Therapy with liposomal doxorubicin in patients with advanced breast cancer after treatment with classical doxorubicin

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Received: 11.05.2015. Accepted: 16.09.2015.

ABSTRACT

Breast cancer is the most common female cancer in the world and in Poland. The improvement of diagnostic and therapeutic methods has led to patients' longer life expectancy. It has also made breast cancer a chronic disease, increasing the risk of late side effects of oncological therapy. More cardiovascular diseases are diagnose in patients over 65 with an oncological history than in those without it and therefore much effort must be made to maximise effectiveness of the therapy with as few side effects as possible. The article presents two breast cancer patients treated with big doses of liposomal doxorubicin with a good response and almost no side effects.

KEY WORDS: breast cancer, non-pegylated liposomal doxorubicin, complications of oncological therapy

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INTRODUCTION

Breast cancer is the most frequent women's tumor in the world. In 2012, there were 1,676,000 new breast cancer cases reported worldwide and 17,000 in Poland [1].

Owing to mammographic screening and women's growing awareness, cancer is more and more often diagnosed at early stages. Surgery constitutes the basic form of early breast cancer treatment. Adjuvant therapy (chemotherapy, radiotherapy, endocrine therapy, targeted therapy) aims at decreasing the risk of cancer recurrence and prolongation of overall survival [3].

Sensitive and specific diagnostic methods as well as more and more effective therapies have resulted in breast cancer's becoming a chronic disease; the number of survivors living for years after they have been diagnosed with cancer is constantly growing. However, overall survival is connected with an increased risk of late complications of oncological treatment. Postmenopausal breast cancer patients are more often diagnosed with circulatory system diseases than their age peers never treated oncologically [2].

Drugs with cardiotoxic potential used in breast cancer treatment include anthracyclines, i.e. cytostatics administered both in early and in advanced breast cancer stages, and trastuzumab – a monoclonal human antibody inhibiting HER2 receptor via blocking HER2 receptor dimerisation with another receptor from the epidermal growth factor receptor family (EGFR). Due to their high therapeutic efficacy, it has not been possible to replace them with any other specifics of a less toxic profile.

Anthracyclines can cause type I (irreversible) cardiotoxicity dependent on the cumulative dose and resulting in permanent changes in cardiomyocyte structure [4]. Trastuzumab, on the other hand, blocking HER2 receptor on the neoplastic cell membrane as well as on the cardiomyocyte membrane, disturbs their function, which is manifested by a lower left ventricular ejection fraction (LVEF). Left ventricular systolic dysfunction, caused by trastuzumab, is most often reversible and asymptomatic, does not depend on the cumulative dose but rather on the patient's general health status, her habits, concomitant diseases and oncological treatment initiated earlier [5]. With follow-up duration time, there is an increased risk of late cardiological complications that can manifest themselves more than one year after discontinuation of the oncological treatment.

CASE 1

Patient with advanced breast cancer treated with liposomal doxorubicin after earlier adjuvant classical doxorubicin-based therapy.

The case presents the medical history of a 38-year-old patient who was diagnosed with left breast cancer in 2012. In January 2014, she reported at the chemotherapy outpatient clinic with increasing dyspnea, cough and decreased effort tolerance. Her general practitioner recommended an antibiotic (amoxicillin with clavulanic acid) with no effect. A chest X-ray was performed and revealed the presence of fluid in the left pleural cavity at the level of the 7th rib.

In June 2012, during a gynecological visit (11th gestational week) the doctor palpated her breast and noted a hard lump (ca. 1 cm) in the upper external left breast quadrant. That is why the patient was urgently referred to an oncological surgeon. During a consultation at the Greater Poland Cancer Center, ultrasound of her breasts and axillary lymph nodes was performed. The examination confirmed the presence of a malignant tumor measuring 11 × 13 × 10 mm in her left breast; bilaterally there were no lymph nodes involved. A core biopsy of the lesion was carried out. A histopathological examination confirmed the presence of invasive ductal cancer cells with overexpression of estrogen and progesterone receptors, no HER2 receptor overexpression, and Ki-67 proliferation marker of 70%. The results were helpful in labeling the cancer as luminal B.

