full cardiovascular competence. She now remains under follow-up of the chemotherapy clinic. The positive response to treatment has persisted, as confirmed in a CT examination of September 2014.

The above case description confirms the efficacy of chemotherapy based on liposomal doxorubicin both with reference to the mediastinum metastasis, and to the local infiltration in the remaining post-BCT breast parenchyma. The patient was offered the possibility of repeated anthracycline treatment without the risk of cardiovascular complications. The treatment has proved efficacious and well-tolerated by the patient. Thanks to the response made evident in the imaging tests performed as well as in the patient's clinical improvement, involving regression of the respiratory system lesions, the patient could go back to hormonal therapy, without the need to undergo a yet another line of cytostatic treatment. It is of great significance, as it makes it possible to administer active cytostatics to the patient in the case of a new episode of neoplastic disease progression. Moreover, no need of being hospitalized and receiving intravenous infusions in a hospital setting of the chemotherapy department is something which has a positive impact on how patients perceive their quality of life, which is of paramount importance in the context of systemic palliative treatment, often conditioning the sense of the treatment as such.

DISCUSSION

Treatment involving non-pegylated liposomal doxorubicin is a valuable therapeutic strategy in patients suffering from metastatic breast cancer. Beneficial results have been observed both in the patients in whom anthracycline was used for the first time as well as in those who had already been treated with a conven-

tional form of the chemotherapeutic drug as part of adjunctive treatment. As a result of the NPLD therapy, the size of the lesions detected in the organs involved decreased, as confirmed in the imaging tests evaluated in accordance with the RECIST criteria. Objective clinical response was additionally associated with the patients' subjective improvement in the quality of life. In the above mentioned cases, there were no signs of cardiovascular toxicity, resulting in dose reduction or cessation of treatment.

Based on the above mentioned case studies as well as on the analysis of the available literature, one can conclude that administration of NPLD in metastatic breast cancer is by all means legitimate. The treatment fulfils the hopes pinned on it both in terms of its efficacy, safety, and patient tolerance. One can even go as far as to say that liposomal doxorubicin is an important step forward, making it possible to administer a well-known and efficacious chemotherapeutic to those patients in whose case its application used to be controversial due to the significant risk of cardiotoxicity.

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