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THE USE OF SODIUM-GLUCOSE COTRANSPORTER TYPE 2 INHIBITORS FOR THE PURPOSE OF TREATING THE CHRONIC CARDIAC FAILURE IN ONCOLOGY PATIENTS RECEIVING CARDIOTOXIC CHEMOTHERAPY: PRELIMINARY RESULTS

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ABSTRACT

BACKGROUND: *Chronic cardiac failure belongs to the most threatening and delayed manifestations of cardiotoxicity in oncology patients receiving the treatment with antitumor medicines. As of today, only two groups of drugs were proven to have significant cardioprotective effects in these categories of patients: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-adrenergic blockers. Recently, the first data were published on the successful use of sodium-glucose cotransporter type 2 inhibitors in patients with chronic cardiac failure, receiving anthracycline therapy.* ***AIM:*** *optimization of cardioprotective therapy in the treatment of chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy.* ***METHODS:*** *A prospective observational open-label research was carried out with an enrollment of 116 oncology patients with verified chronic cardiac failure, which were receiving cardiotoxic chemotherapy, of which 60 patients of the control group were receiving double cardioprotective therapy (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) and the 56 patients of the test group were receiving similar therapy with an addition of Dapagliflozin at a dosage of 10 mg once daily in the morning. The controls of the results were conducted in 6 months by means of laboratory and instrumental examinations, as well as by using additional methods of controlling the results.* ***RESULTS:*** *The groups compared did not differ by the combined primary clinical endpoint (the rate of hospitalizations due to cardio-vascular reasons, the refusal to undergo chemotherapy for the reason of chronic cardiac failure progression and the safety of using the drug products: the presence of urinary tract infections and sepsis), but they differed by the surrogate clinical endpoints that included the dynamic trend of the levels of the groups compared did not differ by the combined primary clinical endpoint (the rate of hospitalizations due to cardio-vascular reasons, the refusal to undergo chemotherapy for the reason of chronic cardiac failure progression and the safety of using the drug products: the presence of urinary tract infections and sepsis), but they differed by the surrogate clinical endpoints that included the dynamic trend of the levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and the global longitudinal strain (GLS) of the left ventricle, determined within the timeframes established for the research — before the initiation of chemotherapy and in 6 months. The patients that have passed all the control tests (n=47), after the end of the 6 months period, underwent a comparison of the levels of troponin T, left ventricle ejection fraction (LVEF), NT-proBNP and GLS. It was found that the dynamic changes of troponin T levels in both groups did not significantly differ (p=0,260), as well as the LVEF indicator (p=0.340), while the NT-proBNP level was significantly decreasing in the test group — by 7.8% comparing to the control group (p=0.006). Comparable data were obtained for the GLS (the decrease in the test group by 6.5% in relative values) comparing to the control group (p=0.008). In 22/47 (46,8%) patients, chronic cardiac failure was diagnosed before the initiation of chemotherapy, in 25/47 (53,2%), chronic cardiac failure was developing during the antitumor medication therapy. In both groups, a total of 17 (16%) fatal outcomes were registered, none of which was caused by the cardiac failure.* ***CONCLUSION:*** *We suppose that the decrease in the levels of the cardiac failure marker and the less intensive impairment of the left ventricle longitudinal strain with a background of adding sodium-glucose cotransporter type 2 inhibitors to baseline therapy for chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy, reflects their cardioprotective potential. Thus, the sodium-glucose cotransporter type 2 inhibitor Dapagliflozin slows down the progression of chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy.*

Keywords: *cardio-oncology; cardiotoxicity; cardioprotection; chronic heart failure; sodium-glucose cotransporter type 2 inhibitors.*

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ПРИМЕНЕНИЕ ИНГИБИТОРОВ НАТРИЙ-ГЛЮКОЗНОГО КОТРАНСПОРТЕРА 2-ГО ТИПА С ЦЕЛЬЮ ЛЕЧЕНИЯ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ, ПОЛУЧАЮЩИХ КАРДИОТОКСИЧНУЮ ХИМИОТЕРАПИЮ: ПРЕДВАРИТЕЛЬНЫЕ РЕЗУЛЬТАТЫ

