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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Real-world data of cardiotoxicity during long-term therapy with trastuzumab in human epidermal growth factor receptor-2-positive metastatic breast cancer

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SUMMARY
Introduction/Objective This study aims to investigate the cardiotoxicity of long-term therapy with trastuzumab in patients with HER-2-positive metastatic breast cancer.
Methods A total of 48 patients with metastatic HER-2-positive breast cancer were analyzed. The patients received long-term trastuzumab (time of application was longer than 20 months). The analyzed characteristics of the patients were the following: age, initial stage of the disease, application of anti-HER-2 therapy and anthracyclines in the adjuvant setting, the number and type of applied systemic therapies concomitant with trastuzumab in the metastatic setting. Cardiac toxicity was assessed using left ventricular ejection fraction (LVEF) values at three time-points: at the beginning, in the middle, and at the end of treatment period for each patient separately.
Results In 17 (35.4%) patients the trastuzumab treatment was temporary discontinued. The average time of trastuzumab therapy interval was 52.2 ± 23.5 months. The mean LVEF values were 66.73 ± 7.02%, 64.62 ± 5.7%, and 63.44 ± 6.1%, respectively. The mean values of LVEF differed significantly in the three observed time-points (F = 4.9 p = 0.009). *Post hoc* pairwise comparison, using Bonferroni correction, confirmed significantly lower mean LVEF values at the end point (at the end of treatment) compared with the mean LVEF values at the beginning of anti-HER-2 treatment (p = 0.019), but within the reference range of LVEF ≥ 50%.
Conclusion The data confirm good safety profile of long-term trastuzumab therapy in HER-2 positive metastatic breast cancer patients considering cardiotoxicity.
Keywords: breast cancer; cardiotoxicity; ejection fraction; safety; trastuzumab

INTRODUCTION

Cancer and cardiovascular diseases represent the leading cause of death and an important contributor to mortality rates worldwide [1]. Female breast cancer (BC) has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases [2]. The human epidermal growth factor receptor 2 (HER-2) status in BC has a prognostic and predictive value and provides information about the prognosis of the disease and the type of appropriate specific treatment, and thus helps in selecting the optimal therapy for patient treatment. HER-2 testing is recommended for all newly diagnosed invasive BCs. The most commonly used methods for testing are immunohistochemical staining and *in situ* hybridization. Approximately 15% of BCs have excessive expression or amplification of HER-2 and have aggressive clinical behavior [3]. There has been a general consensus that the HER-2 oncogene, when overexpressed, is the dominant driver of BC biology, regardless of hormone receptor status [4]. The use of trastuzumab in combination with chemotherapy dramatically improves the prognosis in all stages of HER-2-positive BC [5]. Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER-2. It represents the standard of care in BC patients with HER-2 amplification and/or overexpression, both in the advanced and (neo) adjuvant setting. Adding trastuzumab to standard chemotherapy has led to a significant improvement in survival outcomes [6].

Trastuzumab-mediated cardiotoxicity

Cardiotoxicity is an important segment in HER-2-targeted therapy. Unlike anthracycline-induced cardiotoxicity, trastuzumab-mediated

