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Trimetazidine as a Modifier of Chemotherapy-Induced Cardiovascular Redox-Homeostasis Disturbances

Conflict of interest: nothing to declare.
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Abstract

Introduction. Our research was determined to investigate the Adriamycin + Cyclophosphamide (AC)-mode of chemotherapy-related disturbances of cardiovascular (CV) homeostasis, and possibility of trimetazidine (TMZ)-induced cardioprotection.
Purpose. Assess oxidative state of myocardium during AC-mode of chemotherapy administration, and justification of trimetazidine prescription among under-treatment and post-treatment cancer patient.
Materials and methods. For this study, 80 inbred Wistar rats were randomly divided into four equal experimental groups. A model of lipid peroxidation (LPO)-induced myocardial injury, was attained via doxorubicin and cyclophosphamide co-administration. Trimetazidine was used as a probable limiter of heart and vessels morpho-functional homeostasis aggravations.
Results. The markers of redox-balance, were determined and assessed. The data obtained showed that this TMZ modified the intensification of lipid peroxidation.
Conclusions: 1. AC-mode of chemotherapy has LPO-stimulating and antioxidant-limiting impact. 2. TMZ provide statistically significant and valuable normalization of redox-homeostasis.
Keywords: cardiotoxicity, atherosclerosis, oxidative stress, myocardial metabolism, doxorubicin

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Триметазидин как модификатор химиотерапией индуцированного СПОЛ-повреждения миокарда

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Резюме

Введение. Настоящее исследование направлено на изучение прооксидантного потенциала доксорубицин-циклофосфамидного режима химиотерапии наряду с оценкой возможностей антирадикальной защиты триметазидина.
Цель. Оценить прорадикальное воздействие АС-режима химиотерапии на миокард наряду с обоснованием применения триметазидина.
Материалы и методы. С целью проведения настоящей экспериментальной работы 80 половозрелых инбредных крыс линии Wistar были рандомным образом разделены на четыре равные группы. Модель индуцированного СПОЛ-ассоциированного повреждения миокарда была получена при одновременном применении доксорубицина и циклофосфамида. В качестве потенциального стабилизатора редокс-гомеостаза был использован триметазидин.
Результаты. Определены и оценены маркеры окислительно-восстановительного баланса. Полученные данные подтвердили эффективность применения триметазидина как модификатора СПОЛ-индуцированного повреждения сердца и сосудов развившегося на фоне АС-режима химиотерапии.
Выводы: 1. АС-режим химиотерапии оказывает СПОЛ-стимулирующее и антиоксидант-лимитирующее воздействие. 2. Триметазидин обеспечивает статистически достоверную нормализацию окислительно-восстановительного гомеостаза миокарда.
Ключевые слова: кардиотоксичность, атеросклероз, оксидативный стресс, метаболизм миокарда, доксорубицин

■ INTRODUCTION

Currently, the fact of substantial advancement in the prognosis of cancer patients, along with an increase in life expectancy, is a breakthrough in contemporary medicine. At the same time, the level of hospitalizations for cardiovascular complications among cancer

patients [1]. Per the data obtained from the Pan-European CARDIOTOX-2020 register the rescue of cardiovascular complications among cancer patients is significantly higher [2].

The most challenging problem cardiologists and oncologists are currently encountering is the decision about the possibility or impossibility of commencing, continuing or terminating chemotherapy in the case of CVD. Discussing the AC-mode of chemotherapy-related induction of lipid metabolism disequilibrium processes, the hepatotoxic potential of both components should be additionally considered [3–5]. Thus, the study of the pathophysiological and molecular basis of the proatherogenic reactions deems very promisingly.