The patient was informed about the nature of the neoplastic disease and treatment options in breast cancer during pregnancy. The subsequent abdominal ultrasound examination did not show any significant abnormalities and laboratory tests confirmed normal function of the liver and kidneys. Because of her young age, the patient was referred to genetic counseling. In the 14th week of normal gestation she underwent a surgery: simple left-side mastectomy and sentinel lymph node biopsy using technetium. An intraoperational histopathological examination showed no cancer cells in the sentinel node removed. The postoperative course was smooth and the patient was discharged on the 7th day in a generally good condition. Postoperative histopathological tests revealed the presence of invasive ductal cancer, 10 × 15 × 12 mm in size, manifesting steroid receptors overexpression, Ki-67 of 70% and no metastases in the sentinel lymph node.

In the 17th week of gestation, the patient started adjuvant treatment with chemotherapy (4 × AC doxorubicin 60 mg/m^2,

cyclophosphamide 600 mg/m² iv. every 21 days). The patient manifested fairly good tolerance, there were no serious side effects, she received full doses at times set. The treatment was discontinued in the 26th week and further treatment called for endocrine therapy after delivery. The patient delivered naturally in the 39th week. The newborn was a healthy girl weighing 3250 g. Immediately after birth and 5 and 15 minutes later she scored 10 points on the Apgar scale.

As of February 2013, the patient was put on tamoxifen and leuprorelin. There were no mutations in the BRCA1 gene.

About 10 months later, the patient experienced increasing weakness, which she attributed to the baby care. When cough and periodically increasing dyspnea appeared, she visited her general practitioner who diagnosed pneumonia and initiated antibiotic therapy. However, due to ineffective antibacterial treatment and the presence of fluid in the left pleural cavity, revealed by a chest X-ray, she was referred to an oncologist who recommended laboratory tests, abdominal ultrasound and a chest CT scan. The most noticeable result was a high concentration of CA 15-3 marker > 300 U/ml (normal value < 30 U/ml). Physical examination revealed enlarged lymph nodes in the left axilla. A core biopsy of those lymph nodes was performed. A month later the patient reported again with the CT scan results that showed small lump metastases in both lungs, the presence of liquid in the left pleural cavity and enlarged lymph nodes in the left lung hilus (up to 18 mm). Histopathology results were the same as the 2012 postoperative results (ER+, PgR+, HER2-negative, Ki-67 70%).

Since targeted therapy was excluded, the patient was given liposomal doxorubicin at a dose of 60 mg/m² iv. every 21 days. Prior to that, echocardiography was carried out: LVEF of 65%, there was no systolic or diastolic dysfunction of the left ventricle. Before the 3rd chemotherapy course, a follow-up chest X-ray was done: the liquid volume in the left pleural cavity was reduced. The patient experienced general health improvement. Exertion tolerance increased and cough was only sporadic. The CA 15-3 marker value fell to 140 U/ml. Owing to good tolerance and treatment efficacy, liposomal doxorubicin administration was continued. After another 2 courses (after the 4th course) a chest CT scan was performed which confirmed general image improvement observed on the X-ray examination; the marker fell to 107 U/ml and the patient reported no disturbing complaints.

After the 6th chemotherapy course, echocardiography was carried out. The patient received 4 courses of conventional doxorubicin in combination with cyclophosphamide as adjuvant therapy (240 mg/m²) and 6 courses of non-pegylated liposomal doxorubicin as palliative therapy (360 mg/m²). Since LVEF did not decrease and was of 65%, there were no systolic and diastolic dysfunctions and the patient responded very well to the therapy, a decision to continue the therapy was taken on condition that follow-up echocardiography should be performed before each consecutive chemotherapy course.

After another 2 administrations, the chest CT scan was repeated: the examination confirmed complete metastatic regression and absence of fluid in the pleural cavities. The CA 15-3 marker values returned to normal and the patient did not complain of respiratory problems.

The patient consented to another 4 courses of liposomal doxorubicin, after which she planned a several-month-long holiday abroad. During the therapy, there were no cardiological complications, LVEF after treatment was of 60%, all courses were at planned time and the doses were never reduced. The patient did not have troponin and BNP tests, or strain echocardiography performed.