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cardiotoxicity is not dose-dependent and is reversible. Trastuzumab may lead to an exacerbation and augmentation of cardiotoxicity induced by prior anthracycline treatment by interfering in the mechanism of homeostasis and cell survival and repair pathways [7]. In a leading phase 3 study for trastuzumab [8], as well as in subsequent studies, a significant number of patients with cardiac dysfunction were observed. Those patients received trastuzumab therapy, with special consideration for those patients in which anthracyclines and trastuzumab were administered concomitantly. Additional studies have shown that, in general, cardiotoxicity is reversible and that trastuzumab can be reintroduced in the treatment after establishing regular cardiac function. The U.S. Food and Drug Administration (FDA) has evaluated trastuzumab-mediated cardiotoxicity in four adjuvant trials (NCCTG N9831, NSABP B-31, HERA, BCIRG 006) and found a four- to six-fold increased symptomatic heart dysfunction in patients that received trastuzumab [9]. Myocardial dysfunction and heart failure, mostly described as cardiotoxicity, are the most concerning cardiovascular complications of cancer therapies. Most trials use the definition of cardiotoxicity related to cancer therapeutics defined by the European Society of Cardiology (ESC) as a decrease in left ventricular ejection fraction (LVEF) > 10% points to a value below 50% [10]. According to ESC Guidelines, LVEF should be determined before and periodically during treatment for early detection of cardiac dysfunction in patients receiving potentially cardiotoxic chemotherapy [10]. This group considers the lower limit of normal (LLN) of LVEF in echocardiography as 50%. If LVEF decreases more than 10% to a value below the LLN (LVEF < 50%), angiotensin-converting enzyme inhibitors in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic heart failure.

A cardio-oncology expert panel from the French Working Group of Cardio-Oncology has tried to harmonize the most recent American and European guidelines to propose decision algorithms that would be easy for clinicians in their daily practice [11]. The French Working Group proposes complete cardio-oncological evaluation every three months during HER-2 treatment in all patients. Original trastuzumab-related FDA prescription instructions recommend cardiology consultation and withholding trastuzumab for four weeks if the LVEF falls by ≥ 16% from the baseline, or if LVEF falls ≥ 10% below the baseline and below the LLN. According to the prescribing information, trastuzumab can be safely restarted if the LVEF returns to normal and within 15% of the baseline [12]. According to the European Society for Medical Oncology consensus recommendations for cardiac disease management in cancer patients, asymptomatic patients undergoing trastuzumab treatment who have LVEF decrease of ≥ 10% from the baseline or a drop in LVEF to ≥ 40%; a value < 50% indicates a need for referral for cardiology consultation, preferably with a cardio-oncology specialist and consider initiation of cardioprotective treatments [13]. If trastuzumab is stopped, LVEF within three to six weeks should be repeated and it is recommended to resume trastuzumab therapy if LVEF has normalized to a value > 50%. Screening with an LVEF assessment should be considered at 6–12 months and possibly two years post-treatment, and consideration for reassessment periodically thereafter [14]. Recommendations are that patients undergoing trastuzumab therapy should have a baseline cardiovascular assessment of cardiac function including history, physical examination, EKG with QTc interval and determination of LVEF by quantitative 3D transthoracic echography, cardiac magnetic resonance or multigated acquisition scan. Routine use of cardiac biomarkers (cardiac troponins) in patients receiving or potentially receiving cardiotoxic therapy is insufficiently established. There are different views on the pre-treatment use of angiotensin-converting enzyme inhibitors or beta-blockers in patients at high cardiac risk [11].

Objective

The objective of this longitudinal observational analysis is to examine the safety profile and tolerability of long-term anti-HER-2 therapy with trastuzumab and its real efficacy in the treatment of metastatic HER-2-positive BC (HER-2+ MBC) patients in everyday clinical practice.

METHODS

A total of 48 HER-2+ MBC patients were analyzed retrospectively in this study. All the patients received long-term anti-HER-2 therapy with trastuzumab (period of application was longer than 20 months) simultaneously with other systemic treatment modalities (chemotherapy, hormonal therapy) regarding to characteristics of the disease since July 2004 at University Clinic for Radiotherapy and Oncology in Skopje. In 10 patients, the disease was initially diagnosed in stage IV, while in 38 patients, disease relapse was registered after initial treatment for early-stage BC. The study also included patients who had previously received trastuzumab as part of adjuvant treatment. HER-2 status was determined locally by immunohistochemical analysis or with *in situ* hybridization in accordance with the recommendations of the American Society of Clinical Oncology / College of American Pathologists, initially at primary diagnosis or with analysis of tumor tissue obtained by biopsy of the metastatic (secondary) lesion [15].