The problem of atherosclerosis development among AC mode of chemotherapy administered cancer patient with low CV risk was grab our attention. That's why we have started to research this issue. We have already published 3 clinical cases [6–8] were we comprehensively discus this actual problem. Moreover, our group also published two narrative review which related to this problem, the first one is about pathological pathways of doxorubicin related CV toxicity [9] and the second one about the modern outlook of atherosclerosis development and progression mechanisms [10]. Also, we have obtained data, which indicate that AC-mode of chemotherapy is a hyperhomocysteinemia development trigger, and moreover we have discovered promising pleotropic effects of TMZ – homocysteine stabilizing property [11].

Trimetazidine, a well-known and widely available myocardioprotector, was chosen as a modifier of chemotherapy-driven cardiovascular complications. It is known that this drug is the only cardioprotector included in the protocols for the treatment of patients with CVD, both by the Russian Society of Cardiology and the European Council of Cardiology [12, 13]. TMZ inhibits the mitochondrial 3-ketoacyl-CoA thiolase, improves myocardial metabolism through enhancing the activation of AMPK, and thus improves insulin sensitivity and resultantly relived mitochondrial dysfunction [14, 15].

It should be noted that experimental animals were administered not a single chemotherapy drug but a full chemotherapy mode. The chosen drugs administration method makes the results more extrapolative and outmost comparable with real clinical practice.

■ PURPOSE OF THE STUDY

Assess oxidative state of myocardium during AC-mode of chemotherapy administration, and justification of trimetazidine prescription among under-treatment and post-treatment cancer patient.

■ MATERIALS AND METHODS

For this experimental study, 80 inbred Wistar rats (males, weighing 280–300g) were probed. The animals were kept in a vivarium under the conventional conditions, specifically in plastic cages with wood chips, of 5 individuals in each, at a temperature of 22–24 °C, under the conditions of 12-hour daylight, with free access to food (standard diet) and water (ad libitum). The study with experimental animals was carried out under stringent recommendations stipulated in the "Guide for the Care and Use of Laboratory Animals – NAP, 2012". All manipulations were carried out following the European Convention's provisions for the Protection of Vertebrates Used for Experimental and Other Scientific Purposes (Strasbourg, 1986; ed. Strasbourg, 2006) and legislation on the protection of animals used for scientific purposes (Directive 2010/63 / EU).

At the onset of the study, the experimental animals were randomly divided into 4 equal groups by 20 rats in each:

1. Group № 1 – rats were injected intraperitoneally with a normal saline in a single dose of 10 ml/kg, 3 times a week within 2 weeks.
2. Group № 2 – administrated AC chemotherapy regimen, carried out by intraperitoneal administration of DOX (Actavis plc., USA) in a single dose of 2.5 mg/kg and CY-monohydrate (Belmedpreparaty RUE, Belarus) in a single dose of 25 mg/kg, 3 times a week within 2 weeks.
3. Group № 3 – administered AC-mode of chemotherapy in a similar manner (DOX + CY) with additional intragastric administration of crushed TMZ dihydrochloride (Preductal, Servier, France) in a single dose of 3.0 mg/kg [16]. The preparation was carried out daily, from the beginning to the end of the experimental work.
4. Group № 4 – rats were similarly administered TMZ dihydrochloride at the previously noted dosage, as well as intraperitoneal normal saline per the same group № 1 scheme, during 2 weeks.

The cumulative dosage of DOX was 15 mg/kg [17] and CY 150 mg/kg [18]. On a daily basis TMZ dihydrochloride was administered intragastricly through a probe in a complete dosage of 42 mg/kg. On the days coinciding with chemotherapeutic agents' injection, TMZ was administered one hour before the intraperitoneal chemotherapy injections.

In group № 2 (DOX+CY), by the end of the 2^{d} week of the experiment, the death of 4 rats was recorded. No animal deaths were observed in other groups. The material was collected after the 2 day of final injection.

