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

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

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SUMMARY

Introduction/Objective This study aims to investigate the cardiotoxicity of long-term therapy with trastuzumab in patients with HER2 positive metastatic breast cancer.

Methods A total of 48 patients with metastatic HER2 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: age, initial stage of the disease, application of anti-HER2 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 observed three time points (F=4.9 p=0.009). Post hoc pairwise comparison, using Bonferonni 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-HER2 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 HER2 positive metastatic breast cancer patients considering cardiotoxicity.

Keywords: breast cancer; cardiotoxicity; ejection fraction; safety; trastuzumab

САЖЕТАК

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

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

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 пацијената са HER-2 позитивним метастатским карциномом дојке у погледу кардиотоксичности.

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

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INTRODUCTION

Cancer and cardiovascular diseases represent leading cause of death and an important contributor to mortality rates worldwide [1]. Female breast cancer has now surpassed lung

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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 (HER2) status in breast cancer has 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. HER2 testing is recommended for all newly diagnosed invasive breast cancers. The most commonly used methods for testing are immunohistochemical staining (IHC) and in situ hybridization (ISH). Approximately 15% of breast cancers have excessive expression or amplification of human epidermal growth factor receptor 2 (HER-2) and have an aggressive clinical behavior [3]. There has been a general consensus in fact, that the HER-2 oncogene, when overexpressed, is the dominant driver of breast cancer biology, regardless of hormone receptor (HR) status [4]. The use of trastuzumab in combination with chemotherapy dramatically improves the prognosis in all stages of HER2-positive breast cancer [5]. Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of human epidermal growth factor receptor 2 (HER2). It represents the standard of care in breast cancer (BC) patients with HER2 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].

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Trastuzumab-mediated cardiotoxicity

Cardiotoxicity is an important segment in HER2 targeted therapy. Unlike anthracycline-induced cardiotoxicity, trastuzumab-mediated cardiotoxicity is not dose-dependent and is reversible. Trastuzumab may lead to exacerbation and augmentation of cardiotoxicity induced by prior anthracycline treatment by interfering in mechanism of homeostasis and cell survival and repair pathways [7]. In 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 it is reversible and that trastuzumab can be reintroduced in the treatment after establishing of regular cardiac function. The U.S. Food and Drug Administration **(**FDA) has evaluated trastuzumab-mediated cardiotoxicity in the four adjuvant trials (NCCTG N9831, NSABP B-31, HERA, BCIRG 006) and found 4 to 6-fold increased

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symptomatic heart dysfunction in patients that received trastuzumab [9]. Myocardial dysfunction and heart failure (HF), 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) of >10% points to a value below 50% [10]. According to ESC Guidelines [10], LVEF should be determined before and periodically during treatment for early detection of cardiac dysfunction in patients receiving potentially cardiotoxic chemotherapy. 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 (ACE) inhibitors in combination with beta-blockers (BB) are recommended to prevent further LV dysfunction or the development of symptomatic HF.

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 3 months during HER2 treatment in all patients. Original trastuzumab-related FDA prescription instructions recommend cardiology consultation and withholding trastuzumab for 4 weeks if the LVEF falls by ≥16% from baseline, or if LVEF falls ≥10% below 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 baseline [12]. According ESMO consensus recommendations for cardiac disease management in cancer patients [13], asymptomatic patients undergoing trastuzumab treatment who have LVEF decrease of ≥10% from baseline or a drop in LVEF to ≥40% but <50% should refer for cardiology consultation, preferably a cardio-oncology specialist and consider initiation of cardioprotective treatments. If trastuzumab is stopped, LVEF within 3-6 weeks should be repeated and it is recommended to resume trastuzumab therapy if LVEF has normalized to >50%. Screening with an LVEF assessment should be considered at 6 to 12 months and possibly 2 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 left ventricular ejection fraction by quantitative 3D transthoracic echography, cardiac magnetic resonance (CMR) or multigated acquisition scan (MUGA). Routine use of cardiac biomarkers

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(cardiac troponins) in patients receiving or receiving potentially cardiotoxic therapy is insufficiently established. There are different views on the pre-treatment use of ACE inhibitors or beta-blockers in patients at high cardiac risk [11].

Aim

Aim of this longitudinal observational analysis is to examine the safety profile and tolerability of long-term anti-HER2 therapy with trastuzumab and its real efficacy in the treatment of metastatic HER2 positive breast cancer patients in everyday clinical practice.

