Myocardial dysfunction related to trastuzumab therapy – is effective treatment always possible?

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ABSTRACT

Left ventricle systolic dysfunction manifesting during trastuzumab treatment is defined as cardiotoxicity type II. It is characterized by full reversibility after discontinuation of trastuzumab and cardiological pharmacological treatment. In a group of patients, however, systolic cardiac function does not fully recover. The reasons of this unfavorable prognosis are subject of heated discussion.

KEY WORDS: trastuzumab, cardiotoxicity type II, breast cancer

CASE REPORT

A 55-year old female patient with no risk factors of cardiovascular system diseases was admitted to our clinic due to iatrogenic systolic myocardial dysfunction induced by trastuzumab.

She had cancer of the right breast diagnosed and underwent mastectomy in August 2011, followed by chemotherapy with anthracyclines: from September to December 2011 six cycles according to AC regime (cumulative dose 360 mg/m^2), radiotherapy (February 2012) and trastuzumab therapy: X cycles from April to October 2012, which was discontinued due to symptoms of heart failure (dyspnea on exertion). Echocardiography showed a decrease of the left ventricular ejection fraction (LVEF) from 60–65% (baseline) to 40% during active trastuzumab treatment. Then, within 3 weeks from trastuzumab discontinuation, further decrease of LVEF was observed to about 25%, with accompanying symptoms typical of heart failure in III functional class acc. to NYHA. In a regional oncological centre after consultation with a cardiologist typical treatment was induced, i.e. β-blocker, angiotensin converting enzyme inhibitor and diuretics. The patient was transferred to a reference centre for further treatment.

On admission to the Department of Pulmonary Circulation and Thromboembolic Diseases in Centre of Postgraduate Medical Education, in January 2013 she was in NYHA functional class II/III, in control laboratory tests the concentration of NT-proBNP = 434.6 pg/m, D-Dimer 661.5 ng/ml, high-sensitivity troponin 0.013 ng/ml (normal range up to 0.014 ng/ml). Echocardiography showed mild impairment of global contractility of the left ventricle cardiac muscle (LVEF 43%). In cardiac MRI impairment of global systolic myocardial function was confirmed, with no evident segmental contractility abnormalities, with LVEF~41%, and myocardium signal from the left and right ventricle mildly increased in a uniform way (on average the signal was 2–2.2-times higher than that of skeletal muscles seen at the same cross-section) – the picture may suggest cardiac muscle edema (Figure 1–3). There were no evident features of permanent myocardial damage (Figure 4). In 24-hour ECG (Holter monitoring) there were no episodes of persistent arrhythmia. Pharmacological treatment was modified with the use of carvedilol and ramipril in maximum tolerated doses. Further clinical observation was indicated.

During a follow-up visit in September 2013 the patient was in functional class I acc. to NYHA, clinical examination revealed no abnormalities. Laboratory tests results showed the concentration of NT-proBNP = 528.6 pg/ml, ultra-sensitive troponin was not elevated (0.006 ng/ml). Echocardiography showed normal size of heart chambers, left ventricle wall thickness normal, mild hypokinesis of all walls with LVEF evaluated acc. to Simpson method as about 40%, and impairment of mitral valve influx typical for relaxation disorder. In MRI slight improvement of LVEF was described, with a reduction of end-diastolic volume of the left ventricle (EDV reduction), and with no other changes from the previous examination (Table 1). Typical treatment of left ventricle systolic dysfunction was continued. Endocrinologic consultation was suggested due to increased concentration of TSH (8.02 mIU/l) with normal concentration of free thyroid hormones and lack of hypothyroidism symptoms. The patient was discharged home in good general condition.

On subsequent follow-up visit in March 2014 the patient was still in functional class I acc. to NYHA, with no symptoms of heart failure, professionally active, feeling well. The patient was followed up by an endocrinologist, thyroid hormones were normal.

FIGURE 1.
CMR: Short axis (S.A.) view. T2-STIR image presenting mild signal increase of myocardium in comparison to skeletal muscles.