Biological material sample preparation

After the completion of the above described administration that lasted 14 days and 12 hours prior to the blood collection, the feeding of animals was stopped. Access to the drinking bottle was ad libitum. Before taking the biomaterial, the rats were put under deep anesthesia by means of telazol 20 mg/kg intramuscularly (IM) (Zoetis Inc., USA) and xylanit 6 mg/kg IM (NITA-PHARM, Russia). Thereafter, a thoracotomy was performed, followed by blood sampling from the right atrium with a disposable sterile 10 ml syringe (on average, 5–6 ml of blood was received from each rat). After that, using tweezers and scissors, the heart was isolated, followed by a cutting out the left ventricle (LV) and washing out the latter in 4 °C phosphate buffered saline (PBS).

Homogenate obtaining procedure from the tissues was performed per the test system's commercial kits manufacturer protocols. Left ventricle myocardium was minced with a scissors, and rinsed with cold PBS. After that, myocardium fragments were placed in ice cold 0.1M Tris/HCl buffer (ratio 1 to 25, pH 7.4, containing 0.5% Triton X-100, 5mM β-ME, 0.1 mg/ml PMSF) and homogenized by Ultra-Turrax Tube Drive (IKA, Germany) in DT-20 rotor-tube at 4000 rpm for 8 minutes. After that, homogenate was centrifuged at 14,000 x g for 5 minutes at +4 °C. 250 µl of supernatant was mixed with equal volume 2N perchloric acid, vortex and then centrifuge at 13,000 x g for 10 minutes to remove precipitated protein. Obtained biomaterial was frozen and cryopreserved at –80 °C.

Indices of the redox system in the homogenate of the left ventricular myocardium

Before conducting studies of the redox system indices, quantitative determination of the protein content in the obtained supernatants was carried out by using the Lowry

Protein Quantification Assay Kit test system (ABIN3172698, Antibodies-Online, Germany) (triplicate measurements, 40 µl diluted tissue extract sample for each well). The measuring range was 1.0-1500 µg/ml. The sensitivity of the assay was 1 µg/ml.

Determination of the superoxide dismutase (SOD) activity was performed in the heart tissue homogenate supernatant using the Superoxide Dismutase Activity Assay Kit (Colorimetric) test system. The sensitivity was 0.1 U/ml. The results were presented in U/mg protein.

Determination of the glutathione reductase (GR) activity was performed in the heart tissue homogenate supernatant using the Glutathione Reductase Activity Colorimetric Assay Kit. Assay range was 0.1-40 mU/ml. The results were presented in U/mg protein.

Glutathione peroxidase (GP) activity was determined in the heart tissue homogenate supernatant using the Glutathione Peroxidase Activity Colorimetric Assay Kit. The sensitivity was 0.5 mU/ml. The results were presented in U/mg protein.

Quantitative determination of MDA (malondialdehyde) was performed in the supernatants of heart tissue homogenates using the Lipid Peroxidation (MDA) Assay Kit. The sensitivity of the test system was >1 nmol/well. The results were presented in nmol/g protein.

Statistical analysis. All determined results are presented as mean values (M)± standard deviation of the mean (SD). The analysis of the data obtained was carried out using ANOVA test followed by Tukey's post-hoc test using SPSS 22 (Statistical package for the Social Sciences Inc., USA 14, 0). P-value <0.05 was considered at a significant level.

■ RESULTS

To assess the state of the redox system in the myocardium, both the markers of lipid peroxidation (LPO) damage (MDA), and the LPO limitation reproduction indices (SOD, GR, GP) were assessed. It is well-known that glutathione is the main intracellular thiol-disulfide redox buffer, which is a cofactor of many antioxidant enzymes [19, 20]. After 2 weeks, from the start of the AC-mode of chemotherapy administration, statistically significant intergroup differences were recorded in the rat myocardial homogenate in terms of such indicators of redox homeostasis as the malondialdehyde concentration, and superoxide dismutase, glutathione reductase, and glutathione peroxidase activities (one-way ANOVA, $p<0.0001$) (Table).

■ DISCUSSION

MDA is a comprehensive and universally accepted marker of LPO-associated processes intensification [21]. An increase in MDA and a decrease in the studied antioxidant concentrations in the group № 2 indicated that DOX and CY, in addition to their pro-radical effects, also inhibit the severity of the antioxidant pathway of cardiomyocyte's sanogenesis.