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АННОТАЦИЯ

Обоснование. *Хроническая сердечная недостаточность относится к наиболее грозным и поздним проявлениям кардиотоксичности у онкобольных при лечении противоопухолевыми препаратами. На сегодняшний день лишь две группы препаратов доказали значимые кардиопротективные эффекты у этой категории пациентов: ингибиторы ангиотензинпревращающего фермента/блокаторы рецепторов ангиотензина и бета-адреноблокаторы. Недавно появились первые данные об успешном применении ингибиторов натрий-глюкозного котранспортера 2-го типа у пациентов с хронической сердечной недостаточностью, которые находятся на терапии антрациклинами.* ***Цель исследования*** *— оценить эффективность дапаглифлозина в комплексной кардиопротективной терапии хронической сердечной недостаточности у онкологических больных, получающих кардиотоксичную химиотерапию.* ***Методы.*** *Проспективное наблюдательное открытое исследование, включившее 116 онкологических пациентов с верифицированной хронической сердечной недостаточностью, которые получали кардиотоксичную химиотерапию, из них 60 пациентов контрольной группы получали двойную кардиопротективную терапию (ингибиторы ангиотензинпревращающего фермента/блокаторы рецепторов ангиотензина, 56 пациентов группы исследования — аналогичную терапию с добавлением дапаглифлозина в дозе 10 мг 1 раз утром. Контроль результатов проводился через 6 месяцев с помощью лабораторных и инструментальных методов исследования, а также дополнительных методов контроля.* ***Результаты.*** *Группы сравнения не различались по комбинированной первичной клинической точке (частота госпитализации по сердечно-сосудистым причинам, отказ от химиотерапии по причине прогрессирования хронической сердечной недостаточности, безопасность применения препарата: наличие инфекции мочеполовых путей и сепсиса), но различались по суррогатным клиническим точкам, динамике уровней мозгового предсердного натрийуретического пептида (NT-proBNP) и продольной деформации миокарда левого желудочка (GLS), определяемых в регламентированные исследованием сроки — перед началом химиотерапии и через 6 месяцев. Пациентам, прошедшим все контрольные исследования (n=47), по истечении 6 месяцев проведено сравнение уровней тропонина T, фракции выброса левого желудочка (ФВ ЛЖ), NT-proBNP и GLS. Отмечено, что динамика тропонина в обеих группах значимо не отличалась (p=0,260), также как и показатель ФВ ЛЖ (p=0,340), а уровень NT-proBNP значимо снижался в группе исследования на 7,8% в сравнении с контрольной группой (p=0,006). Сопоставимые данные были получены и по GLS (снижение в группе исследования на 6,5% в относительных значениях) по сравнению с контрольной группой (p=0,008). У 22/47 (46,8%) пациентов была хроническая сердечная недостаточность до начала проведения химиотерапии, у 25/47 (53,2%) хроническая сердечная недостаточность возникла в процессе противоопухолевой лекарственной терапии. В обеих группах зарегистрировано 17 (16%) летальных исходов, из них ни одного по причине сердечной недостаточности.* ***Заключение.*** *Мы полагаем, что снижение маркера сердечной недостаточности и менее выраженное нарушение продольной деформации левого желудочка на фоне добавления ингибитора натрий-глюкозного котранспортера 2-го типа дапаглифлозина к базисной терапии хронической сердечной недостаточности у онкологических больных, получающих кардиотоксическую химиотерапию, отражает их кардио-*

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протективный потенциал. Таким образом, добавление к терапии ингибитора натрий-глюкозного котранспортера 2-го типа может замедлять прогрессирование хронической сердечной недостаточности у онкологических больных, получающих кардиотоксическую химиотерапию.

Ключевые слова: *кардиоонкология; кардиотоксичность; кардиопротекция; хроническая сердечная недостаточность; ингибиторы натрий-глюкозного котранспортера 2-го типа.*

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BACKGROUND

Chemotherapy is successfully used for the treatment of malignant neoplasms, at the same time, a number of medicines induce toxic effects in the cardiac muscle, resulting in the death of cardiomyocytes, decreased contractility and cardiac rhythm disorders, which leads to developing various diseases of the cardiovascular system [1].