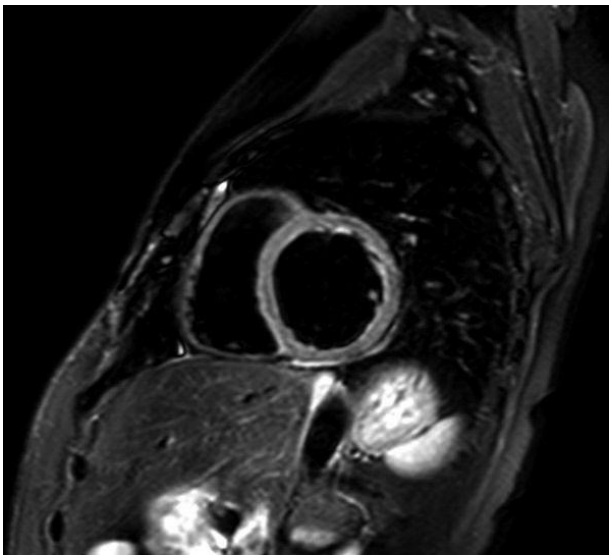


FIGURE 2.
CMR: Left ventricular function quantitative analysis performed by means of IntelliSpace Portal software.

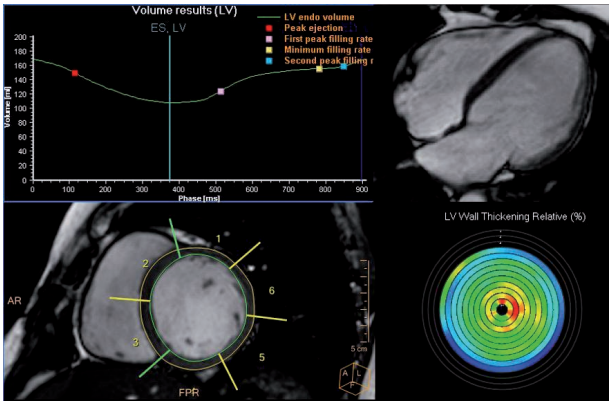


FIGURE 3.
CMR: Ascending aorta quantitative blood flow analysis (PC-FLOW) used for LV stroke volume assessment by means of IntelliSpace Portal software.

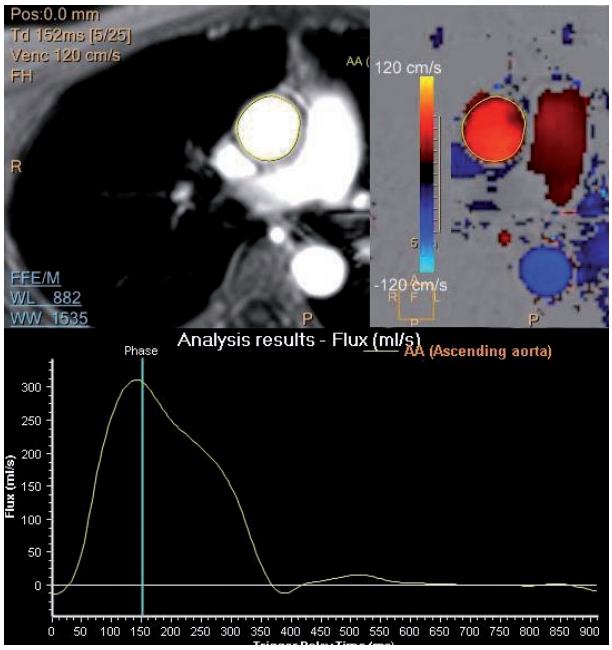
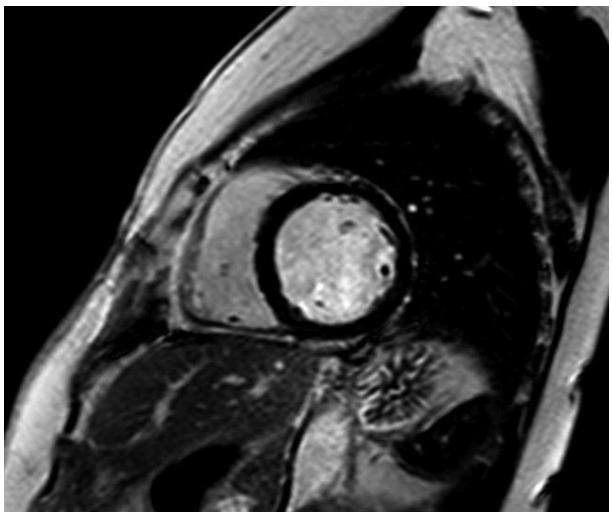


