THE USE OF QUADROTHERAPY OF CHRONIC HEART FAILURE IN CANCER PATIENTS (CASE SERIES)

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Background: *Chronic heart failure (CHF) for a patient with cancer is complex, as it complicates antitumor treatment. In some cases, severe CHF is a contraindication to the chemotherapy or surgical treatment. Despite significant progress in CHF treatment, some groups of drugs, particularly mineralocorticoid receptor inhibitors, angiotensin receptor-neprilysin inhibitors, and sodium-glucose co-transporter type 2 inhibitors, have not been studied related to cancer patients.* ***Clinical case description:*** *In this report, we introduce two clinical cases in which, because of the invaluable contribution of the cardio-oncological team, we have managed to solve complex problems of treating patients with CHF and cancer. In patient 1 with severe CHF, it was possible to achieve regression of systolic dysfunction, despite the progression of bladder cancer T4N1M0. In patient 2 with severe ischemic cardiopathy and CHF, owing to the timely administration of quadruple therapy, we managed to significantly improve the cardiac status and increase the LV EF that the patient underwent gastrectomy and cholecystectomy for cancer of the cardiac part of the stomach cT2N0M0 without complications.* ***Conclusion:*** *The above clinical cases demonstrate the possibilities of a team, multidisciplinary approach in the treatment of complex category of patients with CHF and active oncological disease. Modern therapy of cancer patients with severe heart failure allows successful antitumor treatment.*

Keywords: *cardio-oncology; cardiotoxicity; quadrotherapy of chronic heart failure; sodium-glucose cotransporter type 2 inhibitors; catheter ablation of ventricular arrhythmia.*

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BACKGROUND

Cardiovascular diseases are prevalent among patients with cancer. Patients with chronic heart failure (CHF) are more frequently diagnosed with malignant neoplasms than those without heart and vascular disease [1]. This is primarily because of the increasing life expectancy of patients, which increases the likelihood of developing both diseases. Further, risk factors for cardiovascular disease and cancer often overlap, including low physical activity, obesity, diabetes mellitus, smoking, stress, and environmental factors. Additionally, anticancer treatments can contribute to the development of cardiovascular disease. Cancer patients require an assessment of their risk of cardiovascular complications. Chemotherapy and radiation therapy can have toxic effects on the heart, leading to cardiac rhythm disturbances, thrombosis, embolism, coronary heart disease, arterial hypertension, and CHF [2].

When treating malignant neoplasms with cardiotoxic chemopreparations, such as anthracyclines, irreversible cardiomyocyte death occurs. The extent of this damage is dependent on the total dose of the drugs administered. Moreover, some targeted drugs, such as trastuzumab, can cause reversible myocardial dysfunction. Tyrosine kinase inhibitors and agents that affect endothelial growth factor can cause arterial hypertension, impaired coronary microcirculation, and decreased capillary density [3]. These effects may eventually lead to decreased myocardial contractility and CHF.

Renin–angiotensin–aldosterone system activation and increased natriuretic peptide levels are major contributors to the pathogenesis of ischemic CHF. Modern CHF treatment involves the simultaneous administration of four main groups of drugs, known as quadritherapy. These groups include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, neprilysin receptor inhibitors (e.g., sacubitril/valsartan), mineralocorticoid receptor blockers, beta-adrenoblockers, and sodium–glucose cotransporter type 2 inhibitors. In cancer patients receiving cardiotoxic chemotherapy, only two classes of drugs have proven

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ПРИМЕНЕНИЕ КВАДРОТЕРАПИИ ПРИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ (СЕРИЯ КЛИНИЧЕСКИХ СЛУЧАЕВ)