Chronic heart failure belongs to the most threatful and delayed manifestations of cardiotoxicity in the treatment of antitumor medicines. Chronic heart failure, in case of its development or progression, not only significantly affects the quality of life of the patient, even in cases of successful treatment of malignant neoplasms, but also deteriorates the expected lifetime of the patient [2], and, in a number of cases, compels to interrupt the chemotherapy cycle or to slow it down significantly.

At the present moment, in cancer patients receiving cardiotoxic chemotherapy, only two classes of agents have proven their efficiency in the treatment and prevention of chronic cardiac failure — inhibitors of angiotensin-converting enzyme/angiotensin receptor blockers and beta-adrenergic blockers [3] or their combinations [4]. Gradually, the data is being accumulated on the successful use of the combination of neprilysin receptor inhibitor and of the angiotensin receptor blocker (Sacubitril/Valsartan) in cancer patients with chronic cardiac failure [5, 6]. First data were also obtained on the successful use of inhibitors of sodium-glucose cotransporter type 2 in cancer patients with diabetes mellitus receiving therapy with anthracyclines [7].

Research aim — optimization of the cardioprotective therapy in the treatment of chronic cardiac failure in cancer patients, receiving cardiotoxic chemotherapy.

METHODS

Research design

A prospective observational open-label research was conducted, involving 60 cancer patients with verified chronic cardiac failure, which were receiving cardiotoxic chemotherapy and double cardioprotective therapy: Bisoprolol at a dosage of 1.25 mg once daily in the morning and Perindopril at a dosage of 2.5 mg once daily in the morning (Control group, the dosages were adjusted, if necessary, depending on the blood pressure and heart rate values), along with 56 cancer patients, which were receiving similar therapy with an addition of Dapagliflozin at a dosage of 10 mg once daily in the morning (test group). The controls of the obtained results were arranged after 6 months due to the fact that the patients had a high comorbidity background, and the majority of patients had stage IV of the oncology disease and, as a result, they had a small life expectancy. During the course of the research, 3 patients were excluded. Failure to timely undergo control check-ups (established by the research protocol) was reported for 9 patients. In the control group, after a 6 months period, 24 patients have completely passed all the research controls, while in the test group the number was 23 patients. The patients were distributed using block randomization at a ratio of 1:1. Statins were not included into the therapy scheme due to the absence of proven evidences of their efficiency to the moment of enrollment into the research.

The research design is provided in Fig. 1.

Conformity criteria

Inclusion criteria: consent obtained from the patient for the participation in the research; patients aged from 18 to 85 years; any stage of the oncological disease; presence of chronic cardiac failure class I–IV according