In 38 patients diagnosed initially with early breast cancer (eBC) in whom metastatic disease occurred later after disease-free interval, parameters related to the clinical and pathological features of the primary tumor and the adjuvant oncological treatment were analyzed: primary stage of the disease, hormone receptor status (estrogen receptor and progesterone receptor), adjuvant treatment with anthracyclines, and trastuzumab. The characteristics of metastatic disease and the type of treatment were analyzed in all 48 patients with HER-2+ MBC. Analyzed parameters included: presence of visceral metastases (lung, liver, pleura, peritoneum, pleural effusion, ascites), presence of non-visceral metastases (bones, skin, lymph nodes, contralateral breast),

presence of brain metastases, number and type of systemic therapies for metastatic disease treatment applied concurrently during trastuzumab therapy. The median time to the first progression of the disease (invasive disease-free survival) in 38 patients with initially diagnosed eBC was obtained by this analysis. In all 48 patients, the duration of trastuzumab therapy and trastuzumab toxicity were analyzed by obtaining LVEF values by echocardiography. The initial time-points for the above-mentioned statistical analyses were as follows: the date of initial diagnosis, the date of first relapse of the disease for patients with initially diagnosed eBC, and the date of initiation of trastuzumab therapy for metastatic disease in all 48 patients. The patients who were alive were censored with the date of the final observation point (data cut-off at April 2021).

Cardiac toxicity was assessed by obtaining of LVEF values according to standard clinical practice every three months during anti-HER-2 therapy application period with regard to the protocol (or more frequently as it was indicated). LVEF values were collected and evaluated at three time-points for each individual patient: at the beginning (LVEF before initiating trastuzumab treatment as the first-line treatment for MBC), in the middle (LVEF in mid-treatment period for each individual patient), and at the end of treatment period (LVEF final measurement) for each patient separately. Informed consent from the patients or family members of deceased patients who were included in the analysis was obtained to use their data for scientific purposes. The database with clinical and demographic characteristics of the patients was formed using the medical records and the electronic database of the Clinic.

This study was done in accordance with the institutional standards on Ethics.

Statistical analysis

Statistical analysis of the data was performed in the statistical program IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The obtained data are presented in tabular and graphical form. Categorical variables are represented by absolute and relative numbers. Quantitative variables are presented with descriptive statistics (mean ± SDi, minimum and maximum values, median value, and interquartile range). The Kolmogorov–Smirnov test was used to test the normality of data distribution. The repeated-measures ANOVA analysis was used to compare the value of EF% in the three time-points. Kaplan–Meier survival analysis was used for invasive disease-free survival (iDFS). Statistical significance was defined at the level of $p < 0.05$.

RESULTS

The study included 48 patients with pathohistologically verified HER-2+ MBC. At the time of the study closure, 24 patients were alive and 24 were deceased. Analyzed patients were 27–69 years old, with a mean age of 47.2 ± 9.9 years. In patients with eBC as initial diagnosis (38 in total), the most common stage of disease was II – 19 (39.6%) patients. The distribution of patients by stage of disease is shown in Table 1.

Table 1. Distribution of patients by disease stage

Stage of disease	n (%)
I	3 (6.25)
IC	1 (2.08)
IIA	6 (12.5)
IIB	13 (27.08)
IIIA	5 (10.42)
IIIB	2 (4.17)
IIIC	8 (16.67)
IV	10 (20.83)
Total	48
live	24 (50)
deceased	24 (50)

Analysis of clinical parameters of patients with early breast cancer until metastatic disease onset

Analysis of data for applied adjuvant therapy in patients with initially diagnosed eBC showed that 28 (73.7%) patients received anthracyclines in the adjuvant setting, 18 (47.4%) patients were treated with adjuvant trastuzumab. Treatment with adjuvant trastuzumab in all included patients was conducted after treatment with anthracyclines (sequentially), concomitant with taxane therapy until the completion of one year adjuvant treatment. Locoregional relapse was initially reported in 10 (26.32%) patients and distant metastases in 28 (73.68%) patients. Time to onset of the first relapse of the disease (iDFS) ranged 13–216 months, with an average time of 79.2 ± 52 months. In half of the patients, the time to the first relapse occurrence was less than 55.5 months.