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Обоснование. *Хроническая сердечная недостаточность (ХСН) у пациентов с онкологическими заболеваниями представляет серьёзную проблему, так как повышает риски противоопухолевого лечения, затягивает начало химиотерапии, ухудшает качество жизни и прогноз больного. В ряде случаев тяжёлая ХСН является противопоказанием к проведению химиотерапии или хирургического лечения. Несмотря на значительные успехи в фармакотерапии ХСН, некоторые группы препаратов, в частности блокаторы ангиотензиновых и неприлизиновых рецепторов, ингибиторы натрий-глюкозного котранспортера 2-го типа, не исследованы у онкологических пациентов, опыт их применения основан на малых выборках.* ***Описание клинических случаев.*** *Публикуем два клинических наблюдения, в которых усилиями кардиоонкологической команды удалось решить сложные задачи лечения больных с ХСН и онкологическим заболеванием. В первом случае у пациента с тяжёлой ХСН удалось достигнуть регресса систолической дисфункции, несмотря на прогрессирование рака мочевого пузыря T4N1M0. Во втором случае, благодаря своевременному назначению квадротерапии, больному с тяжёлой ишемической кардиопатией и ХСН удалось улучшить кардиальный статус и повысить фракцию выброса левого желудочка настолько, что он без осложнений перенёс операции гастрэктомии и холецистэктомии по поводу рака кардиального отдела желудка cT2N0M0.* ***Заключение.*** *Приведённые клинические случаи наглядно демонстрируют возможности командного, мультидисциплинарного подхода в лечении сложной категории больных, какими являются пациенты с ХСН и активным онкологическим заболеванием. Современная терапия онкологических больных с тяжёлой сердечной недостаточностью позволяет успешно проводить противоопухолевое лечение.*

Ключевые слова: *кардиоонкология; кардиотоксичность; квадротерапия хронической сердечной недостаточности; ингибиторы натрий-глюкозного котранспортера 2-го типа; катетерная абляция желудочковой аритмии.*

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effective in the treatment and prevention of CHF: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-adrenoblockers [4] or their combination [5]. Single studies have focused on the successful use of a combination of a neprilysin receptor inhibitor and an angiotensin receptor blocker (sacubtril/valsartan) in cancer patients with CHF [6, 7].

The role of statins in the prevention and treatment of CHF in cardio-oncologic patients is discussed. Reliable data on efficacy have not been obtained to date; however, statins are crucial for cancer patients with a high risk of cardiotoxicity, risk factors for atherosclerosis, and coronary heart disease and for patients with atherosclerosis without cancer [8].

In recent years, mineralocorticoid receptor inhibitors, angiotensin and neprilysin receptor blockers, and sodium–glucose transporter type 2 inhibitors have significantly contributed to the treatment of CHF. Although the mechanism of action of the latter on cardiomyocytes is not yet fully understood, this group of drugs has been found to have a multidirectional effect. Adenosine triphosphate production by cardiomyocytes decreases in different phenotypes of CHF. Reduced mitochondrial glucose oxidation causes

a more pronounced mechanism in patients with type 2 diabetes mellitus [9]. Type 2 inhibitors of the sodium–glucose cotransporter increase the level of circulating ketones, which improves mitochondrial function, increases adenosine triphosphate production, and enhances ventricular contractile function [10]. These inhibitors have become the preferred drugs for patients with diabetes mellitus and a high risk of cardiovascular complications [11]. Owing to their multidirectional action, they have already demonstrated high efficacy in treating patients with heart failure, regardless of whether they have reduced or preserved left ventricular ejection fraction (LVEF) [12, 13].

The use of mineralocorticoid receptor inhibitors, angiotensin and neprilysin receptor blockers, and type 2 sodium–glucose cotransporter inhibitors in cancer patients with CHF remains off-label until the results of randomized clinical trials or large meta-analyses are available. Clinical cases of successful use of inhibitors of sodium–glucose cotransporter type 2 in quadritherapy in cancer patients with CHF are of interest.

CLINICAL EXAMPLES

Clinical case 1

Patient's data: Patient K, a 62-year-old woman with a history of ischemic heart disease and inferior myocardial infarction, has arterial hypertension but is not receiving systematic treatment. The patient exhibited risk factors for coronary heart disease, including smoking for more than 30 years, dyslipidemia, arterial hypertension, and past alcohol abuse. Since December 2019, the patient has reported the appearance of blood in the urine. In February 2020, the patient was diagnosed with stage T4N1M0 bladder cancer, pyelocalicoectasia on the left side, secondary shriveled left kidney, and chronic kidney disease stage II. In June 2020, the patient began experiencing shortness of breath during normal physical activity without chest pain.

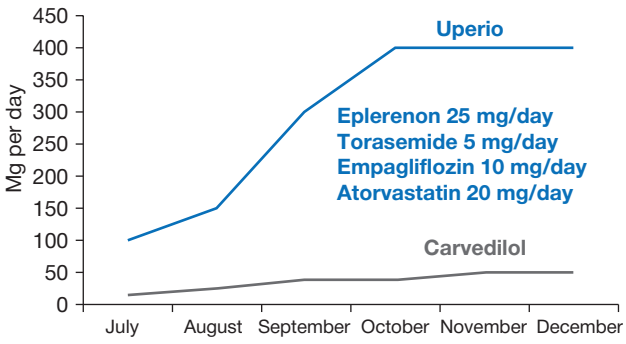

Fig. 1. Doses and duration of cardioprotective therapy in patient K.

