ABSTRACT
Breast cancer is the most frequently diagnosed female cancer in Poland (over 17,500 women). Anthracyclines have become one of the most important drugs in breast cancer systemic treatment. In the treatment of metastatic disease combination chemotherapy with doxorubicin provides the objective response rate of 60–85%, and the median time of progression-free survival is about 12 months. Non-pegylated liposomal doxorubicin (NPLD) in combination with cyclophosphamide is associated with a lower risk of cardiotoxicity, higher efficacy and more favourable toxicity profile as compared with conventional anthracycline regimes.

Two cases of females patients treated with NPLD described in this article demonstrate the importance of the choice of chemotherapy, professional monitoring, early detection and treatment of adverse effects. Non-pegylated liposomal doxorubicin ordained in systemic treatment of stage IV breast cancer prolongs survival and enhances the quality of life. It is a reasonable option for palliative therapy.

Key words: breast cancer, non-pegylated liposomal doxorubicin, treatment
INTRODUCTION
Malignant breast cancer is one of the most frequently diagnosed female tumours in Poland (over 17,500 female patients), and is the second cause of death for malignancies in women (ca. 5,000 deaths annually).

The 5-year survival rate in Poland is around 75% at present (while in Scandinavian countries, it amounts to ca. 85%).

Breast cancer incidence has also been on the rise, growing quicker than that of other cancers, though at the same time survival rates have gone up too (still lower in Poland than in most of the EU countries).

70% of Polish patients suffer from hormone-dependent HER2-negative breast cancer, in 30–40% of those treated at early stages of cancer development, there may be disease recurrence and distant metastases, and 5–6% of the breast cancer cases are diagnosed at an advanced stage already.

 Anthracyclines are the main class of drugs administered in systemic breast cancer treatment. Discovered over 50 years ago, anthracycline antibiotics (isolated from *Streptomyces* bacteria) are amongst the most efficacious drugs used in anti-cancer therapy [1].

In the treatment of metastatic disease, multi-drug regimens based on doxorubicin enable remission in 60–85% of the patients, with the mean duration of remission totalling ca. 12 months [2].

The use of conventional anthracyclines is usually burdened with the risk of cardiovascular toxicity. Early and late symptoms of cardiotoxicity emerge in 5–23% of patients. They include reduced physical performance, and progressive signs of heart failure [3, 4]. Extreme cases of heart failure are diagnosed in 2–4% of patients [5].

The risk of toxicity following the administration of doxorubicin is dose-dependent, and amounts to 5% at the cumulative dose of 400 mg/m², increasing to as much as 25% at the dose of 700 mg/m² [6, 7].

In patients with additional risk factors (age < 18 and > 65, concomitant cardiac diseases, e.g. hypertension, left ventricular hypertrophy, coronary heart disease, diabetes, prior radiotherapy), the total dose should not exceed 450 mg/m² [8]. Anthracyclines are successfully used at every stage of breast cancer treatment (neoadjuvant, adjuvant and palliative treatment). It is worth noting that each dose of anthracyclines, no matter how small, may be conducive to the risk of myocardial dysfunction.

Non-pegylated liposomal doxorubicin, approved for use 17 years ago, may be administered, in accordance with the registered indications, in combination with cyclophosphamide as first-line treatment in breast cancer patients with metastases (60–75 mg/m² and 600 mg/m², respectively, every 21 days).

The available clinical data indicate that the use of non-pegylated liposomal doxorubicin (NPLD) in combination with cyclophosphamide in the first-line treatment of metastatic disease significantly reduces the risk of cardiotoxicity (5-fold), is associated with a higher response rate (31% v. 11%) and better treatment tolerance [9, 10].

Using non-pegylated liposomal doxorubicin is well-grounded in patients previously treated with conventional doxorubicin at the dose of at least 200 mg/m² (a higher dose may constitute an additional heart failure risk factor) [11].

The cases presented below, discussing NPLD treatment in 2 patients, are a good example of NPLD use in patients with metastatic breast cancer.

**CASE 1.**
Breast cancer is rarely diagnosed in young patients, i.e. those below the age of 35. Young women constitute ca. 7% of all breast cancer patients. That age group is more likely to include carriers of mutations that increase the risk of breast and ovarian cancer as well as other neoplasms. Management of younger patients is associated with several important issues such as the need to use contraception, efforts made at protecting the patient’s fertility, and adjusting treatment to their professional and family lives.

Prognosis of breast cancer patients is ever better, which is why following anti-cancer therapy one should pay close attention to monitoring late sequelae of treatment, including cardiovascular complications or bone mineralization disorders.