FIGURE 4.
CMR: Short axis (S.A.) view obtained by delayed contrast enhancement method 20 min after 0.1 mmol/kg b.w. Gadolinium injection. No pathologic enhancement is present.



Control MRI showed normal morphology, decrease of stroke volume (SV) and related values calculated using different methods, as compared to previous evaluations (Table 1).

The presented case seems interesting for a number of reasons. First, despite regular echocardiography during trastuzumab therapy, according to ESMO and Polish guidelines, iatrogenic myocardial dysfunction was not diagnosed at an early, asymptomatic stage. In addition, after trastuzumab discontinuation progressive decrease of LVEF was seen. Also, despite optimum cardiological treatment initiated when myocardial dysfunction was diagnosed, complete recovery of left ventricle systolic function was not achieved.

The described case suggests the need for a change in the current cardiologic diagnostic-therapeutic algorithm in patients treated with trastuzumab.

DISCUSSION

In clinical practice there are two types of cardiac muscle dysfunction induced by anticancer treatment (**CRCD**, *chemotherapy related cardiac dysfunction*): **CRCD type I** – anthracyclines-induced abnormalities in morphology and function of the cardiac muscle, and **CRCD type II** – abnormalities noted during trastuzumab therapy [1].

Cardiotoxicity type II is different from type I: it is not dose-dependent, it is not present in all patients, varies in clinical severity and is not connected with ultrastructural changes in the myocardium, and is usually reversible [2]. According to some studies, a significant risk factor for type II cardiotoxicity is anthracycline therapy [3]. Most probably type II cardiotoxicity results from decreased compensatory capability of the cardiac muscle damaged by anthracyclines [4].

RISK FACTORS

One of the largest studies in women with breast cancer revealed that during adjuvant treatment with sequential use of anthracyclines and trastuzumab, risk factors for cardiotoxicity were: initial LVEF value and treated arterial hypertension [5]. Other multicenter studies confirmed that, apart from initial LVEF, the dose of anthracyclines, presence of obesity and age were important [6, 7]. In the HERA study significantly higher risk of cardiac dysfunction during trastuzumab therapy was connected with higher cumulative dose of doxorubicin (287 vs 257 mg/m^2) or epirubicin (480 vs 422 mg/m^2). It is worth to notice that our patient received doxorubicin in cumulative dose 360 mg/m^2 (six cycles of AC regime).

The analysis of randomized multicenter studies implies that smaller total percentage of cardiotoxicity in HERA study may result from two main issues:

a. before the onset of trastuzumab therapy the lowest LVEF value was ≥55%, while other studies included patients with lower LVEF
b. time span between anthracyclines and trastuzumab therapy was longer than in other studies (12 weeks).

TABLE 1.
The results of cardiac magnetic resonance imaging in a patient with cardiac systolic dysfunction induced by trastuzumab. Analysis of LV function was calculated by 3D method with the inclusion of trabecular and papillary muscle to the LV cavity in diastolic phase and turning them into the LV wall in systolic phase.