Analysis of clinical parameters of patients with metastatic disease

This group includes 48 patients (10 patients who were initially diagnosed with stage IV disease and 38 patients with eBC beginning from the moment of metastatic disease diagnosis). Table 2 shows the most common sites of distant metastases, the data for applied systemic therapies concomitant with trastuzumab, types of systemic therapy (lines of chemotherapy and endocrine therapy applied sequentially), treatment discontinuation, and causes for treatment discontinuation. The average duration of trastuzumab treatment was 52.2 ± 23.5 months. The shortest time of receiving trastuzumab was 20 months (in one patient), while the longest was 113 months (also in one patient). In half of the patients, the duration of trastuzumab treatment was longer than 48 months. Data on duration of trastuzumab treatment are shown in Table 3.

In 17 (35.4%) patients the treatment was discontinued; in 11 (22.92%) patients the interruption lasted longer than four months, while in six (12.5%) the interruption was shorter than four months. The reason for discontinuation of trastuzumab treatment longer than four months was initiation of a

Table 2. Sites of relapses, types and lines of applied concomitant systemic therapies, treatment discontinuation and causes for treatment discontinuation in patients with metastatic breast cancer

DM type	n (%)
visceral	15 (31.25)
non-visceral	17 (35.4)
brain	2 (4.17)
mixed (visceral + non-visceral)	11 (23.4)
mixed (visceral + brain)	3 (6.25)
Applied lines of chemo +/- hormone therapy	
1	18 (37.5)
2	15 (31.25)
3	6 (12.5)
4	6 (12.5)
5	2 (4.17)
6	1 (2.08)
Type of therapy	
chemotherapy	17 (35.42)
chemo+ hormone therapy	26 (54.17)
hormone therapy	5 (10.42)
Discontinuation of treatment	
yes	17 (35.42)
no	31 (64.58)
Cause of treatment discontinuation	
Decline of LVEF	3
Anthracyclines toxicity	8
other	6
Discontinuation of treatment (months)	
< 4 months	6 (12.5)
> 4 months	11 (22.92)

DM – distant metastases; LVEF – left ventricular ejection fraction

Table 3. Duration of anti HER-2 treatment with trastuzumab (months)

Descriptive statistics		
Duration of trastuzumab treatment (months)		
Mean ± SD	Median (IQR)	Min–max
52.2 ± 23.5	48 (35–66)	20–113

IQR – interquartile range

new line of treatment with chemotherapy regimen containing anthracyclines or therapy with T-DM1 (ado-trastuzumab emtansine). There was no discontinuation in trastuzumab treatment in 31 (64.58%) patients. Three (6.25%) patients had discontinuation of trastuzumab because of a decline of LVEF below 50%. In two of these three patients, discontinuation of treatment was longer than four months and anti-HER-2 treatment was resumed after normalization of LVEF. In one patient, anti-HER-2 treatment was not continued due to low LVEF and disease progression. Table 2 presents the causes for treatment discontinuation.

The mean LVEF values were 66.73 ± 7.02%, 64.62 ± 5.7% and 63.44 ± 6.1%, at the beginning, median, and end of treatment, respectively (Table 4). According to the results in Table 5, the mean values of LVEF differed significantly in the observed three time-points (F = 4.9 p = 0.009). *Post hoc* pairwise comparison, using Bonferroni correction, confirmed significantly lower mean LVEF values at the endpoint (at the end of treatment) compared with the mean LVEF values at the beginning of anti-HER-2 treatment (p = 0.019) but within the reference range of LVEF ≥ 50%.