Physical, laboratory, and instrumental diagnosis: During the examination on June 6, 2020, the patient was in satisfactory condition with a height of 176 cm and weight of 62 kg. Her blood pressure and heart rate was 140/90 mmHg and 78 beats/min with a correct rhythm, respectively. Upon auscultation, an S3 tone was detected at the heart apex. No signs of stasis in the lungs were detected, only dry rales. The liver was not enlarged, and no edema was present. Laboratory data showed elevated levels of NT-proBNP (3656 pg/mL; normal range: up to 300) and troponin T (24 pg/mL; normal range: up to 15). Urea was measured at 7.7 mmol/L and glucose at 8.64 mmol/L. The glomerular filtration rate according to the Cockcroft–Gault method was 68 ml/min. The echocardiogram revealed an left ventricular (LV) end-diastolic volume of 225 ml, LV end-systolic volume of 147 ml, stroke volume of 78 ml, and pulmonary artery systolic pressure of 35 mmHg. The patient had local LV contractility disorders, specifically akinesis of the posterior and posterolateral LV walls. Additionally, global myocardial contractility decreased, resulting in an LVEF of 33%.

Treatment, dynamics, and outcomes: During the cardio-oncology conference, the patient's treatment plan was discussed. It was determined that radical surgery or neoadjuvant therapy with cardiotoxic drugs would be unwarranted because of the high risk of cardiac complications. Immunotherapy was recommended. The patient was initially treated with sacubitril + valsartan at a dose of 50 mg twice a day, carvedilol 6.125 mg twice a day, and furosemide 40 mg twice a day. The patient was prescribed sacubitril + valsartan 200 mg twice daily (with a maximum daily dose of 2.5 months), carvedilol 12.5 mg twice daily, eplerenone 25 mg daily, torasemide 5 mg daily, and atorvastatin 20 mg daily (Fig. 1). Following the initial consultation, the optimal dosage was titrated over a period of 1.5 months. The doses of sacubitril + valsartan and beta-blockers were gradually increased owing to the patient's tendency to hypotension. Empagliflozin was added to the therapy at a dose of 10 mg daily from the first month of treatment. In August 2020, the patient began therapy with the immune response checkpoint inhibitor pembrolizumab. Treatment, laboratory, and instrumental studies were conducted at the patient's place of residence, and cardiologist consultations were conducted remotely. Treatment monitoring was performed with the participation of family members. During therapy, the signs of heart failure improved. The LVEF increased to 45%, and the levels of cardiac markers decreased (troponin T up to 5 pg/mL,

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NT-proBNP to 370 pg/mL) (Fig. 2). The patient received the prescribed immunotherapy for 10 months.

After 14 months, the patient's bladder tumor had grown. Without consulting the cardio-oncologist, the patient was switched to carboplatin and gemcitabine chemotherapy. The first infusion of the drugs was administered; however, the therapy was accompanied by general weakness and a single episode of chest discomfort, for which the patient did not seek medical help. Additionally, her hemoglobin level decreased to 80 g/l and leukopenia was experienced.

Two weeks later, just before the second course of chemotherapy, the patient had a sudden cardiac arrest in a hospital. Despite resuscitative measures, the patient could not be revived and passed away. No autopsy was performed.

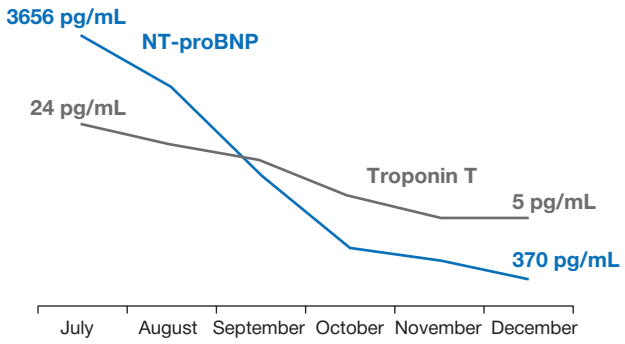

Fig. 2. Change of patient K's cardiomarkers in dynamics.

Clinical case 2

Patient's data: Patient I, a 71-year-old male, had a history of Q-shaped myocardial infarction of inferior localization in 2002, followed by mammary–coronary and aortocoronary bypass surgery in 2003. He experienced a repeated myocardial infarction of inferolateral localization on January 06, 2021. The patient had risk factors for coronary heart disease, including arterial hypertension and dyslipidemia and has a history of alcohol abuse. In February 2020, the patient sought medical attention from the Federal Medical and Biological Agency of Russia.