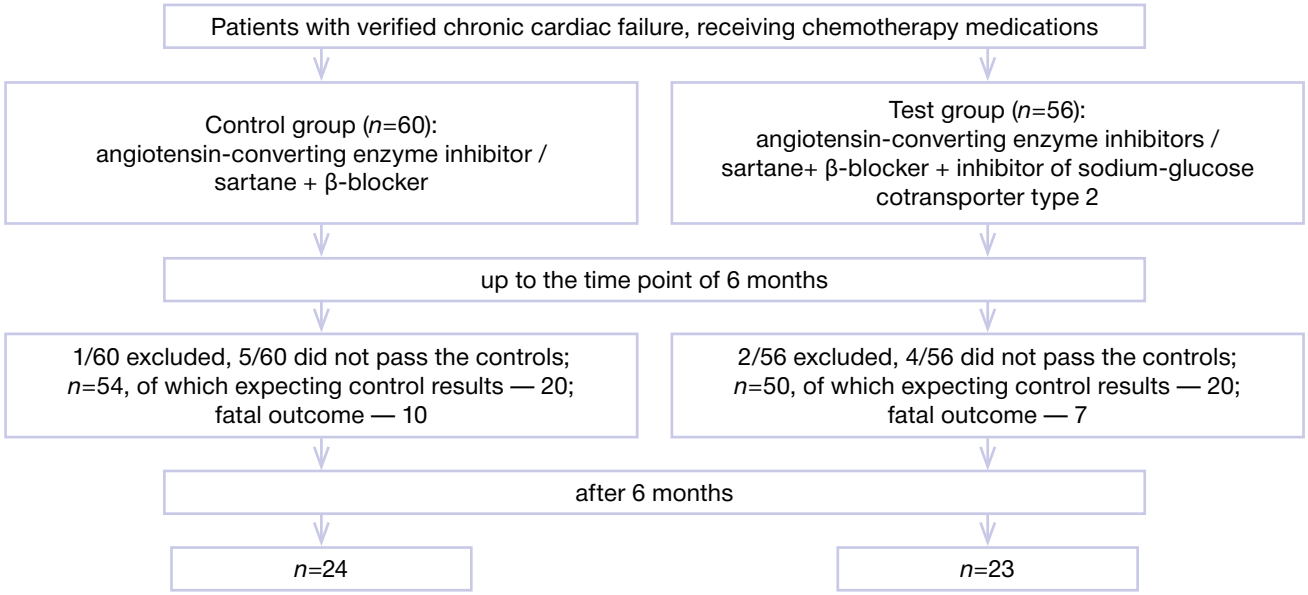

Fig. 1. Study design.

to the classification issued by the New York Heart Association (NYHA), which was defined as an elevation of the levels of N-terminal fragment of cerebral natriuretic peptide (N-terminal prohormone of brain natriuretic peptide, NT-proBNP) >300 pg/ml in the absence of atrial fibrillations or >900 pg/ml in case of having atrial fibrillations in the individuals aged under 75 years old, for the patients older than 75 years — >450 pg/ml, as well as the presence of clinical-instrumental data, which includes the analysis of the functional status of the patient, echocardiography data and clinical signs (including shortness of breath, the noncardiac origin of which has been ruled out); estimated glomerular filtration rate calculated using the CKD-EPI formula — >30 ml/1.73 m^2 per minute; blood pressure above the levels of 100/60 mm. Hg.; patients with diabetes mellitus type 2 and or without diabetes. It should be noted that, during the initial stage of the research, there were no indications for prescribing Dapagliflozin in patients with chronic cardiac failure without diabetes mellitus and the patients that had no diabetes mellitus were included already during the on-going research. The patients were enlisted into the research during the first chemotherapy cycle or during further chemotherapy cycles upon the verification of chronic cardiac failure already during the course of therapy.

Exclusion criteria: refusal of the patient to participate in the research; patients aged less than 18 years and more than 85 years; absence of chronic class I–IV cardiac failure acc. to NYHA classification; acute heart failure at the decompensation stage, requiring the intravenous administration of diuretics, vasodilating agents, inotropic agents or mechanical support of circulation within the 1st hospitalization week; acute myocardial infarction, major cardiac surgeries, as well as transitory ischemic attack or stroke episode during the last 3 months; glomerular filtration rate (calculated using the CKD-EPI formula) values of <30 ml/1.73 m^2 per minute; arterial hypotension (blood pressure below the levels of 100/60 mm. Hg.); acute infectious diseases; autoimmune diseases.

Research facilities

The treatment and follow-up procedures were carried out within the premises of the Federal State Budgetary Institution "Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technologies" of the Federal Medical-Biological Agency of Russia (FSBI FSCC of the FMBA).

The patients were selected from two departments — the Oncology Department No. 1 and the Department of Antitumor Medication Therapy.

The procedures of controlling the compliance (passing all the control points) were carried out at the Federal State Budgetary Institution FSCC of the FMBA and remotely within the medical institutions at the place of residence.

Research duration

The recruitment of patients was conducted during the time period from December 2021 until December

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2023 (inclusive). The data provided includes the patients with a status description compiled to the date of 01.08.2023.

Medical procedure description

After receiving an informed consent, the patients were enlisted to participate in the research and underwent long-term follow-up procedures. The whole spectrum or required tests was divided into the laboratory and the instrumental ones. As the primary documentation, the medical records of the patients were analyzed: initial examination, examinations by dedicated specialists, laboratory and instrumental findings. Then followed the additional examination within the framework of the claimed protocol of collecting all the necessary data.

Laboratory tests. All the patients (before the initiation of chemotherapy) had their blood samples collected for performing the following laboratory tests: clinical hematology panel, blood biochemistry panel, coagulation panel, determination of the levels of troponin T and NT-proBNP in blood plasma, the last one was the clinical urinalysis. The NT-proBNP levels were determined before the initiation of chemotherapy and after 6 months. The troponin T blood tests were carried out before each chemotherapy cycle.

