# Left Ventricular Systolic Dysfunction in Metastatic Breast Cancer Patients: A Polish Multicenter Registry

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**Abstract.** *Background: The knowledge of the epidemiology of left ventricular systolic dysfunction (LVSD) in relationship with cardiovascular diseases, their risk factors and history of previous anticancer therapy may lead to development of safer and more effective therapeutic strategies in patients with breast cancer (BC). Patients and Methods: Oncologists from various Polish Centers reported 299 new cases of metastatic BC requiring chemotherapy. All registered previous cardiological and oncological therapies should be conducted in accordance with the mandatory guidelines. Results: Twelve new cases (4%) of LVSD were recognized in echocardiography before current chemotherapy. Multivariate logistic regression analysis revealed a significant association of LVSD with hypercholesterolemia (odds ratio (OR)=8.83; 95% confidence interval (CI)=1.44-54.16; p<0.02), prior myocardial infarction (OR=26.81; 95%CI=2.26-318.43; p<0.01), prior antracycline-based therapy either neoadjuvant (OR=13.21; 95%CI=2.18-80.12, p=0.005) or adjuvant (OR=6.94; 95%CI=1.003-47.985, p<0.05). Conclusion: LVSD in metastatic BC reflects common negative effects of hypercholesterolemia, coronary events and neoadjuvant/adjuvant chemotherapy with anthracyclines.*

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Cardiotoxicity of anthracyclines may lead to premature death in short-term observation (1) and also contribute to poor prognosis in long-term follow-up of patients with cancer (2). The latter is of particular interest for patients with a relatively favorable prognosis, such as breast cancer. However, recent data have revealed an increasing rate of cardiovascular complications after adjuvant therapy for breast cancer. The highest rate is documented in patients treated with trastuzumab and anthracyclines (3, 4). Predictive factors include not only the classical risk factors of atherosclerosis and heart failure but also type of cancer therapy (5). Nevertheless, anthracyclines still remain one of the most effective groups of drugs in the treatment of breast cancer, both in adjuvant and neoadjuvant therapy, and often offer best control in advanced disease.

Treatment of a patient with a recurrent metastatic disease, who had already received anthracyclines therapy, becomes a real challenge. One of the reasons is lack of comprehensive reports on cardiological profile of patients with metastatic breast cancer after adjuvant or neoadjuvant treatment. In

addition, the real effect of recommended treatment regimes based on anthracyclines, with acceptable and relative low cumulative doses, is not known.

The aim of this prospective study was to analyze the epidemiology of left ventricular systolic dysfunction (LVSD) in relationship with cardiovascular diseases and their classical risk factors, as well as the five-year history of previous anticancer therapy in patients with metastatic breast cancer at the start of subsequent chemotherapy. The results may help develop safer and, thus, more effective therapeutic algorithms of chemotherapy in the future.

## Patients and Methods

This study was based on a multicenter cardio-oncological registry in Poland launched as LDD Trial, led by the East European Branch of the International CardiOncology Society. Oncologists from several Polish centers where asked to report all new cases of metastatic breast cancer requiring chemotherapy. Each report included data from patients' cardiological and oncological five-year history. According to local ethics guidelines, all patients gave an informed consent for further retrospective analyses of their medical records.

The main inclusion criteria comprised: (i) cardiological therapy conducted in accordance with the mandatory guidelines of the European Society of Cardiology; (ii) previous anticancer therapy used in accordance with recommendations of the European Society of Medical Oncology, American Society of Clinical Oncology or National Comprehensive Cancer Network; (iii) previous anticancer therapy completed during last 5 years; (iv) lack of clinical symptoms of heart failure and echocardiographic signs of cardiac dysfunction at the end of earlier chemotherapy; (v) present indication for 1st- or 2nd- or 3rd-line chemotherapy due to metastatic breast cancer (6). Patients after adjuvant therapy with trastuzumab were not registered because it helped to avoid mixing of cardiotoxicity type I and II (7).

