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Cardiotoxicity in patients with early breast cancer treated with adjuvant trastuzumab

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Introduction. Breast cancer is the most common cancer among women in Poland. The aim of this study was to evaluate the incidence of cardiotoxicity in patients treated with adjunctive trastuzumab, as well as to determine risk factors for cardiotoxicity.

Material and methods. The study covered 100 patients who completed one year of trastuzumab therapy or discontinued treatment due to acute cardiac complications. They underwent an oncological, cardiological, questionnaire and laboratory follow-up.

Results. Acute cardiac complications (CC(+)) occurred in 11 (11%) patients. Patients in the CC(+) group were more likely to have hypertension, ischemic heart disease, hypothyroidism, and were more likely to smoke compared to the group without cardiac complications (CC(–)). They had a lower left ventricular ejection fraction before, during and after trastuzumab therapy, and larger left ventricular dimensions in systole and diastole after treatment. The CC(+) received a higher dose of anthracyclines compared to CC(–). The NT-proBNP value remained elevated in the CC(+) group after treatment, despite normal LVEF values, and was higher than in the CC(–) group.

Conclusions. Based on the study, type II cardiotoxicity, diagnosed early and treated appropriately, was found to be reversible.

Key words: cardiotoxicity, anthracyclines, trastuzumab, breast cancer

Introduction

Breast cancer treatment outcomes have improved in recent years. In many countries, despite an increase in incidence, a decrease in mortality from this cancer has been achieved [1]. This improvement is due to earlier detection of breast cancer, as well as more intensive treatment. The introduction of systemic perioperative treatment (radiotherapy, chemotherapy, immunotherapy, and hormone therapy) has reduced the risk of recurrence and increased overall survival time for patients with early breast cancer. However, this success has been associated

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with an increased risk of early and late complications. The use of anthracyclines – cytostatics with high efficacy in the treatment of breast cancer – is inextricably related to the problem of cardiotoxicity, which can be exacerbated by the use of trastuzumab, a human monoclonal antibody directed against the HER2 receptor [2]. Therefore, it is very important to correctly qualify for various treatments, use possible prophylaxis, and monitor the patient's condition during and after anticancer treatment. Such management is aimed at effective treatment of the cancer with as few complications as possible.

The aim of this study was to determine the incidence of cardiac complications in patients with early breast cancer treated with adjuvant trastuzumab, as well as to identify risk factors predisposing to cardiotoxicity.

Material and methods

The study, conducted between 2012 and 2014, included 100 patients (99 women and 1 man) with a diagnosis of HER2--positive breast cancer who received trastuzumab after surgery as an adjuvant treatment, and who consecutively reported to the oncology clinic for a follow-up visit. The patients were aged between 34 and 77 years, with a mean age of 55.7 years. 95 patients received postoperative chemotherapy, the other five were not treated with cytostatics due to contraindications.

After chemotherapy, patients received trastuzumab at a saturating dose of 8 mg/kg body weight *i.v.*, followed by a maintenance dose of 6 mg/kg body weight *i.v.* every 21 days. Complementary treatments used in the study group are shown in table I.

During the follow-up visit, each time a subjective examination (asking about comorbidities, addictions, medications taken, oncological treatment used, and internal medicine, as well as family history of cancer), physical examination, laboratory tests, taking into account potential biomarkers of cardiotoxicity (glucose, total cholesterol, TSH, hs-Tnt, NT-proBNP were determined), and electro- and echocardiographic tests were performed. In apical projections, the left ventricular ejection fraction was calculated based on the biplanar method.

Table I. Type of adjuvant treatment used in the study group of patients

Type of treatment	Number of patients (%), n = 100
chemotherapy	95 (95%)
AC x 4 ± paclitaxel/docetaxel	63 (63 %)
AC x 6	27 (27%)
TAC or FAC x 6	5 (5%)
radiotherapy	61 (61%)
left side	31 (31%)
right side	30 (30%)
complementary hormonal treatment	53 (53%)
tamoxifen	46 (46%)
aromatase inhibitors	7 (7%)

AC – doxorubicin, cyclophosphamide; FAC – fluorouracyl, doxorubicin, cyclophosphamide; TAC – docetaxel, doxorubicin, cyclophosphamide

Symptoms of cardiotoxicity during trastuzumab therapy were considered to be: a decrease in the left ventricular ejection fraction (LVEF) to less than 50% , symptoms of heart failure, and cardiac arrhythmias.