For the adjuvant treatment, the patient received 4 courses of classical doxorubicin (240 mg/m²) followed by 12 courses of non-pegylated liposomal doxorubicin (720 mg/m²) in palliative therapy, altogether – 960 mg/m². Neoplastic changes regressed completely before the maximal cumulative dose of liposomal doxorubicin was reached (1260 mg/m²), above which the risk of cardiotoxicity increases significantly [6].

Breast cancer in pregnancy is a malignancy diagnosed during pregnancy or within 12 months after its termination. More frequently than in older women, the malignancy is genetically determined [7].

Pregnancy does not worsen patients' prognoses and breast cancer therapy in pregnancy does not differ much from that of non-pregnant patients. The basic limitation is the time of therapy initiation: optimally, it is the second gestational trimester due to foetal organogenesis that occurs during the first weeks of gestation and an absolute ban on endocrine and trastuzumab therapy throughout pregnancy [7]. Because of breast cancer patients' young age and sometimes long-lasting overall survival rates, one can expect (at least in some of them) late complications after oncological therapy. Therefore, every effort must be made to protect the circulatory system from cardiotoxic side effects. In the case of the patient with advanced breast cancer presented in this ar-

ticle, the use of large anthracycline doses was connected with a positive response to the therapy and lack of serious side effects thanks to close monitoring of therapeutic safety. All complaints impairing the patient's life comfort disappeared, which allowed for normal functioning and discontinuation of treatment.

CASE 2

Patient with advanced HER2-positive breast cancer treated with liposomal doxorubicin after classical doxorubicin therapy discontinuation due to cardiotoxic side effects

In March 2013, a 67-year-old women, previously (in 2008) treated for right breast cancer, reported to her oncologist. The patient complained of body weight loss (ca. 5 kg within 2 months), general weakness and recurrent pains in the right subcostal region radiating to the back. Until then, she was treated by her general practitioner, who suspected gallstones. Abdominal ultrasound revealed metastases to the liver, so she was referred to an oncologist for further diagnosis and treatment.

In 2008, the patient reported to an oncological surgeon due to a lump detected during breast self-examination. Physical examination revealed a lump, ca. 20 × 30 mm, located behind the right breast nipple, with no pathologically enlarged axillary lymph nodes. Mammography and breast ultrasound examinations were made because of a suspected right breast cancer. Abdominal ultrasound and chest X-ray did not show any significant abnormalities. A biopsy of the lump revealed cells of invasive ductal cancer with an overexpression of estrogen and progesterone receptors (ER, PgR) and no overexpression of HER2 receptor. Intraoperative examination of the sentinel lymph node showed breast cancer metastasis infiltrating the lymph node capsule. Patey`s mastectomy was performed and histopathology results confirmed the diagnosis made via core biopsy. The size of the tumor and lymph nodes invasion was evaluated at pT2N1M0 using the pTNM scale. Cancer cells manifested an overexpression of steroid receptors (ER, PgR) and no HER2 overexpression; lymphovascular tumor emboli were also present. The adjuvant treatment offered consisted of chemotherapy and endocrine therapy. The patient rejected chemotherapy because she was occupationally active and her work required her total commitment; she did agree to daily administration of 1 pill of tamoxifen, which she continued to use until February 2013.

After some time, she visited her oncologist with abdominal ultrasound results that showed uncountable metastases in the liver; she also complained of general weakness, loss of appetite and pains in the lumbar area. Another abdominal ultrasound was made confirming the earlier diagnosis. Also, chest and lumbosacral area X-ray examinations and blood tests were performed. The most noticeable were hepatic tests values (ALAT 40 U/l, ASPAT 55 U/l) and degenerative changes in the lumbar area. An urgent subcapsular metastatic hepatic lesion biopsy was performed. Histopathology results showed breast cancer metastasizing to the liver with an overexpression of steroid and HER2 receptors; the Ki-67 value was of 40%. A comparative analysis of the hepatic biopsy material and preparations from the tumor removed in 2008 showed recurrent cancer.