Instrumental examinations. All the patients underwent two-dimensional echocardiography with an estimation of the left ventricle ejection fraction using the Simpson's method and with the obligatory measurement of the global longitudinal strain of the myocardium (GLS) using the General Electric Vivid 7 equipment. These parameters were also tracked before the initiation of chemotherapy and after 6 months. The routine measurements in all the patients included the electrocardiogram readings with using 12 leads before each chemotherapy cycle. Besides, for the purpose of evaluating the treatment efficiency and for the objectivization of symptoms, at the end of the 6 months period, all the patients had filled in the modified Kansas City Cardiomyopathy Questionnaire (KCCQ), which allows for objectifying the presence of symptoms of chronic cardiac failure, its severity and dynamic changes during the whole follow-up period. All the patients have also underwent a Six Minute Walk Test for the purpose of defining the functional class of chronic cardiac failure.

Research outcomes

During the course of the research, the following primary (combined) endpoint was evaluated: hospitalization due to cardio-vascular reasons, cessation of chemotherapy for the reason of progressive chronic cardiac failure, safety of using the therapeutic agent: the presence of urinary tract infection or sepsis. Secondary endpoint: total clinical index, which is defined as the functional status of the patient and the sum of factors, determining the quality of life and social restraint. The surrogate endpoints (evaluation of dynamic changes in the levels of NT-proBNP, troponin T, left ventricle ejection fraction and GLS) were measured within the timeframes established for the research — before the initiation of chemotherapy and after 6 months.

Ethical review

The procedures were carried out within the framework of the research named "The use of sodium-glucose cotransporter type 2 inhibitors for the purpose of treating the chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy", approved by the local Ethics Committee of the Federal State Budgetary Institution FSCC of the FMBA, which was established and which is acting in accordance with the Declaration of Helsinki of the World Medical Association (WMA), with the ICH GCP and with the Law of the Russian Federation on Circulation of Medicines (protocol No. 5, issued on 14.06.2022).

Statistical analysis

The procedures of collecting the data for statistical analysis were carried out manually by systematizing them in the Excel table with further processing them using the SPSS Software. Quantitative variables were presented as a median with adding the interquartile range (Me [Q1; Q3]). The sample size was not analyzed, for the research included only the patients that met the inclusion criteria. The obtained differences were considered statistically significant at the p level of <0.05 (95% confidence).

RESULTS

Research sample (participants)

A total of 104 patients participated in the research, of which 63 (61%) were females and 41 (39%) were males (table 1). The mean age was 68 years. More than 14 various locations of the oncological diseases were presented: 8 (7.69%) patients had several locations of the oncological process; lung cancer was diagnosed in 12 (11.5%) patients, mammary gland cancer — in 14 (13.4%), gastric cancer — in 11 (10.2%), colorectal cancer — in 18 (17.3%), ovarian cancer — in 12 (11.5%),

Table 1

Characteristics of the studied patient groups

Parameter	Control group *n*=54 (%)	Test group *n*=50 (%)
Gender: • male • female	 20 (34.07) 34 (62.96)	 21 (42) 29 (58)
Age, years, Me [Q1; Q3]	66 [43–84]	72 [48–84]
Location of the oncological process: • mammary gland • stomach • lungs • colorectal cancer • ovaries • pancreatic gland • other locations	 9 (16.67) 6 (11.11) 5 (9.26) 8 (14.81) 8 (14.81) 1 (1.85) 21 (38.89)	 5 (10) 5 (10) 8 (16) 10 (10) 4 (8) 4 (8) 18 (36)
Monochemotherapy	9 (16.67)	7 (12.96)
Combined therapy: • fluoropyrimidines • taxanes and platinum-based drugs • anthracyclines • other schemes	45 (83.33) 18 (33.33) 12 (22.22) 4 (7.41) 18 (33.33)	43 (86) 22 (44) 7 (14) 5 (10) 16 (32)
Stages of oncological diseases: • I • II • III • IV	 5 (9.26) 6 (11.11) 15 (27.78) 29 (53.7)	 3 (6) 8 (16) 16 (32) 27 (54)
Lethal outcomes	10 (18.52)	7 (14)
Hypotension	2 (3.7)	1 (2)