The detailed cardiological history included: (i) arterial hypertension defined as self-reported physician diagnosis and use of antihypertensive treatment; (ii) hypercholesterolemia defined as self-reported physician diagnosis or as a total cholesterol level ≥190 mg/dl or medication use; (iii) overweight if body mass index was ≥25 kg/m$^2$; (iv) diabetes defined as self-reported physician diagnosis or use of diabetes medication; (v) tobacco smoking; (vi) age; (vii) acute coronary events/myocardial infarction diagnosed in the past; (viii) cardiac arrhythmias recognized previously; (ix) stroke diagnosed in the past; (x) exercise intolerance: mild correlated with class I according to The New York Heart Association (NYHA) classification, moderate corresponded to II or III class. The detailed oncological history included data on: (i) regimen of neoadjuvant treatment; (ii) regimen of adjuvant treatment; (iii) earlier hormonal treatment; (iv) earlier treatment for diagnosed stage IV breast cancer.

Patients were registered if the doses of anthracyclines were consistent and acceptable according to recommendations of the European Society of Medical Oncology/American Society of Clinical Oncology/National Comprehensive Cancer Network. In neoadjuvant and adjuvant therapy, depending on the chosen regimen, no more than 300 mg/m$^2$ of doxorubicin or 450 mg/m$^2$ of epirubicin could be given. In palliative therapy, a maximum dose of 400 mg/m$^2$ doxorubicin or 600 mg/m$^2$ epirubicin could be administered.

The primary goal of the registry was to analyze the epidemiology of new recognized left ventricular systolic dysfunction (LVSD) in relationship with cardiovascular diseases and their classical risk factors, as well as the five-year history of previous anticancer therapy in patients with metastatic breast cancer at the start of subsequent chemotherapy. Left ventricular systolic dysfunction (LVSD) was diagnosed in echocardiography by the measurement of the left ventricular ejection fraction (LVEF) below 50%.

The secondary goal was to evaluate the prevalence of exercise intolerance (typical symptom of heart failure) in comparing to values of LVEF.

Epidemiological data were expressed as percentages of patients' population. Values of odds ratios (ORs) and respective 95% confidence intervals (CIs) were estimated with logistic regression models. All statistical analyses were performed using the STATISTICA Version 8.0 software ( http://www.statsoft.com).

## Results

Among 299 patients there were only 5 males (1.7%). The median age was 60 years and the range between the lowest and highest quartile was 53 - 66 years of life.

The oncological history data are presented in Table I. In 191 cases (63.9%), cancer was estrogen receptor-positive, while "tripple-negative" diagnosis was made in 67 (22.4%) patients. HER2 receptor was over-expressed in 70 (23.4%) patients.

Prior neoadjuvant and adjuvant therapies were administered to 47 (15.7%) and 166 (55.6%) patients, respectively. Neodjuvant therapies were in all cases based on anthracyclines with the most common AT (doxorubicin+docetaxel) regimen given to 21 patients. Adjuvant therapies with anthracyclines were administered to 138/166 patients. The most common regimen was AC or FAC (doxorubicin+cyclophosphamide ±fluorouracil) given to 57/138 and 39/138 patients, respectively.

Most patients, 200 (66.9%), at the time of registration were scheduled to receive chemotherapy for metastatic disease for the first time. Some patients, however, had already received one (83 patients, 27.8%) or two (16 patients, 5.4%) prior palliative chemotherapies that were based on anthracyclines only in 44 patients usually with doxorubicin. More often, patients received non-anthracycline type of palliative treatment usually based on taxanes.

Altogether, at the time of registration, 229 (76.6%) patients had been treated with different anthracycline-based regimens (neoadjuvant, adjuvant or palliative). Previous hormonal treatment was used in 57 (19.1%) patients.