Physical, laboratory, and instrumental diagnosis: Upon examination, the patient's heart rate was recorded at 62 beats/min and sinus rhythm was observed. Blood pressure was measured at 100/70 mmHg. No signs of stasis were observed in the small and large circulatory circles. However, the patient reported experiencing dyspnea and weakness during minimal physical activity. Coronary angiography and shuntography revealed occlusion of the anterior interventricular and envelope branches of the left coronary artery and right coronary artery. The distal segments of the coronary arteries were filled through functioning mammarocoronary and aortocoronary shunts. Echocardiographic results showed significant LV cavity dilatation with an LV end-diastolic volume of 190 ml and a left ventricular end-systolic volume of 140 ml. Additionally, there were significant left atrial volume expansion, degree III mitral regurgitation, degree II pulmonary hypertension, and diffuse reduction of left ventricular myocardial contractile function with LVEF of up to 26%. Myocardial scintigraphy results revealed extensive zones of hypoperfusion at rest and during exertion. At the time of referral in 2020, the patient had persistent atrial fibrillation with normosystole and was taking amiodarone (200 mg/day), direct oral anticoagulants, statins, and loop diuretics. Laboratory data from August 2021 showed that the patient had an atrial natriuretic hormone level of 3255 pg/mL and a persistently elevated supersensitive troponin T level. The estimated glomerular filtration rate was 59 ml/min.

Treatment, dynamics, and prognosis: Considering the impossibility of myocardial revascularization, the patient was prescribed optimal drug therapy. This included a combination of sacubitril + valsartan, with dose titration from 50 mg twice a day (increased to 150 mg twice a day over 3 months), spironolactone 50 mg once a day, torasemide 10 mg once a day, carvedilol 12.5 mg twice a day, atorvastatin 40 mg once a day, and rivaroxaban 20 mg once a day. At the outpatient stage, dapagliflozin was prescribed at a dose of 10 mg once a day. Holter electrocardiogram monitoring revealed unstable paroxysms of ventricular tachycardia. To prevent sudden death, a dual-chamber cardioverter–defibrillator was implanted in August 2021. After 3 months, the patient's LVEF increased by up to 35% during repeated examination. The patient's condition remained satisfactory for 10 months with optimal drug therapy, and there were no hospitalizations for heart failure. Due to pronounced mitral regurgitation, the patient underwent a planned percutaneous intervention (endovascular mitral valve clipping). In May 2022, routine esophagogastroduodenoscopy revealed infiltrative cancer of the cardiac section of the stomach, which was classified as cT2N0M0 and morphologically identified as low-differentiated G3 adenocarcinoma.

The patient was discussed with the cardio-oncologic advice. Based on the early stage of the oncologic disease, absence of regional and distant metastases, and impossibility of chemotherapy, surgical treatment was recommended despite the high cardiac risk of

complications. On June 21, 2022, video-assisted gastrectomy, lymphodissection, Roux reconstruction, and cholecystectomy were performed under general anesthesia. The postoperative course was stable, and parenteral nutrition was administered. During the early postoperative period, the patient received anticoagulants and diuretics through injections. Starting on postoperative day 2, tablet therapy was administered through a nasoduodenal tube. The patient was mobilized within the hospital within 7 days. Ten days after surgery, upon discharge from the hospital, the patient reported experiencing heart palpitations, which triggered the use of an implantable cardioverter–defibrillator. During the following month, the patient was hospitalized seven times because of persistent paroxysms of "slow" ventricular tachycardia, which required external electrical cardioversion (Fig. 3).

The combined use of antiarrhythmic drugs from groups 1 and 3 was ineffective. Therefore, on August 16, 2022, an intracardiac electrophysiological study and radiofrequency ablation of ventricular extrasystole/tachycardia were performed under intracardiac ultrasound control (without fluoroscopy). The postoperative course was smooth. The patient was discharged on postoperative day 3 (Fig. 4). At the follow-up examination on September 28, 2022, no paroxysms of ventricular tachycardia were detected, and signs of heart failure did not increase. The patient's LVEF was 35%, and the level of atrial natriuretic peptide was 525 pg/mL. The therapy was continued with spironolactone, dapagliflozin, carvedilol, atorvastatin, and rivaroxaban. Because of persistent hypotension, sacubitril + valsartan was temporarily discontinued and restarted 2 months later.