The obtained results indicate a physiological state of myocardial redox homeostasis, both in control and only TMZ treated rats. During pairwise comparisons between groups No. 1 (control) and No. 4 (TMZ), no statistically significant differences were found in the MDA level, as well as in the activity of SOD, GR and GP (Tukey's post-hoc test, $p>0.05$). The most pronounced, concerning group No. 1 (control) and No. 4 (TMZ), deviations in redox-balance status were observed in the group of doxorubicin + cyclophosphamide co-administration (Tukey's post-hoc test, $p<0.05$). Such wise, in group No. 2, the MDA level is

Indicators of the redox balance determined in the myocardial homogenate

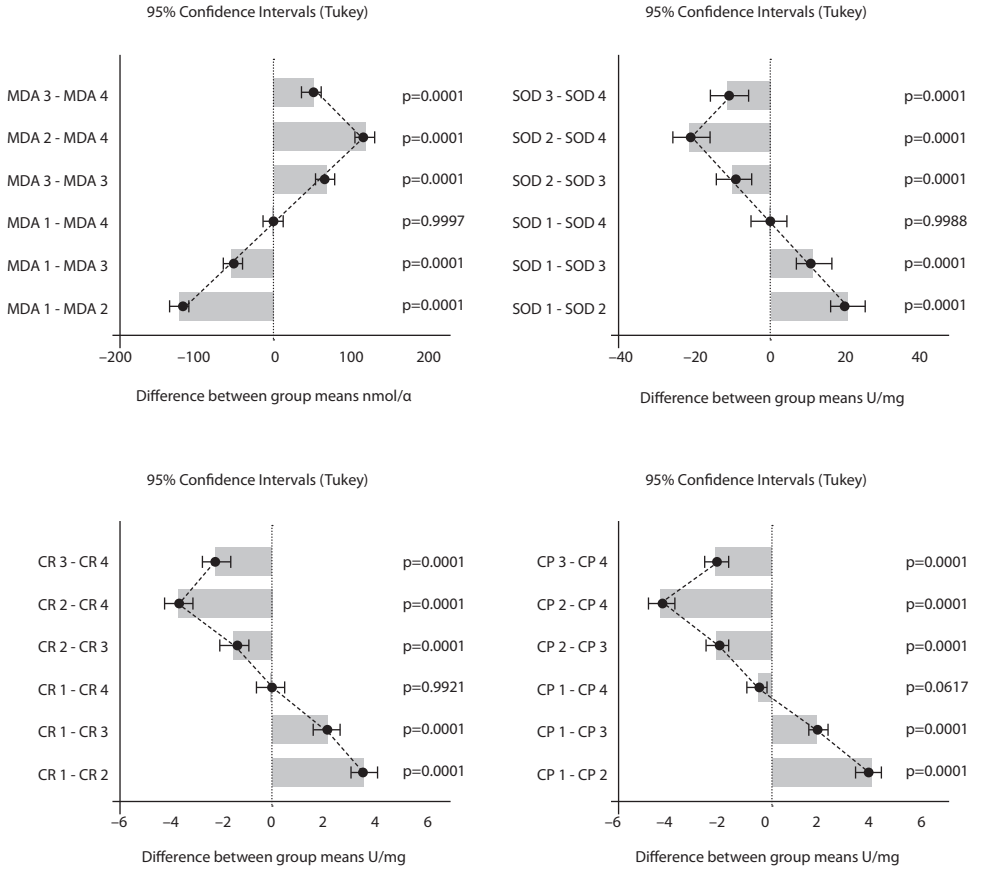
Marker	Group 1, NaCl	Group 2, AC-mode	Group 3, AC-mode + TMZ	Group 4, TMZ	Tukey's post-hoc Test
Malondialdehyde/ MDA F=246.40 p<0.0001 (nmol/g)	56.35±7.08	174.83±26.96	107.41±12.96	55.85±9.12	P_{1-2}=0.0001 P_{1-3}=0.0001 P_{1-4}=0.9997 P_{2-3}=0.0001 P_{2-4}=0.0001 P_{3-4}=0.0001
Superoxide dismutase / SOD F=62.68 p<0.0001 (U/mg)	34.95±2.84	14.42±4.19	23.80±4.06	35.22±9.23	P_{1-2}=0.0001 P_{1-3}=0.0001 P_{1-4}=0.9988 P_{2-3}=0.0001 P_{2-4}=0.0001 P_{3-4}=0.0001
Glutathione reductase / GR F=138.50 p<0.0001 (U/mg)	5.84±0.95	2.25±0.54	3.72±0.58	5.90±0.53	P_{1-2}=0.0001 P_{1-3}=0.0001 P_{1-4}=0.9921 P_{2-3}=0.0001 P_{2-4}=0.0001 P_{3-4}=0.0001
Glutathione peroxidase / GP F=221.90 p<0.0001 (U/mg)	5.43±0.49	1.60±0.51	4.13±0.51	5.31±0.78	P_{1-2}=0.0001 P_{1-3}=0.0001 P_{1-4}=0.0617 P_{2-3}=0.0001 P_{2-4}=0.0001 P_{3-4}=0.0001