pancreatic cancer — in 5 (4.8%). Other malignant tumors were found in 39 (37.5%) cases. Combined chemotherapy was prescribed to 88 (85%) patients. Monochemotherapy was used in 16 (15%) patients. Combined chemotherapy with fluoropyrimidines was used in 40 patients (38.4%), taxanes and platinum-based drugs — 19 (18.2%), anthracyclines — 9 (8.6%), other schemes were used in 34 (32.6%) cases. A total of 56 (53%) patients were diagnosed with stage IV of the oncological diseases, another 31 (29.8%) had stage III, while 14 (13.4%) and 8 (7.6%) had stages II and I, respectively. The registered number of fatal outcomes was 17 (16%), however, fatal outcomes due to cardiac failure were not reported in any of the two groups.

The patients had a complicated comorbidity background, which has increased their total cardiovascular risk (table 2): arterial hypertension was reported in 77 (74%) patients, atrial fibrillation — in 11 (11.5%), ischemic heart disease — in 32 (31%), diabetes mellitus — in 26 (25%), increased body mass index or obesity — in 16 (15%).

The patients that have passed all the control examinations (*n*=47), after 6 months from the initiation of the research, underwent a comparison of the levels of troponin T, NT-proBNP, GLS and the left ventricle ejection fraction. The patients were distributed based on the inclusion criteria with using block randomization at a ratio of 1:1. Eventually, 24 patients were selected

Table 2

Data on the distribution of comorbid nosologies by study groups

Nosology	Control group *n*=54 (%)	Test group *n*=50 (%)
Arterial hypertension	37 (68.52)	40 (82)
Atrial fibrillations	4 (7.41)	7 (14)
Ischemic heart disease	17 (31.48)	15 (30)
Diabetes mellitus type 2	8 (14.81)	18 (36)
Body mass index, or obesity	7 (12.96)	9 (18)

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to represent the control group and 23 were enrolled into the test group. As a result, it was found, that the dynamic changes of troponin T levels in both groups did not significantly differ (p=0.26), while the levels of NT-proBNP had significantly decreased in the test group — by 7.8% comparing to the control group (p=0.006). Comparable data were also found for the GLS levels (a decrease in the test group by 6.5% comparing to the control group; p=0.008). The values of the left ventricle ejection fraction, upon dynamic assessment, practically did not change (p=0.340).

A total of 22 (46.8%) patients had chronic heart failure before the initiation of chemotherapy, while 25 (53.2%) had the disorder developing during the course of antitumor medication therapy.

Main research outcomes

At the end of the 6 months period, all the patients with chronic cardiac failure had filled in the modified Kansas City Cardiomyopathy Questionnaire.

In the control group, 10 (41.67%) patients had the total clinical index value (calculated with taking into consideration the functional status and the sum of factors, determining the quality of life and social restraint) of 50–69%, which corresponds to moderate quality of life and the presence of moderate restraint regarding the physical aspects of life; 13 (54%) patients had a total clinical index of 70–89% (good quality of life, some restrictions regarding the physical activity or other aspects of life), while only in 1 (4.17%) patient this index was 30–49% (low quality of life, serious restraint of physical functions and other aspects of life). In the test group, 8 (34.78%) patients had a total clinical index of 50–69%, 14 (60.87%) patients had the same index at the level of 70–89%, while 1 (4.35%) patient had a total clinical index of 30–49%. As a result, it was found, that the dynamic changes of the total clinical index values in both groups did not differ (p=0.343).

Two cases of hospitalization were registered as related to the cardio-vascular reasons (one in each group): paroxysm of atrial fibrillations and acute myocardial infarction. Death caused by sepsis caused by developing pneumonia was reported for 5 patients (3 in the control group and 2 in the test group). No cases of urinary tract infections and refusal to undergo chemotherapy for the reason of progressing chronic cardiac failure were registered. No significant statistical differences were reported regarding the combined primary endpoint (p=0.317).