At the beginning of 2016, a young (33-year-old) patient diagnosed with breast cancer, with bone, liver, left lung, cerebellum and pancreatic metastases, was qualified for cytostatic treatment and zoledronic acid. Her general condition was relatively good. For many years, she had suffered for bronchial asthma and depression. She had a family history of cancer: her mother died of...
ovarian cancer, mother’s sister was treated for breast cancer, and her father was treated for colorectal cancer.

The patient’s oncological history went back to 2002, when breast cancer was diagnosed in the then 19-year-old patient, and right-sided mastectomy was performed with axillary lymph node dissection. Histopathology results confirmed the presence of invasive G2 breast cancer (pT1c pN1b) without steroid receptor expression. The patient received 4 courses of AC chemotherapy (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² every 21 days) and adjuvant radiotherapy.

Due to her young age and positive family history, the patient was referred to a genetic clinic, where the basic test was performed, including the BRCA1 and BRCA2 mutations. The test did not reveal the presence of pathogenic mutations. That concluded genetic diagnostics at the time.

Following anti-cancer treatment, the patient was under regular follow-up, and gave birth to 2 healthy daughters.

In 2013, she reported to the chemotherapy clinic for an urgent appointment due to a cough that had persisted for several weeks, and progressive dyspnoea. The necessary diagnostics was carried out, including the history-taking and physical examination, lab tests, chest CT, abdominal ultrasound, and gynaecological examination. Chest CT revealed hilar lymph involvement and left lung tumour. Lab test results confirmed elevated levels of the Ca 15-3 marker, while other tests revealed no significant abnormalities.

Tumour biopsy was performed, confirming breast cancer relapse. Immunohistochemistry panel determined steroid receptor expression and no HER2 receptor overexpression. At that time, the patient received 12 courses of paclitaxel dosed at 80 mg/m² every 7 days, with good treatment tolerance. Thanks to the treatment administered, complete remission was accomplished in chest CT, and the Ca 15-3 marker went down. It was decided to start the patient on tamoxifen as maintenance therapy. The patient stopped menstruating during chemotherapy.

In November 2015, there was another disease recurrence, with a subcutaneous nodule appearing on the patient’s nape. As part of diagnostics, a fine-needle biopsy was performed, confirming a metastatic lesion of hormone-dependent breast cancer. PET-CT was also confirmed, revealing numerous metastatic lesions in the bone, liver, left lung, cerebellum and pancreas. Lab test results demonstrated liver function abnormalities, and a significant increase in the Ca 15-3 marker. In light of a multi-organ crisis, MC chemotherapy was initiated (non-pegylated liposomal doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² every 21 days), and zoledronic acid was administered at a standard dose.

Further diagnostic procedures were performed, focusing on the central nervous system, with brain MRI revealing 3 metastatic lesions. Following neurosurgical consultation, the patient was qualified for surgery. However, due to cardiac rhythm disturbances during anaesthesia, the surgery was aborted. Consequently, in April 2016, the patient underwent palliative brain radiotherapy. Chemotherapy was also continued, leading to partial metabolic response after 7 courses, as demonstrated in PET-CT, and a reduction in the Ca 15-3 concentration.

As the EMBRACA clinical study, dedicated to BRCA1 or BRCA2 mutation carriers, was available at the clinic at the time, participation in the study was offered to the patient. During the pre-screening visit, BRCA1 and BRCA2 gene sequencing test was performed. If the presence of mutations was confirmed, the patient could receive PARP (poly ADP-ribose polymerase) inhibitor treatment, i.e. talazoparib, or another chemotherapy regimen selected by the attending physician. However, no pathogenic mutations were detected in the patient despite her young age and positive family history.

As the patient tolerated the MC chemotherapy well, and the treatment outcomes were as expected, 4 more courses were administered. Follow-up echocardiography was performed before each consecutive course. Throughout the therapy the patient’s LVEF was within normal range. After the last chemotherapy course, though, the patient’s started complaining about poorer tolerance of exercise. ECG and echocardiography tests were performed, revealing LVEF drop to 35–40%, which is why cardiovascular treatment was initiated (ACE-inhibitor and β-blocker). 6 weeks later, the patient’s clinical condition improved, and LVEF increased to ca. 45%. Cancer advancement was additionally assessed with the use of PET-CT, which confirmed complete metabolic response. The patient was started on exemestane plus goserelin. Treatment tolerance remains good.

Over the past 6 months, the patient’s condition has not changed, with no signs of active neoplastic processes reported. The Ca 15-3 marker level normalized, and the imaging tests performed confirmed complete metabolic response. The patient is under regular cardiac follow-up, her LVEF remains at the level of around 50%, and she complains about poorer tolerance of exercise only occasionally, which may also be linked to episodes of asthma exacerbation.
The use of chemotherapy at the time of metabolic crisis was unavoidable, and it brought about expected results. Despite the unsuccessful neurosurgical intervention, radiotherapy prevented the progression of CNS lesions, and the patient’s condition has remained stable.