Data from cardiological past history are presented in Table II. The most frequent co-existing cardiological disease was arterial hypertension, diagnosed in 131 (43.8%) patients. All patients received at least one anti-hypertensive drug. Thirty-seven (12.4%) patients also received treatment for lipid abnormalities. In some women, cardiometabolic risk factors

Table I. *Demographic and oncological characteristics of patients with metastatic breast cancer.*

| Characteristics | No. of patients (%) | |
|---|---|---|
| Status of receptors | HER2 positive & ER and/or PR negative: 41 (13.7%)<br>HER2 negative & ER and/or PR negative: 67 (22.4%)<br>HER2 negative & ER and/or PR positive: 162 (54.2%)<br>HER2 positive & ER and/or PR positive: 29 (9.7%) | |
| Prior endocrine therapy | 57 (19.1%) | |
| Prior anthracycline-based neoadjuvant chemotherapy | 47 (15.7%) | AT: 21 (7%)<br>AC: 9 (3%)<br>FAC: 7 (2.3%)<br>FEC: 6 (2%)<br>ET: 3 (1%)<br>EC: 1 (0.3%) |
| Prior anthracycline-based adjuvant chemotherapy | 138 (46.2%) | AC: 57 (19.1%)<br>FAC: 39 (13%)<br>FEC: 16 (5.4%)<br>AT: 11 (3.7%)<br>EC: 6 (2%)<br>AP: 4 (1.3%)<br>TAC: 3 (1%)<br>ET: 2 (0.7%) |
| Prior nonanthracycline adjuvant chemotherapy | 28 (9.4%) | CMF: 26 (8.7%)<br>TC: 2 (0.7%) |
| Prior anthracycline-based palliative chemotherapy | 44 (14.7%) | AT: 16 (5.4%)<br>AC: 11 (3.7%)<br>FAC: 8 (2.7%)<br>AP: 3 (1%)<br>ET: 2 (0.7%)<br>FEC: 2 (0.7%)<br>EP: 2 (0.7%) |
| Prior nonanthracycline palliative chemotherapy | 71 (23.7%) | Taxane-based: 58 (19.3%)<br>Others: 13 (4.3%) |
| Present considered line of chemotherapy (palliative) due to metastatic breast cancer: | | |
| 1st line | 200 (66.9%) | |
| 2nd line | 83 (27.8%) | |
| 3rd line | 16 (5.4%) | |

A, Doxorubicin; C, cyclophosphamide; E, epirubicin; F, fluorouracil; M, methotrexate; P, paclitaxel; T, docetaxel; ER, estrogen receptor; PR, progesterone receptor.

for cardiac disease were present: 75 (25.1%) were overweight and 30 (10%) had diabetes. Additionally, 33 (11 %) patients reported discomfort connected with cardiac arrhythmias (mainly palpitations) or had mild arrhythmias diagnosed: atrial fibrillation, supraventricular tachycardia, single ventricular premature complexes, ventricular bigeminy/trigeminy. Additionally, 25 (8.4%) patients reported active smoking. Serious past cardiovascular events in patients with metastatic breast cancer were rare: 9 (3 %) cases of myocardial infarction and 3 (1%) cases of brain stroke.

All patients from our study were evaluated in echocardiography including LVEF assessment. According to the current criteria, left ventricular systolic dysfunction (LVSD) was diagnosed in 12 women (4% of the studied population). None of the women with prior endocrine therapy and none of the men had diagnosis of LVSD.

Table II. *Prevalence of cardiovascular co-morbidities and their classical risk factors in patients with metastatic breast cancer.*

| Disease | No. of patients (%) |
|---|---|
| Arterial hypertension | 131 (43.8%) |
| Hypercholesterolemia | 37 (12.4%) |
| Overweight | 75 (25.1%) |
| Diabetes mellitus | 30 (10%) |
| Smoking | 25 (8.4 %) |
| Coronary artery events/Myocardial infarction in past medical history | 9 (3%) |
| Arrhythmias | 33 (11%) |
| Stroke in past medical history | 3 (1%) |
| Exercise intolerance | |
| Mild | 31 (10.4%) |
| Moderate | 30 (10%) |
| Left ventricular ejection fraction on echocardiography (LVEF) <50% | 12 (4%) |