A retrospective evaluation of the cardiovascular system during cancer treatment was conducted based on the echocardiographic results performed before and during trastuzumab therapy.

Statistics

The statistical package statistica.pl ver. 10 and the Excel 2010 program, which is part of the Microsoft Office package, were used to perform statistical analysis of the results.

During the statistical analysis of the results, the following statistical tools were used: elements of descriptive statistics, comparisons of structure indicators, correlations between values of statistical characteristics.

Results

Among the 100 patients who participated in the study, trastuzumab treatment was discontinued in 11 (11%) due to: asymptomatic decrease in LVEF to less than 50% (in 9 patients) or symptoms of heart failure (in 2 patients). No other symptoms of cardiotoxicity were observed.

All patients who developed cardiac complications had a left ventricular ejection fraction of at least 50% before therapy, and there were no contraindications to anthracycline treatment. During trastuzumab therapy, the left ventricular ejection fraction dropped below 50% in 9 patients, to the lowest value of 20%, and 2 patients had symptoms of heart failure despite normal LVEF values. The patients received between 1 and 12 administrations of trastuzumab (an average of 6), before they developed symptoms of cardiotoxicity (tab. II). Patients with cardiac complications received a significantly higher dose of anthracyclines compared to patients without cardiac complications: 441.82 *vs.* 382.3 mg.

Echocardiographic evaluation of patients

The left ventricular ejection fraction is one of the parameters that determines the left ventricular systolic function. It was above 50% in all patients participating in the study before and after trastuzumab therapy. Its mean value was statistically significantly higher in the group without cardiac complications both before and during treatment, 73.21% *vs.* 68.55%; $p = 0.0074$ and 64.58% *vs.* 40.27%; $p < 0.0001$, respectively. There were no statistically significant differences between the mean LVEF values in both groups after treatment.

A decrease in the mean left ventricular ejection fraction value was observed during trastuzumab therapy, followed

Table II. Characteristics of the group of patients who developed symptoms of cardiotoxicity

Patient	LVEF before treatment	LVEF during treatment	LVEF after treatment	CHTH used	Radiotherapy	Number of trastuzumab administrations
1	73	30	50	6 x AC + docetaxel	L	6
2	65	20	68	4 x AC	P	4
3	71	25	50	4 x AC + paclitaxel	P	6
4	78	47	70	4 x AC	L	12
5	65	45	65	4 x AC	P	10
6	69	40	60	6 x AC	–	10
7	65	57	51	6 x AC + docetaxel	–	1
8	72	60	77	4 x AC	–	2
9	71	35	60	4 x AC	–	1
10	55	30	60	6 x AC	L	11
11	70	40	78	6 x AC	P	6

LVEF – left ventricular ejection fraction; L – left side radiotherapy; P – right side radiotherapy; AC – doxorubicin, cyclophosphamide; CHTH – chemotherapy

by an increase after the completion of treatment. However, the mean LVEF value after completion of targeted therapy was significantly lower in both the group with and without cardiac complications than the LVEF value measured before trastuzumab therapy (tab. III).

After completion of oncological treatment, during follow-up visits, a larger left ventricular dimension in both the systole and diastole was observed in the group of patients who had cardiac complications compared to the group of patients without cardiac complications (tab. IV, V).

Biomarkers (NT-proBNP, hs-Tnt)

The group without cardiovascular complications had a statistically significantly lower mean NT-proBNP value (154.28 pg/ml) than the group with cardiovascular complications (369.80 pg/ml), based on results from measurements during the follow-up visit ($p = 0.0038$).

No statistically significant differences were observed in hsTnt levels in the group with and without cardiac complications during the follow-up visit (8.81 *vs.* 8.61 pg/ml).

Radiotherapy

61 patients received adjuvant irradiation, seven from the group with cardiac complications (63.64%) and 54 from the group without cardiac complications (60.67%). Irradiation to the left side of the chest was used in three patients in the group with cardiac complications (27.27%) and 28 patients in the group without cardiac complications (31.46%). Irradiation to the right side of the chest was used in four patients in the group with cardiac complications (36.36%)

Table III. Comparison of mean left ventricular ejection fraction (LVEF) values between groups with and without cardiac complications

Period	Group without cardiac complications (%)	Group with cardiac complications (%)	Standard (%)
before treatment	73.21	68.55	50.00
during treatment	64.58	40.27	50.00
after treatment	66.69	62.18	50.00