CASE 2.

It happens less and less frequently that breast cancer is advanced at the time of diagnosis, but when it does, it is still a difficult therapeutic problem. A considerable percentage of such patients are candidates for several treatment lines, with the selection of the best available treatment regimen being of great significance. It should ensure maximum therapeutic efficacy with minimum toxicity, as every complication may limit further therapeutic options, thus worsening the already severe patient prognosis. Therapies based on anthracyclines are believed to be amongst the most efficacious in the treatment of breast cancer. One of the drugs from that class is non-pegylated liposomal doxorubicin. The unique structure of the drug, locking the active substance within a lipid capsule, increases the drug’s efficacy, while decreasing the exposure of healthy tissues to the cytostatic drug, which in turn translates into a lower risk of cardiotoxicity. The case presented below involves a patient in whom non-pegylated liposomal doxorubicin was administered as first-line treatment.

In April 2013, the 51-year-old patient reported to the oncology clinic due to a left breast tumour. Additionally, she complained about thoracic spine pains that had persisted for several months and required regular use of painkillers. There were no previous diseases in the patient’s history. Her mother, on the other hand, had been treated for Hodgkin's lymphoma. The patient had had her last menstruation at the age of 42, she had given birth once, and had had 2 miscarriages. The physical examination revealed an ulcerated 7 cm left breast tumour with serosanguinous effusion. No other abnormalities were found. Core biopsy was performed, based on which the patient was diagnosed with ductal invasive G2 carcinoma. Her receptor status was the following: ER > 90%, no progesterone receptor expression. The HER2 receptor expression was assessed as negative (1+). The patient’s Ki67 expression was assessed as negative (1+). The patient’s Ca15-3 index was 40%. Abdominal ultrasound was performed, revealing 3 focal lesions resembling angiomas in the liver. The CA 15-3 marker was significantly elevated – 670 U/ml (normal range < 32,4 U/ml), and additional lab findings included mild hypercalcaemia and elevated concentration of alkaline phosphatase. In search of metastatic foci, abdominal CT and MRI tests were performed, which confirmed the nature of the previously described lesions as metastatic. Lung metastases were also detected. Bone scintigraphy revealed numerous metastatic foci, within the spine, pelvis and femoral shafts.

With the improvement of the patient’s quality of life in mind, she was qualified for the Madden palliative mastectomy. The procedure was performed on 20 May 2013. Taking into consideration the massive dissemination of disease that metastasised to the patient’s bones and visceral organs, as well as the persisting clinical symptoms (pains), the patient was qualified for first-line chemotherapy based on non-pegylated liposomal doxorubicin in combination with cyclophosphamide. The treatment initiated in June 2013, with the drugs administered at their standard doses.

Additionally, zoledronic acid was administered every 3 weeks at the dose of 4 mg i.v. The patient’s baseline LVEF was 65%. Before each consecutive chemotherapy course her blood haematology and biochemistry parameters were monitored. She was also under regular cardiovascular follow-up, undergoing ECG and echocardiography tests every 2 chemotherapy courses. Initially, the patient complained about nausea and grade 2 vomiting with a significant psychogenic component. Those complications were controlled with lorazepam dosed at 1 mg, administered one day before and on the day of the consecutive chemotherapy course. Since then, the patient’s subjective treatment tolerance improved. Following the second course of treatment, she reported a significant reduction in the pain experienced. On several occasions, there was asymptomatic thrombocytopenia (grade 1 according to CTCAE), which required prolonging the intervals between chemotherapy courses.

After the fourth chemotherapy course, liver enzymes were elevated, exceeding four times the upper limit of normal, with normal bilirubin levels. It was decided to reduce the dose by 25% of the standard dose, and since the fifth course of chemotherapy, the patient continued receiving the reduced dose. Liver enzymes went down, and until the end of doxorubicin therapy remained at the level of twice the upper limit of normal.

Starting from the tenth cycle, the patient reported grade 2 fatigue, lasting for around a week and a half. ECG and EF measurements did not reveal poorer cardiac performance than at baseline. Assessment of treatment efficacy following the fourth cycle revealed complete remission of the liver lesions, and partial remission of lung and bone metastases. The CA 15-3 concentration at the time was 64 U/ml (670 U/ml at baseline). Assessment after the eighth cycle confirmed complete remission of the visceral lesions, and maintenance of partial remission of bone metastases.
ses as well as normalization of the CA 15-3 levels. Altogether, the patient received 11 chemotherapy cycles, arriving at the cumulative dose of non-pegylated liposomal doxorubicin of 750 mg/m². Imaging tests performed after the eleventh cycle revealed disease remission. The treatment was completed in March 2014 in view of the follow-up test results and treatment tolerance.