higher by 102.5 and 103.2%, SOD activity is lower by 83.2 and 83.8%, GR activity is lower by 88.8 and 89.6% and GP activity is lower by 109, 0 and 107.8% than in groups No. 1 and No. 4, respectively.

The MDA concentration exaggeration (concerning group № 1) indicated the presence of oxidative stress. Because of MDA excessive formation, the highly reactogenic MDA-driven adducts were formed in the cellular matrix, which overstimulates the multiple processes of cardiomyocytes' functional activity deterioration [22]. Meanwhile, due to the limited antiradical reserve, the heart sanogenetic mechanisms could not utilize the consequences of LPO-associated injuries [23]. Consequently, inadequate oxidation products accumulation and cardiomyocyte's inability to self-normalization results in profibrotic reaction generation [24]. Considering the glutathione system's role in the AH development [25], GP and GR concentrations changes should be regarded as a risk factor for hypertension development.

It is noteworthy that TMZ, having shown its cardioprotective effect [26], was favorably reflected in the myocardial redox system parameters. When comparing groups No. 3 and No. 2, it was noted that the use of TMZ was associated with a decrease in the concentration of MDA by 47.8%, as well as an increase in SOD activity by 49.1%, GR by 49.2% and HP by 88.3% (post-hoc Tukey test, $p<0.05$). TMZ-induced MDA reduction, as well as SOD production stimulation, looks impressive. Moreover, the TMZ-associated GP and GR normalization will positively influence stable normal blood pressure values achievement.

The accepted mechanism of ROS formation upon doxorubicin administration is as follow: the quinone fragment of anthracyclines is sensitive to the monovalent recovery to



Intergroup differences in the concentration of MDA, SOD, GR and GP after 2 weeks from the start of AC-mode chemotherapy, U/mg (difference in mean, ±95% CI, one-way ANOVA, post-hoc Tukey test

semiquinone radicals by several cellular oxidoreductases, which destabilize redox-balance and act as a trigger for ROS formation [27]. Also, we developed some cellular mechanisms of chemotherapy-driven ROS generation, notably dysfunctional nitric oxide synthases (NOSs) and nicotinamide adenine dinucleotide phosphate oxidases (NOXs) pathways [28].

■ CONCLUSION

The AC-mode of chemotherapy is an inducer for pro-arteriosclerotic continuum aggravation, and TMZ could play a required role in the limitation of this process. However, despite the obtained statistically proven and significant results, future studies remain unavoidably necessary to strengthen evidence of TMZ administration to AC-mode of chemotherapy cancer patient.

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