Table III. *Multivariate logistic regression analysis for the association between left ventricle systolic dysfunction (LVSD) and possible cardio-oncological risk factors.*

| Risk factors | Odds ratio | 95% Confidence interval | *p*-Value |
|---|---|---|---|
| Arterial hypertension | 0.791 | 0.138-4.548 | 0.792 |
| Hypercholesterolemia | 8.832 | 1.440-54.161 | 0.019 |
| Overweight | 0.625 | 0.095-4.121 | 0.624 |
| Smoking | 0.768 | 0.060-9.856 | 0.839 |
| Diabetes mellitus | 3.961 | 0.532-29.492 | 0.178 |
| Coronary artery events/Myocardial infarction in past medical history | 26.812 | 2.257-318.433 | 0.009 |
| Arrhythmias | 2.033 | 0.279-14.835 | 0.483 |
| Prior anthracycline-based neoadjuvant chemotherapy | 13.212 | 2.179-80.119 | 0.005 |
| Prior anthracycline-based adjuvant chemotherapy | 6.936 | 1.003-47.985 | 0.0497 |
| Prior nonanthracycline adjuvant chemotherapy | 5.492 | 0.344-87.708 | 0.227 |
| Prior anthracycline-based palliative chemotherapy | 3.908 | 0.576-26.502 | 0.162 |
| Prior nonantracycline palliative chemotherapy | 1.209 | 0.225-6.492 | 0.825 |
| Age (each year) | 1.015 | 0.944-1.091 | 0.684 |
| Status of HER2 receptor: positive | 2.459 | 0.405-14.932 | 0.327 |
| Status of ER/PR receptor: positive | 0.473 | 0.095-2.358 | 0.36 |

ER, Estrogen receptor; PR, progesterone receptor.

Multivariate logistic regression analysis revealed that LVSD was significantly more frequent (Table III) in patients with hypercholesterolemia (OR=8.83; 95%CI=1.44-54.16; $p<0.02$), myocardial infarction in the past (OR=26.81; 95%CI=2.26-318.43; $p<0.01$) and patients after neoadjuvant therapy including anthracyclines (OR=13.21; 95%CI=2.18-80.12, p=0.005) or adjuvant therapy with anthracyclines (OR=6.94; 95%CI=1.003-47.985, $p<0.05$).

Exercise intolerance, evaluated by oncologists according to NYHA criteria, were reported in 61 cases (Table I). Moderate exercise intolerance were recognized in 8 of 12 patients with LVEF<50% (Table IV). Moreover, 30 of 213 patients with LVEF>55% had exercise intolerance symptoms. In univariate logistic regression, the presence of any symptoms of exercise intolerance was significantly correlated with LVEF value: OR=0.89, 95%CI: 0.85-0.93, $p<0.00001$, for each percentage point. The occurrence of symptoms NYHA II or III was more strongly associated with the LVEF value: OR=0.82, 95%CI=0.76-0.88, $p<0.00001$, for each percentage point.

Table IV. *Distribution of exercise intolerance symptoms in relationship with values of left ventricular ejection fraction (LVEF).*

| LVEF | <50% (n=12) | 50-55% (n=74) | 56-65% (n=138) | >65% (n=75) |
|---|---|---|---|---|
| Asymptomatic (n=148) | 3 | 52 | 117 | 66 |
| Mild exercise intolerance (n=31) | 1 | 9 | 14 | 7 |
| Moderate exercise intolerance (n=30) | 8 | 13 | 7 | 2 |

## Discussion

Our study is based on a register created by oncologists to show the magnitude of cardiovascular problems in patients with metastatic the breast cancer. Our results demonstrate a real scale of cardiological problems in patients with metastatic breast cancer qualified for subsequent chemotherapy. To best of our knowledge, this is the first pragmatic description of this problem in the literature. The study describes genuine epidemiology of cardiovascular diseases in women with breast cancer after adjuvant or neoadjuvant chemotherapy who suffer from recurrent disease in the form of distant metastases.