Starting from April 2014, the patient was started on maintenance letrozole, and continued to receive bisphosphonates every 4 weeks. She did not report any significant complaints. Periodic imaging tests and blood biochemistry demonstrated continued remission. The patient went on to receive aromatase inhibitor hormone treatment for 2 years. In March 2016, she complained about pelvic pain. Bone scintigraphy revealed progression of the bone lesions, including new lesions in the sacral bone, sternum, and bilateral third and fourth ribs. No other lesions were reported. The patient underwent palliative single-fraction radiotherapy of the pelvis. Taking into consideration her clinical condition and preferences, it was decided to switch the treatment over to tamoxifen, which the patient has continued to receive to this day. Regular CT and scintigraphy tests confirm stabilization of the bone lesions.

The patient’s general condition has remained very good. She is under regular cardiovascular follow-up, including LVEF assessment and ECG. Over 3 years from the completion of chemotherapy, no cardiovascular incidents have been observed. The treatment described above enabled long-term disease remission in extraskeletal locations as well as noticeable symptom reduction. Throughout the treatment, the patient has remained professionally active.

DISCUSSION

The first case involves a young, presently 34-year-old patient, who received 9 cycles of NPLD plus cyclophosphamide. Complete metabolic response accomplished in a patient with CNS, bone, liver, left lung and pancreatic metastases testifies to a very high efficacy of treatment.

Appropriate follow-up, involving echocardiography tests performed at least every 2 chemotherapy cycles, and upon exceeding the total dose of 200 mg/m², repeated before each consecutive treatment cycle, made it possible for the attending physician to discontinue treatment at a right time, administer standard therapy with an ACE-inhibitor and β-blocker, and receive a satisfactory therapeutic effect 6 weeks later (LVEF increase from 35% to 45%).

It is worth noting that NPLD therapy should be stopped in the case of symptomatic cardiotoxicity (LVEF drop of at least 10 points as compared with baseline, to a value below 53%, with symptoms of heart failure exacerbation). On the other hand, asymptomatic drop in LVEF by fewer than 10 points should not result in treatment cessation [12].

The detected anthracycline-induced cardiomyopathy (LVEF < 45%) was subjected to standard treatment of systolic left ventricular dysfunction. Combination of an angiotensin-converting enzyme inhibitor and a β-adrenolytic is currently the best therapeutic option that improves the heart’s systolic function and reduces mortality [13].

When taking decisions on initiating NPLD treatment in patients with metastatic disease, one should take into account the time that has passed from the completion of adjuvant therapy with conventional doxorubicin to the spread of disease (at least 12 months). There should also be no advanced cardiovascular diseases involved (symptomatic NYHA III or IV heart failure, LVEF < 40%, sustained myocardial infarction < 6 weeks before, persistent ventricular tachycardia or ventricular fibrillation in the patient’s history, uncontrolled arterial hypertension, unstable angina pectoris, grade III or IV) [14].

In light of the potential cardiotoxicity related to the prior use of conventional doxorubicin, one should remember that the total lifetime dose should also be calculated as the sum of all doses of doxorubicin formulations (when using first- and second-generation anthracyclines, one has to count the doxorubicin equivalent doses) [15].

The second case discussed involves a 51-year-old patient with advanced breast cancer (with liver, lung and bone metastases), who received 11 NPLD cycles as first-line treatment.

Due to the elevated liver enzymes, exceeding four times the upper limit of normal, the dose was reduced by 25%, starting from the fifth cycle, in accordance with the SmPC.

As NPLD is mainly metabolized in the liver, and excreted with bile, one should assess liver function before the initiation of treatment, and then follow-up on it throughout the therapy, adjusting the cytostatic dose to the liver enzymes and bilirubin levels, based on the recommendations included in the SmPC.

Treatment with NPLD may lead to myelosuppression. A meta-analysis, provided in the SmPC, demonstrated a significant-
ly lower incidence of grade 4 neutropenia, nausea and emesis, diarrhoea > grade 3, with no differences in terms of anaemia, thrombocytopenia and febrile neutropenia compared with conventional doxorubicin.

In the case of haematological toxicity, standard procedure involves extending the intervals between chemotherapy cycles or reducing the cytostatic dose.

The patient completed NPLD treatment following the eleventh cycle (total dose of 750 mg/m²) due to persistent grade 2 fatigue, lasting for a week and a half, and in light of the continued partial remission of metastatic lesions.

Systemic treatment of stage IV breast cancer prolongs patient survival and improves the quality of life, but is not curative, which is why it is so important to limit treatment-induced toxicity, while at the same time accomplishing satisfactory therapeutic outcomes.

Non-pegylated liposomal doxorubicin has a role to play here due to its unique structure and pharmacokinetics.

References

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