	TEST I	TEST II	TEST III
DATE	**30 Jan. 2013**	**20 Sept. 2013**	**21 Mar. 2014**
Left ventricular ejection fraction (LVEF)	41.8%	48.5%	45.5%
Stroke volume (SV)	68.1 ml	68.4 ml	55.1 ml
Stroke index	37.5 ml/beat/m	37.6 ml/beat/m	30.3 ml/beat/m
Cardiac output	4.3 l/min	4.3 l/min	3.3 l/min
Cardiac index	2.4 l/min/m	2.4 l/min/m	1.8 l/min/m
End-diastolic (ED) volume	162.95 ml	140.90 ml	121.09 ml
End-systolic (ES) volume	94.83 ml	72.51 ml	65.97 ml

RECOVERY OF TRASTUZUMAB--INDUCED CARDIAC DYSFUNCTION

Long-term observation of women from HERA study showed that trastuzumab therapy was discontinued if an episode of severe heart failure (primary end point) or significant left ventricle systolic dysfunction (secondary end point) were noted [8]. There were 86 such cases in total, which constitutes 5.1% of the treated population. Significant decrease in LVEF was defined as a decrease by at least 10 percentage points from the initial value or a decrease of LVEF below 50%. **Severe heart failure** was defined as a significant decrease in LVEF and manifestation of symptoms NYHA class III or IV confirmed by a cardiologist. **Symptomatic heart failure** was defined as a significant decrease in LVEF and manifestation of clinical symptoms confirmed by a cardiologist. **Significant systolic dysfunction** was defined as a significant decrease of LVEF with symptoms NYHA class I or II, if normalization of LVEF was not seen in subsequent echocardiographic examination (Table 2). The so called reached acute recovery was assessed. Recovery was noted if LVEF ≥ 50% had been confirmed in subsequent imaging studies. The date of the first noted LVEF ≥ 50% from the moment of cardiological event was the onset of recovery time. Also, basing on LVEF, cardiological prognosis for these patients was established. According to Experts (CAB, *cardiac advisory board*), favorable prognosis was connected with LVEF above 50%. Unfavorable prognosis was connected with LVEF below 50%. Among 59 women in whom improvement of the cardiac function was achieved 42 had sustained improvement (LVEF ≥ 50%), and 17 experienced further decrease in LVEF < 50%. The Experts of CAB analyzed all these 17 women and determined the cause of progression of cardiac dysfunction only in 6 cases. However, out of 14 patients in whom no early clinical improvement was seen, 5 had good prognosis, i.e. normalization of LVEF in the future, while 8 had poor long-term prognosis, and in one case this distant prognosis could not be established. In summary, among 14 women with unfavorable long-term cardiologic prognosis (LVEF < 50%), 6 showed early improvement of LVEF, 13 were previously treated with anthracyclines and typical cardiological treatment was reported only in 7 of these patients.

In NSABP B-31 and NCCTG N9831 studies complete cardiological analysis was preformed by a group of Experts: 3 cardiologists and 3 oncologists (ACREC, *Adjuvant Cardiac Review and Evaluation Committee*) [9]. In the group of women treated with trastuzumab heart failure class NYHA II was more common, while in the group treated with chemotherapy alone heart failure class NYHA IV was more frequent. There were also significant differences as to the efficacy of implemented treatment. In this study, in contrast to previous observations, in all women with complications typical pharmacological treatment of left ventricle systolic dysfunction was applied (Table 3). Complete recovery was more common in the group of women treated with trastuzumab – 55.5%. However, in the group treated with chemotherapy alone recovery was seen only in 14.3% of cases. Partial recovery was probable to a similar degree (28.6% vs 30.6%). Interestingly, cardiac dysfunction caused by trastuzumab more frequently required specific oral therapy with β-blocker and digoxin.

TABLE 2.
HERA trial – longer-term assessment of cardiac systolic dysfunction (modified from Procter M et al. [8]).

Cardiac end point	Reached acute recovery	Time to acute recovery (months)
Severe heart failure (n = 13)	9 (69.2%)	11.6 (1.3–28.7)
Symptomatic heart failure (n = 32)	25 (78.1%)	5.5 (0.0–28.7)
Confirmed significant LVEF drop (n = 60)	50 (83.3%)	6.3 (0.0–33.1)

TABLE 3**.**
NSABP B-31 and NCCTG N9831 trials – long-term assessment of cardiac systolic dysfunction (modified from Russell SD et al. [9]).