Table IV. Left ventricular internal dimension in diastole (LVIDD) values after completion of treatment

Period	Group without cardiac complications (mm)	Number of patients (n)	Group with cardiac complications (mm)	Number of patients (n)	Standard (mm)
echo 1	42.59	89	48.95	11	39.00–59.00
echo 2	41.55	32	49.05	7	39.00–59.00
echo 3	42.80	8	48.48	5	39.00–59.00

Table V. Left ventricular internal dimension in systole (LVIDS) values after completion of treatment

Period	Group without cardiac complications (mm)	Number of patients (n)	Group with cardiac complications (mm)	Number of patients (n)	Standard (mm)
echo 1	27.28	89	35.74	11	21.00–40.00
echo 2	26.96	32	34.15	7	21.00–40.00
echo 3	26.66	8	34.27	5	21.00–40.00

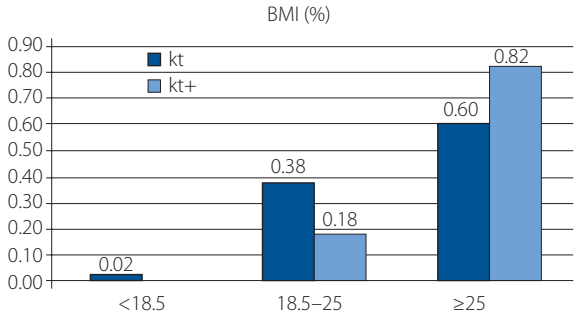

Figure 1. Distribution of the study population by body-mass index (BMI) and the presence of cardiac complications

and in 26 patients in the group without cardiac complications (29.21%).

Risk factors

The mean age in the study population was 55.71 ± 9.71 years and was statistically significantly higher in the group with cardiac complications than in the group of patients without complications (60.18 ± 6.31 *vs.* 55.16 ± 9.94 years), median age 61 *vs.* 56 years. Overweight (BMI > 25) was found more often in the group of patients with cardiotoxic symptoms than in the group without cardiac complications (82% *vs.* 60%) – figure 1.

Statistically, there were significantly more smokers ($p = 0.0177$), patients with hypothyroidism ($p = 0.0215$), hypertension ($p = 0.0042$), and ischemic heart disease ($p < 0.0001$) in the group with cardiac complications than in the group without cardiac complications.

Discussion

Over-expression of the HER2 receptor in breast cancer is associated with a poor prognosis, short time to recurrence, and short overall survival. When a human antibody directed against the HER2 receptor was developed in the late 20th century, it was initially introduced to treat advanced, then early breast cancer. The addition of trastuzumab to anthracycline-based chemotherapy proved successful. However, an increase in time to progression by 67% and an increase in response by 50% in disseminated disease, as well as an increase in disease-free time by about 50% and overall survival by about 30% in early breast cancer were associated with a risk of cardiovascular complications [3, 4]. Therefore, the problem of cardiotoxicity has become the main subject of research, not only by oncologists, but also by cardiologists.

One of the objectives of our study was to determine the incidence of acute cardiac complications among patients treated with trastuzumab.

Among the 11 patients with cardiotoxicity (11% of the study group): two patients had heart failure symptoms in NYHA class III/IV with preserved EF, five patients had decreased EF below 40%, another four patients had EF values in the range of 40–49%.

In the present study, the analysis of cardiotoxicity was conducted based on historical standards for diagnosing cardiovascular incidents in oncology [5]. In 2016, the European Society of Cardiology, in its first expert position statement on cardiovascular toxicity associated with anticancer treatment, indicated the diagnosis of cardiotoxicity when the left ventricular ejection fraction EF decreases by more than 10 percentage points to below normal, i.e., less than 50% [6]. In December 2021, a new definition of cardiotoxicity proposed by the International Cardio-Oncology Society was published [7]**.** For the first time, the diagnosis of the severity of myocardial damage caused by cancer drugs was standardized. Any decrease in EF below 40% was defined as severe cardiotoxicity. Such a situation occurred in 5 patients in the study population. The term severe cardiotoxicity (exactly: cancer therapeutics related cardiac dysfunction) is associated with an unfavorable prognosis. Indeed, it was shown in a large European registry (CARDIOTOX registry) that such EF was significantly associated with the risk of premature death from any cause (shorter overall survival) [8]. Moderate cardiotoxicity was proposed to include the onset of heart failure symptoms requiring intensification of cardiac treatment – it should be assumed that this was the case for 2 patients in the analyzed population who experienced NYHA III/IV symptoms despite a normal EF. However, moderate cardiotoxicity can also be diagnosed on the basis of echocardiography, when EF decreases to the range of 40–49% and this was the case in another 4 patients (two of whom had borderline EF = 40%).