In the control group, 10 (41.67%) patients died comparing to 7 patients (30.43%) in the test group. The details of the fatal outcomes are the following: 5 patients had succumbed due to sepsis caused by developing pneumonia; 6 patients have passed away due to the progression of the oncological process, 1 patient has deceased after an episode of COVID-19 infection, while in 5 patients the cause of death remained unknown. The statistics of fatal outcomes shows that a little less than 1/5 of the total number of patients, which is 17 (16%) patients, have deceased before the end of 6 months period. Six (5.7%) patients had a fatal outcome resulting from the progression of the main disease. This indicates the small life expectancy in oncology patients. It should also be noted that no significant role of cardiovascular system disorders was found in the thanatogenesis. Fatal outcomes caused by cardiac failure were not observed in any of the two groups.

Undesirable phenomena

When analyzing the data for both groups during the whole follow-up period, a total of 3 hypotension episodes with a background of taking basic cardioprotective therapy were reported. One of the patients was taking the research medication (Dapagliflozin), which, according to the Instructions for use and according to the results of the latest multi-center randomized clinical researches, is practically not capable of affecting the blood pressure levels (a decrease by a maximum of 3 mm. Hg. was noted) [8]. There were no cases of significant hypoglycemia, requiring a consultation by the Endocrinologist, as well as no cases of urogenital infections, requiring a consultation by the Urologist.

DISCUSSION

The possibility of cardioprotection in cancer patients, receiving cardiotoxic chemotherapy, has been studied for quite a long time. Sufficient data were obtained for the effects caused by various groups of antitumor agents in terms of the cardio-vascular system, resulting in the development of cardiac failure, atrial fibrillations, arterial thromboses, acute coronary syndrome along with the spasms of the vessels and venous thromboembolism [9, 10]. There are also successful results obtained for large samples within the framework of secondary prevention of chronic cardiac failure, for example, combination of angiotensin-converting enzyme inhibitors and beta-adrenergic blockers [11]. The main parameter defining the contractile function of the heart is considered the left ventricle ejection fraction [12], however, the decrease in the said parameter is an

indicator of already existing myocardial dysfunctions, which is why it is important not to let it develop. The research of cardiotoxicity markers has a major importance in preventing myocardial dysfunctions [1].

A comparison was carried out for the onset of the outcomes by the combined primary endpoint (the rate of hospitalizations caused by cardio-vascular reasons, refusals to continue chemotherapy due to the progression of chronic cardiac failure, infections of the urinary tracts and sepsis). The infections of the urinary tracts were defined as subfebrile fever (>37°C), leukocytosis found in the clinical hematology panel (WBC count >11.0×10^9/l) and proteinuria (>0.5 g/day). The results happened to be comparable in both groups and did not statistically differ. This is probably related to the sample size and to the short duration of following up the patients.

According to our data, when analyzing the troponin T levels, a positive trend was found in the test drug group, however, the result was statistically insignificant. Troponin T is the earliest marker of myocardial damage in response to various effects, hence, it cannot be considered as strictly specific for the processes of developing chronic cardiac failure induced by antitumor therapy.

When comparing the dynamic changes in the levels of the left ventricle ejection fraction, no significant and strong inter-relation was detected, which is probably affected by the time factor and the high number of patients with intact left ventricle ejection fraction, included in the research.

Upon the evaluation of the NT-proBNP levels, a clear significant positive dynamic trend was found in a group of patients taking Dapagliflozin. Taking into consideration the specificity of NT-proBNP in terms of diagnostics and further progression of chronic cardiac failure, the prognostic and clinical significance can be supposed for the intake of the said medicinal product for the purpose of treating the chronic cardiac failure at the early stage (within the timeframe of up to 6 months).

The analysis of the GLS levels show the presence of clear significant positive dynamic trend in a group of patients taking Dapagliflozin. The trend is similar to the one observed for the natriuretic propeptides, which, probably, indicates the commonness of the pathomorphological processes taking place in the myocardium under the effects of chemotherapy, also indicting the changes in the cardiac muscle in response to the given effects.