METHODS

A total of 48 patients with metastatic HER2 positive breast cancer (HER2+ MBC) were analyzed retrospectively in this study. All the patients received long-term anti-HER2 therapy with trastuzumab (period of application was longer than 20 months) at the same time 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 breast cancer. The study also included those patients who have previously received trastuzumab as part of adjuvant treatment. HER2 status was determined locally by immunohistochemical analysis (IHC) or with in situ hybridization (ISH) in accordance with the recommendations of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) [15], initially at primary diagnosis or with analysis of tumor tissue obtained by biopsy of metastatic (secondary) lesion.

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 -ER and progesterone receptor-PR), adjuvant treatment with anthracyclines, and trastuzumab. The characteristics of metastatic disease and the type of treatment were analyzed in all 48 patients with HER2+ MBC. Analyzed parameters included: presence of visceral metastases (lung, liver,

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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- IDFS) in 38 patients with initially diagnosed early breast cancer 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: the date of initial diagnosis, the date of first relapse of the disease for patients with initially diagnosed early breast cancer, 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 in every 3 months during anti-HER2 therapy application period regarding to the protocol (or more frequently as it was indicated). LVEF values were collected and evaluated at 3 time points for each individual patient: at the beginning (LVEF before initiating trastuzumab treatment as 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.

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Statistical analysis

Statistical analysis of the data was performed in the statistical program SPSS Statistics for Windows, Version 23.0. 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 to iDFS. Statistical significance was defined at the level of $p < 0.05$.

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RESULTS

The study included 48 patients with pathohistologically verified HER2+ MBC. At the time of the study closure, 24 patients were alive and 24 were deceased. Analyzed patients were at age between 27 to 69 years, with a mean age of 47.2 ± 9.9 years. In patients with early breast cancer 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.

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 early breast cancer 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 (invasive disease-free survival-iDFS) ranged from 13 to 216 months with an average time of 79.2 ± 52.0 months. In half of the patients, the time to the first relapse occurrence was less than 55.5 months.

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Analysis of clinical parameters of patients with metastatic disease

This group includes 48 patients (10 patients who were initially diagnosed in stage IV disease and 38 patients with early breast cancer 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

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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 4 months, while in 6 (12.5%) the interruption was shorter than 4 months. The reason for discontinuation of trastuzumab treatment longer than 4 months was initiation of a 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 4 months and anti-HER2 treatment was resumed after normalization of LVEF. In one patient, anti-HER2 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 Bonferonni 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-HER2 treatment ($p = 0.019$) but within the reference range of LVEF ≥50%.

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DISCUSSION

This longitudinal observational analysis included 48 patients with metastatic breast cancer 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 4 months, while in 6 (12.5%) the discontinuation was shorter than 4 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 4 months and anti-HER2 treatment was resumed after normalization of LVEF, while in 1 patient anti-HER2 treatment was not continued due to

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low LVEF and disease progression. The mean LVEF was 66.73 ± 7.02%, 64.62 ± 5.7%, and 63.44 ± 6.1%, respectively, at the beginning, middle, and end of treatment. Post hoc pairwise comparison, according to Bonferonni 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 HER2 positive breast cancer. However, data on the safety of long-term use of trastuzumab in metastatic setting are modest. One review study detected four trials for long-term safety of trastuzumab in metastatic breast cancer [16]. The LHORA study [17] reported 2.2% of trastuzumab-related cardiotoxicity in patients with progression-free survival > 3 years receiving first-line treatment with trastuzumab without discontinuation of the treatment. This may be particularly important in the context of the new clinical reality which is the use of novel anti-HER2 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 HER2-targeting antibody–drug conjugate approved for patients with advanced HER2+ MBC based on the results from study DESTINY-Breast01 [18, 19]. According to 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-HER2 agents. Ongoing trial DESTINY-Breast09 will evaluate the efficacy and safety of trastuzumab deruxtecan, either alone or in combination with pertuzumab, in treating patients with HER2-positive breast cancer 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 combination of all above characteristics. The patient population in daily clinical practice is generally less selected or unselected compared to randomized

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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-HER2 therapy with pertuzumab/ trastuzumab and taxanes as standard of care in first-line treatment setting for MBC HER2-positive patients. A particularly interesting research area is possible increase in cardiotoxicity because of dual anti-HER2 blockade. In addition, future trials for new agents targeting HER2 should focus on cardiotoxicity as they represent a new standard in subsequent treatment settings. Women's Heart Centers are 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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Conflict of interest: None declared.

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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)

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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 (MBC)

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

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Table 3. Duration of anti HER2 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

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Table 4. Mean values of LVEF (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

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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

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