It should be noted that modern echocardiography was not used in the analyzed population along with assessment of GLS (global longitudinal strain), i.e. a global longitudinal strain of the left ventricle. Indeed, mild cardiotoxicity can be diagnosed when GLS decreases by more than 15% from baseline and/or there is an increase in biomarkers defined as an increase in cardiac troponin I/T above the 99th percentile, BNP ≥ 35 pg/ml, NT-proBNP ≥ 125 pg/ml.

In the analyzed study, the group without cardiac complications had statistically significantly lower NT-proBNP levels than the group with cardiac complications, while no differences were observed in troponin levels. According to recent standards, it would be necessary to check how many patients with normal EF and no clinical symptoms had an increase in biomarkers or GLS changes during oncological treatment.

A number of risk factors for cardiotoxicity were found in the analyzed study, their identification is consistent with results from other publications. Through the knowledge of these risk factors, specific algorithms for the baseline assessment of patients before potentially cardiotoxic anticancer treatment were developed [9]. Baseline risk stratification is currently determining the frequency of follow-up testing (echocardiography, biomarkers) during and after active cancer treatment [10, 11].

Initial cardiovascular status prior to the start of oncology treatment is undoubtedly the most important factor determining the successful completion of potentially cardiotoxic therapy. Comorbidities, addictions, and habits shape overall health status. The co-occurrence of certain features in one patient may increase the risk of cardiotoxicity during cancer treatment, while the same features in another combination may have no effect on the cardiovascular system.

The study results on the role of trastuzumab in breast cancer treatment (HERA, Kremer et al., Pein et al.) highlighted the problem of cardiotoxicity of anti-HER2 therapy, which was inextricably related to the cumulative dose of doxorubicin [12–14]. In the present study, the mean cumulative dose of anthracyclines was significantly higher than the dose above which the risk of cardiotoxic complications increased (doxorubicin > 300 mg/m^2 according to Kremer's study) and was 387 mg/m^2 [13].

The BCIRG 006 trial is a study in which in one arm patients received trastuzumab without anthracycline treatment (6 courses of TCH), while other patients were treated sequentially with an AC regimen and docetaxel with or without trastuzumab [15]. In our study, 5 patients treated with trastuzumab did not receive anthracycline-containing chemotherapy due to cardiac contraindications or previous chemotherapy for second breast cancer. It is noteworthy that the BCIRG 006 trial showed similar efficacy of chemotherapy with and without anthracyclines (TCH regimen), with a higher safety profile of chemotherapy containing carboplatin and docetaxel [15].

More than 50% of breast cancer cases are diagnosed between the ages of 50 and 69, at which time the incidence of cardiovascular disease also increases. In the Slamon study of advanced breast cancer [16], as well as the Russo study [17] and the NSABP B – 31 [18], older patients treated with trastuzumab were more likely to be diagnosed with cardiotoxic complications. In Serrano's study, conducted in 2012 on adjuvant treatment of breast cancer in women over 70 years of age, older age and associated internal medicine (heart disease, diabetes) increased the risk of cardiovascular disease in patients treated with trastuzumab [3]. This was confirmed by Russo, who added impaired glomerular filtration in the kidneys, which increases with age, to the list of risk factors [17]. In contrast, in the Naumann study mentioned above, age was not an independent factor in the occurrence of cardiac incidents, but in a subgroup analysis of patients who experienced cardiac complications (15.72%), an inverse correlation was observed between age and time to complications [14]. Similar conclusions were drawn on the basis of our study, the age of the patients remained unaffected by cardiovascular risk. However, in the subgroup analysis, patients over 60 years of age predominated among those with cardiac complications (72.73%).

Conclusions

According to our study, the return of LVEF to normal and the alleviation of heart failure symptoms in all patients indicate the reversibility of type II cardiotoxicity. Regular echocardiographic examinations during trastuzumab therapy are extremely important. Rapid detection of asymptomatic and symptomatic complications as well as immediate implementation of cardiac therapy can prevent permanent heart damage. Therefore, it seems crucial to search for new diagnostic methods to isolate the group of patients at high risk of cardiac complications in order to safely carry out oncological treatment.

Conflict of interest: none declared

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