The high significance factor for cancer patients with chronic cardiac failure is the physical activity. If the Six Minute Walk Test defines only the functional class of cardiac failure, which did not significantly change under the effects of chemotherapy, the results of using the Kansas City Cardiomyopathy Questionnaire have demonstrated an insignificant positive tendency in patients taking the study drug, however, the difference was statistically insignificant. This is probably related to the fact of the research including predominantly patients with intact ejection fraction of the left ventricle (93%). Similar results were demonstrated in a complementary research [13]. Nevertheless, even the small positive dynamic trend in such a comorbid cohort of patients, the functional activity of which can be restrained by the effects of chemotherapeutic agents or by complications developing upon the progression of the main disease, gives ground for proposing the improvement of the motor activity and the increase in the quality of the patients' life.

The important fact was the relatively favorable safety profile of Dapagliflozin. Oftentimes cancer patients receive strong immunosuppressive therapy, which increases the risk of developing inflammatory and infectious diseases. No substantial adverse effects of taking the test drug were observed to the present moment.

Data on the primary, the secondary and the surrogate endpoints is described in Table 3.

We suppose that the observed positive trends occur under the influence of taking Dapagliflozin and can indicate its role in the prevention and treatment of chronic cardiac failure.

Thus, according to our research, no differences were observed in terms of the primary endpoint between the research groups, which is related to small sample size and does not allow for judging on the effects of sodium-glucose cotransporter type 2 inhibitors in terms of clinical outcomes in cancer patients, receiving cardiotoxic chemotherapy. Along with this, the NT-proBNP and GLS levels had significantly decreased with a background of study drug therapy, which can indicate its protective role in the prevention of cardiac failure. The preliminary data raises the hopes, though, evidently, the sample is rather small, which is why larger scale research works are necessary along with further monitoring the patients, including the participation of the multidisciplinary team of specialists.

Research limitations

The research limitations include the design (prospective observational open-label) and the research facilities (in a single medical center, though

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Table 3

Data on primary, secondary and surrogate endpoints

Parameter	Control group *n*=54	Test group *n*=50	*p*
Primary endpoint, *n* (%)			
Combined (death caused by cardio-vascular diseases, refusal to undergo chemotherapy, presence of urinary system infections or sepsis)	4 (6.67%)	3 (5.36%)	0.317
Secondary endpoint, Me [Q1; Q3]			
Total clinical index (%)	65.22 [37–83]	66.46 [34–86]	0.343
Surrogate endpoints, Me [Q1; Q3]			
Troponin T	20.14 [3.37–48.80]	18.67 [3.35–59.81]	0.260
Brain (atrial) natriuretic peptide (NT-proBNP)	608 [56–9345]	511 [60–3163]	0.006
Left ventricle ejection fraction	56.2 [51–60]	55.9 [48–63]	0.340
Global longitudinal strain of the myocardium (GLS)	-17.6 [-22.6; -16.3]	-18.8 [-22.8; -14.3]	0.008

the grouping was done using the random sample method). We did not analyze the outcomes separately in patients with diabetes mellitus or without diabetes, for the reason that, during the initial stage, there were no indications for prescribing Dapagliflozin in patients with chronic cardiac failure without diabetes mellitus, and the patients without diabetes mellitus were enrolled into the research already at the stage of its execution after registering the corresponding indications.

CONCLUSION

The addition of the sodium-glucose cotransporter type 2 inhibitor Dapagliflozin to basic therapy for chronic cardiac failure in cancer patients, receiving chemotherapy, did not statistically affect the rate of hospitalization caused by cardio-vascular reasons, the rates of refusing to undergo chemotherapy due to the progression of the chronic cardiac failure or the rates of developing urinary tract infections and sepsis. At the same time, the addition of Dapagliflozin to baseline therapy for chronic cardiac failure in cancer patients, receiving cardiotoxic chemotherapy, resulted in a significant decrease in the NT-proBNP levels and to a less prominent decrease of the longitudinal strain of the left ventricle myocardium.

We suppose that the decrease in the levels of the cardiac failure marker and the less intensive impairment of the longitudinal strain of the left ventricle with a background of adding sodium-glucose cotransporter type 2 inhibitor to baseline therapy for chronic cardiac failure in cancer patients, receiving cardiotoxic chemotherapy, reflects the cardioprotective potential of the study drug and it can slow down the progression of chronic cardiac failure.

ADDITIONAL INFORMATION

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