The study was not only devoted to the cardiotoxicity of anthracyclines but also concentrated on the five-year history of patients who had been treated according to mandatory recommendations with available therapeutic regimes. We did not analyze the doses of drugs, including anthracyclines, as this issue has been described in many reports. We were interested to create a cardiological profile of these patients already subjected to chemotherapy that is effective but also cardiotoxic. Survival of patients increased with increasing rate of cardiological problems that have to be managed properly with professional cardiological care.

Identification of cardiovascular diseases in patients after chemotherapy is one of the main issues in cardio-oncology (8). Many of these diseases constitute complications of anticancer treatment, which has been best documented in lymphomas (9). Recently, several experts have suggested that

prior anticancer treatment (in particular with regimes including anthracyclines) should be regarded as stage A heart failure (10). Our study justifies such diagnosis. The five-year history of previous adjuvant or neoadjuvant treatment with anthracyclines in acceptable and recommended doses is seriously correlated with the diagnosis of significant myocardial systolic dysfunction, *i.e.* at least stage B heart failure (Table III). The accuracy of recognition of symptoms suggesting stage C seem to be the next key problem in cancer patients (Table IV ).

According to the European Society of Medical Oncology (ESMO) criteria, LVSD defined as LVEF<50% may become the main obstacle for further anticancer treatment (11). In addition, it has been demonstrated that many patients after anticancer treatment, also including anthracyclines, do not receive optimal cardiological care (12). Diagnosis of LVSD is usually made when the patient requires subsequent lines of oncological treatment and an oncologist suggests a cardiological consultation. However, optimization of cardiological treatment in these patients significantly increases the quality of their life and prolongs overall survival (71% *vs.* 41% during follow-up; $p<0.05$) (13). Complete normalization of systolic myocardial function is possible, provided that cardiological intervention takes place sufficiently early (14).

Our study confirms that diagnosis of LVSD is made when the patients are qualified for the subsequent line of chemotherapy. The frequency of LVSD diagnosis was 4%, which is similar to observations of Ammon *et al.* and Yoon *et al.*, despite the fact that in these reports patients with diagnoses other than breast cancer where taken into account, and the definition of LVSD was made at LVEF<45% or LVEF<55%, respectively (12, 13). It should be stated that the main question is how to define the normal value of LVEF in cancer patients receiving effective chemotherapy (15).

Our study confirmed the correlation between hypercholesterolemia and significantly higher risk of LVSD that seems to be an important observation for daily practice. It may justify recommendation of statins as a primary prevention of this type of cardiac injury. There is a report demonstrating that chronic administration of statins significantly decreases the risk of iatrogenic LVSD related to anthracyclines – about three-fold (hazard ratio (HR)=0.3 (95% CI: 0.1-0.9; $p=0.03$) (16). The mechanism responsible for the cardioprotective effect of statins probably results from the reduction of oxidative stress and inflammatory reaction in blood vessels wall during anthracyclines therapy (17). This effect has been confirmed on animal models (18). Our study clearly shows that hypercholesterolemia is one of the strongest risk factors for heart dysfunction in patients with breast cancer. Therefore, lipid metabolism control by administration of statins may directly translate into a decrease of heart failure in this population of cancer patients. Moreover, our study confirmed that LVSD in metastatic breast cancer patients reflects common negative effects of hypercholesterolemia, coronary artery events and neodjuvant/adjuvant chemotherapy with athracyclines. A preventive strategy with statins may become the optimal choice against all of the aforementioned conditions.

Our study stresses yet another important cardio-oncological aspect of breast cancer therapy. It seems obvious that exercise intolerance, as a typical symptom for heart failure, is significantly correlated with decreasing LVEF. It appears logical that a decreasing value of LVEF is the effect of adjuvant/neoadjuvant chemotherapy and past coronary events and one of the main reasons of deteriorating quality of life in breast cancer patients.