DISCUSSION

This longitudinal observational analysis included 48 patients with metastatic BC treated with trastuzumab for more than 20 months. The mean duration of trastuzumab treatment was 52.2 ± 23.5 months. In 17 (35.4%) patients the treatment with trastuzumab was temporarily discontinued, in 11 (22.92%) of them the discontinuation was longer than four months, while in six (12.5%) the discontinuation was shorter than four months. Discontinuation of trastuzumab therapy was mostly due to initiation of anthracycline-containing regimen because of disease progression. Only in three (6.25%) patients, the reason for discontinuation of treatment was decline in LVEF below 50%. Of these three patients, in two patients the discontinuation of treatment was longer than four months and anti-HER-2 treatment was resumed after normalization of LVEF, while in one patient anti-HER-2 treatment was not continued due to low LVEF and disease progression. The mean LVEF was 66.73 ± 7.02%, 64.62 ± 5.7%, and 63.44 ± 6.1%, at the beginning, middle, and the end of treatment, respectively. *Post hoc* pairwise comparison, according to Bonferroni correction, showed significantly lower mean value of LVEF in the third analyzed point (last evaluation of LVEF at the end of treatment) compared to the starting point (p = 0.019), but this difference did not exceed the referent values. These results support favorable safety profile of long-term therapy with trastuzumab, which was 52 months in this study. Trastuzumab is a milestone in the treatment of HER-2-positive BC. However, the data on the safety of long-term use of trastuzumab in a metastatic setting are scarce. One review study detected four trials for long-term safety of trastuzumab in metastatic BC [16]. The LHORA study reported 2.2% of trastuzumab-related

Table 4. Mean values of left ventricular ejection fraction (beginning, median, and end of treatment)

Variable	Descriptive statistics		
	Mean ± SD	median (IQR)	Min–max
1. LVEF% (start of treatment)	66.73 ± 7.02	66 (61.5–69)	58–101
2. LVEF% (median of treatment)	64.62 ± 5.7	64 (60–68)	55–83
3. LVEF% (end of treatment)	63.44 ± 6.1	64 (60–68)	46–75

IQR – interquartile range; LVEF – left ventricular ejection fraction

Table 5. *Post hoc* pairwise comparison (Bonferroni correction)

Repeated measures ANOVA F = 4.9; p = 0.009 sig		
	2	**3**
1	0.20ns	**0.019 sig**
2		0.459 ns

ns – non-significant; sig – significant; ANOVA – analysis of variance; adjustment for multiple comparisons: Bonferroni

cardiotoxicity in patients with progression-free survival > 3 years receiving first-line treatment with trastuzumab without discontinuation of the treatment [17]. This may be particularly important in the context of the new clinical reality which is the use of novel anti-HER-2 targeted therapies that enable significant increase in disease-free survival and overall survival in patients MBC (pertuzumab, trastuzumab emtansine, lapatinib, neratinib, trastuzumab deruxtecan, margetuximab, tucatinib).

Trastuzumab deruxtecan (T-DXd) is a HER-2-targeting antibody-drug conjugate approved for patients with advanced HER-2+ MBC based on the results from the DESTINY-Breast01 study [18, 19]. According to the DESTINY-Breast03 study, the most common treatment emergent adverse event associated with treatment discontinuation for T-DXd was interstitial lung disease / pneumonitis, while LVEF decline was seen in 2.7% [20]. Many ongoing trials evaluate toxicity profile and safety of combined anti-HER-2 agents. Ongoing DESTINY-Breast09 trial will evaluate the efficacy and safety of trastuzumab deruxtecan, either alone or in combination with pertuzumab, in treating patients with HER-2-positive BC as a first line of treatment (San Antonio Breast Cancer Symposium 2021 Abstract OT1-14-02).