The patient's prognosis is expected to be favorable if all recommendations are followed and quadritherapy is continued.

DISCUSSION

Cardiovascular disease is a common occurrence in cancer patients. CHF may coexist with cancer or may develop or worsen during antitumor therapy [14]. Additionally, atherosclerotic heart disease can be associated with cancer because of the shared risk factors of the two diseases. The treatment of patients with CHF and reduced LVEF involves the use of four types of medication, also known as quadritherapy: renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor blockers, beta-adrenoblockers, and sodium–glucose cotransporter type 2 inhibitors. This approach reduces mortality and hospitalization due to heart failure [15]. Efficacy has only been proven for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-adrenoblockers. However, randomized studies on the efficacy and safety of quadritherapy in patients with cancer and CHF are lacking.

These clinical examples, along with other individual studies [6, 7, 16], demonstrate the potential for treating CHF syndrome in patients with cancer using modern approaches. In the first case, quadritherapy of CHF with empagliflozin administration led to a significant improvement in LV contractile function in a patient with bladder cancer. The therapy proceeded without

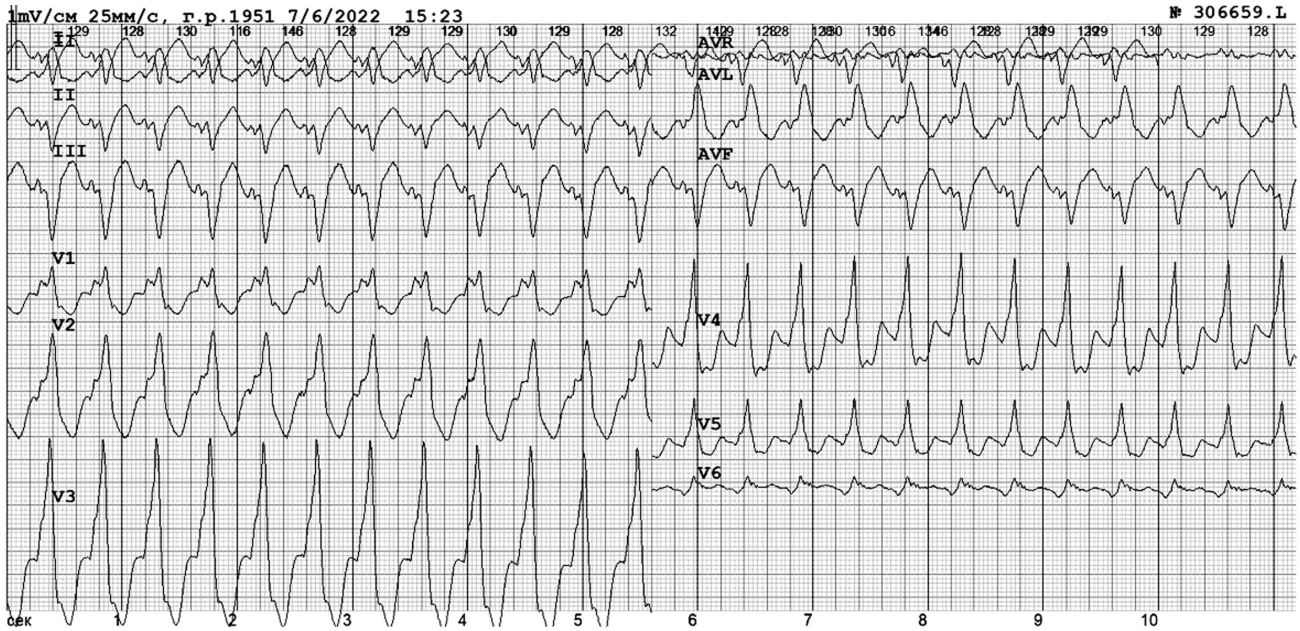

Fig. 3. Paroxysm of sustained ventricular tachycardia in patient I.