The main role for adjuvant therapy is to prevent potential disease progression, therefore, its effectiveness has been always considered as the most important attribute. However, long-term complications, such as cadiotoxicity, should be also taken into account. Recently, British experts suggested that administration of a regimen without anthracyclines may compensate the risk of long-term cardiotoxicity and potential secondary neoplasms (19). Our results recommend that CMF regimen seems to be safer in adjuvant therapy from the cardiological standpoint. However, there are data indicating its lower anticancer efficacy: higher risk of recurrence and higher risk of mortality as compared with anthracyclines (20). There are also proofs that adjuvant therapy with cyclophosphamide, methotrexate and fluorouracil may be detrimental to general cardiovascular risk if the patient is subsequently treated with epirubicin (21). The question of optimal neoadjuvant chemotherapy regimen is still open too. Regimes based on taxanes are less cardiotoxic but their efficacy needs to be verified (22, 23). Another option is to ask a cardiologist for consultation to implement prevention strategy based on drugs, such as carvedilol or angiotensin convertase inhibitors. The OVERCOME study demonstrated that combination of these drugs prevents the composite observation point of death and cardiac failure (6.7% *vs.* 22%, $p=0.036$) or death, cardiac failure and decrease of LVEF below 45% (6.7% *vs.* 24.4%, $p=0.02$) (24). Further studies are required, also in breast cancer patients, to establish the role of these drugs for such indication. The other important, although not new, aspect is to find a sensitive marker of individual susceptibility of anthracyclines' cardiotoxicity. Monitoring of the molecular changes may soon become the key to prognosis of clinically significant cardiotoxicity. There are data suggesting that decreased activity of HER2 receptor characterizes patients with more severe clinical course of acute heart failure (25). The serum concentration of neuroregulin, however, correlates with changes in LVEF during chemotherapy with anthracyclines (26)

We conclude that anthracycline-related cardiotoxicity is a significant health problem for cancer patients affecting both

further cancer treatment and general condition. We analyzed only up to 5 years of last history of chemotherapy because we tried to avoid the late toxicity associated with radiotherapy that may appear after this period. We excluded regimens with anti-HER2 drugs because there are many ongoing and published trials investigated cardio-oncological problems related to trastuzumab, lapatinib or pertuzumab (3-5). Moreover, cardio-oncological analyses, including anti-HER2 drugs, should carry out the special differential diagnosis between cardiotoxicity type I and type II, a task that is not so easy in clinic.

Our relatively short-term observation revealed significant adverse cardiac events in patients with metastatic breast cancer. Historical studies based on cardiac muscle biopsy revealed that even a single dose of anthracyclines leads to significant changes in cardiomyocytes (27, 28). The clinical course of cardiotoxicity is undoubtedly individual, depending on adaptive capabilities of the patient, coexisting cardiological and oncological risk factors and time span form the discontinuation of treatment (29). Therefore, the knowledge about the epidemiology of these additional risk factors is the first step to develop a guideline for significantly better cardiological monitoring and treatment in patients during and after anticancer treatment (30). Further international multicenter trials are required to evaluate cardiovascular complications in significantly longer follow-ups with better cardiological management and proper evaluation of the importance of neoadjuvant/adjuvant therapy with anti-HER2 drugs. Such an approach will potentially improve quality of life and general prognosis of patients with metastatic breast cancer after previous cardiological events and oncological therapy.

In conclusion, new cases of LVSD are recognized in patients with metastatic BC before subsequent chemotherapy as the consequence of previous anthracycline-based adjuvant or neoadjuvant chemotherapy, as well as the complication of coronary artery events and hypercholesterolemia. The results confirm the need for a common strategy of primary prevention against all these risk factors.

## Conflicts of Interest

The Authors do not have any conflicts of interests to declare.

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