The patient was put on trastuzumab following earlier anthracyclines and taxanes therapy, after which she consented to chemotherapy. Echocardiography did not show any left ventricle systolic and diastolic dysfunction, LVEF of 65%. After the 2nd AC chemotherapy course (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² iv. every 21 days), she was hospitalized at an internal diseases ward of a regional hospital due to atrial fibrillation (AF), which disappeared after reinstating electrolyte balance. Then the patient had another chemotherapy with a generally good health status. She did not complain of any cardiovascular problems; neither electrocardiography nor echocardiography showed any abnormalities, LVEF of 60%. Owing to a marked clinical improvement, after 2 courses of chemotherapy and an improved abdominal ultrasound picture, therapy with anthracyclines was continued, while classical doxorubicin was substituted for its liposomal form. After another 2 chemotherapy courses, there was a further regression of the metastases in the liver, an improved well-being and an increase in body weight. After 6 liposomal doxorubicin and cyclophosphamide courses, the planned abdominal CT scan showed complete regression of hepatic metastases and normal liver function confirmed by blood tests. The patient then consented to undergo another 4 chemotherapy courses to be followed by endocrine therapy. She received 10 courses of liposomal doxorubicin (600 mg/m²) and 2 courses of classical doxorubicin (120 mg/m²). The tolerance was good and except for AF, there was no cardiotoxicity and the patient was regularly attended to by a cardiologist. Before each chemotherapy course, she had echocardiography done.

For the next 8 months she took letrozole with a good tolerance. In September 2014, she started complaining again of weakness accompanied by dyspnea while climbing stairs. She had an urgent abdominal CT scan, chest X-ray and echocardiography to assess left ventricular systolic function after treatment with large

doses of anthracyclines. The examinations showed the presence of liquid in the right pleural cavity at the 5th costal level, numerous metastases in both lungs and their absence in the liver. Using pleurocentesis, 900 ml of liquid from the right pleural cavity was removed and the patient's condition markedly improved: she stopped complaining of weakness and dyspnea. The patient then agreed to continue the therapy, so she was put on docetaxel at a dose of 100 mg/m² iv. every 21 days. After the first course, she developed neutropenic fever. Two days later, following empirical antibiotic therapy, the fever dropped below 37°C. After another docetaxel course, pegfilgrastim was given prophylactically at a dose of 6 mg sc. Following 4 docetaxel courses, a control chest X-ray was done; it showed partial metastatic regression in the lungs. Abdominal ultrasound revealed previously unobserved 4 hepatic and 2 spleen metastases. At that moment, docetaxel was discontinued and trastuzumab was administered as monotherapy, because the patient did not agree to continue cytostatic treatment.

Before trastuzumab was initiated, LVEF was reassessed: it was of 55% with no abnormalities. The patient's general state was good, she did not complain of any ailments linked to the neoplastic disease.

Currently, the patient is continuing trastuzumab therapy with good tolerance.

What is worth noticing here is the fact that histopathological tests of the primary tumor did not show HER2 overexpression even though it was found in the metastases, which opened up prospects for targeted molecular therapy. Despite AF during classical doxorubicin therapy, no further cardiotoxicities occurred during either liposomal doxorubicin or docetaxel therapy.

DISCUSSION

Liposomal doxorubicin use in patients with advanced breast cancer in first-line therapy may be an effective therapeutic option, particularly in those patients who previously underwent anthracyclines therapy [8]. Owing to its liposomal form, even large doses of this type of doxorubicin (maximal cumulative dose – 1260 mg/m²) significantly lower the risk of cardiotoxcity, more than its classical form, and with a fairly good tolerance [6].

While using liposomal doxorubicin, the doses of all the previously administered anthracyclines should be added up and calculated as a dose of classical doxorubicin. After overextending the cumulative dose of 550 mg/m² of classical doxorubicin, it is necessary to assess the left ventricular function before each consecutive liposomal doxorubicin course [9]. Such an assessment is most often done via echocardiography and, in extraordinary cases, via magnetic resonance imaging (MRI), which is still not commonly available in everyday clinical practice.

CONCLUSIONS

1. In the case of relapse occurring at least 12 months after adjuvant therapy based on anthracycline, it is worth resuming chemotherapy with doxorubicin, this time in its liposomal form.
2. Administration of large doses of liposomal doxorubicin involves a lesser cardiotoxicity risk than in the case of classical doxorubicin.
3. Once the cumulative dose of 550 mg/m² has been overextended, echocardiography must be done before each consecutive liposomal doxorubicin course.

Acknowledgments

Authors report no conflict of interest.

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