	AC → T		AC → TH	
	number	%	number	%
Symptomatic heart failure	7	87.5	34	94.4
Cardiac death	1	12.5	2	5.6
NYHA				
I	1	***14.3***	0	***0***
II	0	***0***	9	***26.5***
III	4	57.1	20	58.8
IV	2	**28.6**	4	**11.8**
Improvement				
complete	1	**14.3**	20	**55.5**
partial	2	28.6	11	30.6
Oral cardiological drugs	7	100	34	100
ACE-inhibitors	6	85.7	30	88.2
β-blockers	3	***42.9***	23	***67.6***
digoxin	2	***28.6***	19	***55.9***
diuretics	5	71.4	28	82.4
Intravenous cardiological drugs	4	57.1	4	11.8
diuretics	4	**57.1**	4	**11.8**
inotropic agents	0	0	1	2.9

Legends: A – doxorubicin; C – cyclophosphamide; T – taxanes; H – trastuzumab.

The results of discussed multicenter studies confirm the necessity of early prevention. Treatment of trastuzumab induced cardiac dysfunction is not always effective, although sometimes it can be very spectacular [10]. The knowledge on potential prognostic and predictive factors for type II cardiotoxicity is incomplete. Only Cardinale et al. demonstrated that increase of troponins in serum may be a potential prognostic marker for unfavorable course [11].

THE ROLE OF MODERN IMAGING STUDIES

The ESMO experts recommend control of cardiac function in all patients on adjuvant anthracyclines or trastuzumab treatment before therapy, after 3, 6 and 9 months of therapy and then after 12 and 18 months from the onset of treatment (level of evidence I, grade of recommendations A) [12]. Additional evaluations are indicated if clinically justified.

In the context of cardiotoxicity monitoring, the opinion of Steingard et al. seems important; these authors claim that there is not such thing as a safe or toxic dose of anthracyclines [13]. Subclinical symptoms of cardiotoxicity type I and II may manifest relatively early after the onset of anticancer treatment [14, 15].

Fallah-Rad et al. demonstrated that modern imaging methods may identify patients who are going to develop significant cardiac systolic dysfunction as early as in the 3rd month from trastuzumab therapy onset [16]. No such result was seen with biochemical markers, both troponin and natriuretic peptides. Among

42 patients treated with trastuzumab, in 10 cases clinically significant cardiotoxicity was seen, and these patients had subclinical abnormalities: in MRI the so called delayed enhancement of the lateral wall of the LV within the mid-myocardial portion, and in echocardiography significant changes in diastolic parameters (lateral S') and peak global longitudinal and radial strain. If these changes were regarded as early symptoms of cardiotoxicity, they may become indications for early preventive cardioprotection.

Negishi et al. used decreased global longitudinal strain of the heart muscle GLS ≥ -11% as an indication for cardioprotective administration of β-blockers in patients treated with anthracyclines and trastuzumab [17]. The study demonstrated that such strategy is clinically justified. Patients with GLS ≥ -11% who received β-blockers did not show progress of cardiotoxicity, in contrast to those from the control group, in whom LVEF continued to decrease.

POLISH MULTICENTER STUDY

There is a valuable initiative of a multicenter Polish study – **Pol--PinCO: Prevention in Cardio-Oncology: impact of genetic susceptibility, early detection, and primary/secondary prevention on chemotherapy-induced cardiotoxicity and its health and socio-economic consequences**.

The aim of the project is creation and implementation of a new, based on scientific evidence, strategy to evaluate the risk of cardiotoxicity, its early detection and individual decisions as to primary or secondary prophylaxis.

Evaluation of early cardiac muscle damage after 3 and 15 months will include, among others, levels of biomarkers and miRNA profile, and imaging studies: modern echocardiography and MRI.

Expected project results include:

1. mi-RNA - based test determining individual resistance/susceptibility to cardiotoxicity of anticancer treatment
2. cost-effective, based on biomarkers, protocol of early detection of cardiotoxicity as an alternative for cardiac imaging studies
3. identification of determinants (i.e. genetic) of cardiotoxicity
4. algorithm enabling implementation of individualized prophylaxis to decrease the occurrence of cardiotoxicity, costs of health care and increase of the quality of life.

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