The data obtained in our study related to cardiac toxicity, which was registered in 6.25% of the patients, are comparable to those obtained in the CLEOPATRA study [21]. In this study, the median follow-up time was longer than 50 months, with reported left ventricular dysfunction lower in the pertuzumab group than in the control group (6.6% *vs*. 8.6%). The data on the toxicity of long-term use of trastuzumab in daily clinical practice are of great importance in decision making for patients' treatment with poorer performance status, comorbidities, older age, symptomatic disease, or the combination of the aforementioned characteristics. The patient population in daily clinical practice is generally less selected or unselected compared to randomized clinical trials, while data from these studies may be somehow limited in terms of data generalization.

The presented data are obtained mostly from observational studies prior to the introduction of dual anti-HER-2 therapy with pertuzumab/trastuzumab and taxanes as standard of care in a first-line treatment setting for MBC HER-2-positive patients. A particularly interesting research area is a possible increase in cardiotoxicity due to dual anti-HER-2 blockade. In addition, future trials for new agents targeting HER-2 should focus on cardiotoxicity, as they represent a new standard in subsequent treatment settings. Women's Heart Centers are a globally adopted follow-up solution and can offer comprehensive care for women cancer survivors [22].

CONCLUSION

The presented data are in correlation with the favorable safety profile and tolerability of trastuzumab in patients with MBC treated with prolonged trastuzumab therapy. The low incidence of registered cardiac events confirms the favorable safety profile of long-term therapy. However, cardiac monitoring on regular intervals tailored to each patient during and after treatment is necessary, especially for high-risk patient subgroups. In patients with stable heart function and low cardiac risk, it is possible to adjust the period of cardiac monitoring to longer time intervals. Data from daily clinical practice confirm the efficacy of trastuzumab in an unselected patient population.

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Кардиотоксичност код дуготрајне анти-HER2 терапије трастузумабом у случају болесника са метастатским карциномом дојке позитивним на HER2 – подаци из свакодневне клиничке праксе

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САЖЕТАК

Увод/Циљ Ова анализа има за циљ да истражи кардиотоксичност дуготрајне терапије трастузумабом код болесника са метастатским карциномом дојке позитивним на HER2.

Методе Студија је ретроспективно анализирала 48 болесница са метастатским карциномом дојке позитивним на HER2. Болесници су примали дуготрајну анти-HER2 терапију трастузумабом (време примене дуже од 20 месеци). Анализиране су следеће карактеристике болесника: старост, почетни стадијум болести, примена анти-HER2 терапије трастузумабом и антрациклинима у адјувантном контексту, број и врста аплицираних системских терапија конкурентно са трастузумабом у лечењу метастатске болести. Кардијална токсичност је процењена коришћењем вредности левовентрикуларне ејекционе фракције (ЛВЕФ) у три временске тачке: на почетку, на средини и на крају периода лечења сваког болесника.

Резултати Код 17 (35,4%) болесника лечење трастузумабом је привремено прекинуто. Просечна вредност ЛВЕФ-а била је 66,73 ± 7,02%, 64,62 ± 5,7% и 63,44 ± 6,1%, појединачно. Просечне вредности ЛВЕФ-а су се значајно разликовале у евалуиране три временске тачке ($F = 4,9$; $p = 0,009$). Пост-хок анализа парова, коришћењем Бонферонијеве корекције, показала је значајно ниже средње вредности ЛВЕФ-а на крају третмана (на крајњој тачки), у поређењу са средњим вредностима ЛВЕФ-а на почетку анти-HER2 третмана трастузумабом ($p = 0,019$), али унутар референтне вредности ЛВЕФ-а ≥ 50%.

Закључак Резултати потврђују добар безбедносни профил дуготрајне анти-HER2 терапије трастузумабом код болесника са метастатским карциномом дојке позитивним на HER-2 у погледу кардиотоксичности.

Кључне речи: рак дојке; кардиотоксичност; ејекциона фракција; безбедност; трастузумаб