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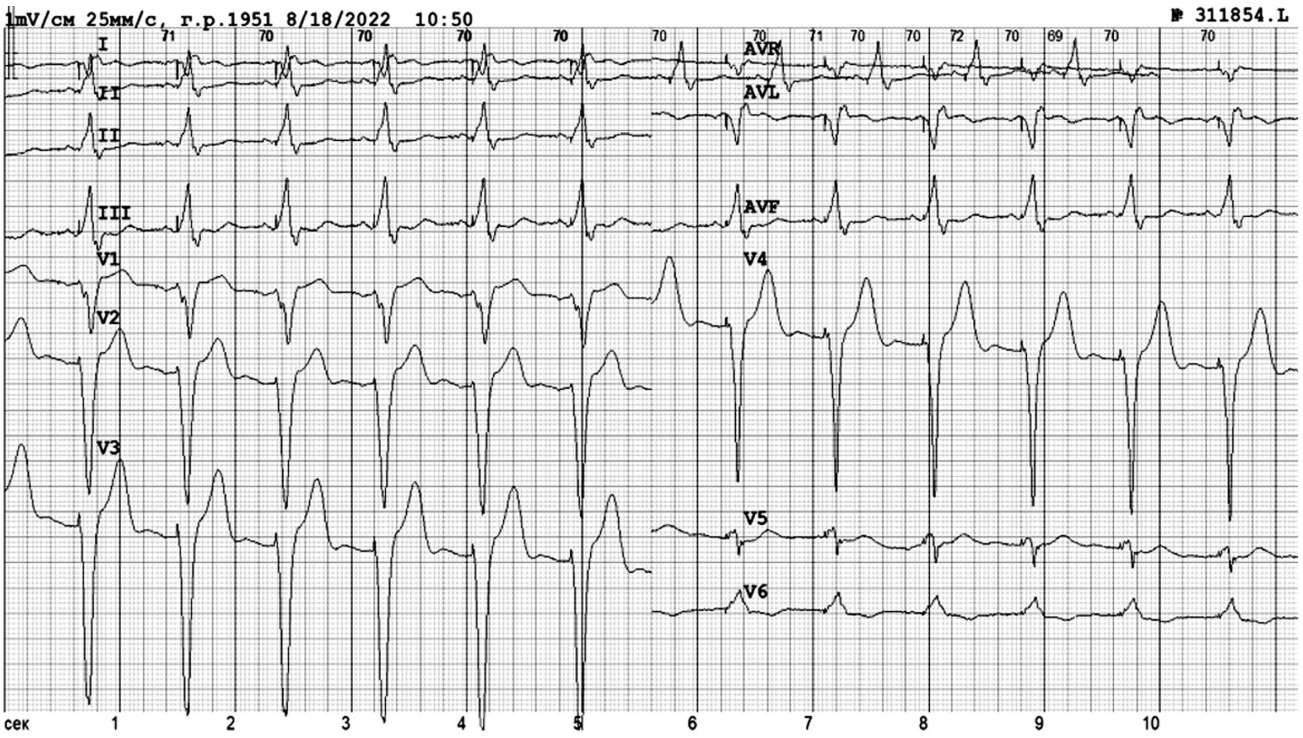

Fig. 4. Electrocardiogram of patient I.: Rhythm of P-synchronized ventricular pacing.

complications and did not result in a urinary tract infection. The patient underwent regular laboratory examinations, including general analysis and urine culture. During the first year, the patient underwent effective immunotherapy for bladder cancer without complications. Quadritherapy successfully regressed heart failure. However, 1 year after antitumor therapy initiation, malignant tumor growth was observed, and the patient was transferred to potentially cardiotoxic chemotherapy at the place of residence. Notably, carboplatin although rare, can cause heart failure, pulmonary embolism, cerebrovascular disorders, bleeding, hemorrhage, and hypotension. Gemcitabine often leads to anemia and thrombocytopenia, and in rare cases, it may worsen ischemic heart disease [17]. Whether coronary reserve testing, such as a stress test or coronarography, could have been beneficial for patient K before receiving this antitumor therapy regimen is unclear.

In the second case, the patient's condition of severe ischemic cardiopathy and CHF was improved by the administration of drugs from the four groups. This improvement was significant enough to allow the patient to undergo gastrectomy and cholecystectomy without complications. Additionally, patient I, who was at high risk of sudden cardiac death, received a dual-chamber cardioverter–defibrillator for prophylaxis, as per class I indications. Following gastrectomy, the patient experienced episodes of "slow" ventricular tachycardia. The implanted cardioverter–defibrillator was ineffective during these episodes, and antiarrhythmic therapy did not provide relief. Therefore, percutaneous ablation of ventricular arrhythmia was performed, which resulted in a positive clinical outcome.

Mineralocorticoid receptor antagonists are a key component for treating CHF, particularly in patients with low LVEF. The addition of these antagonists to double and triple cardioprotective therapy for cancer patients receiving cardiotoxic chemotherapy is justified because of their ability to reduce myocardial fibrosis and block aldosterone effects. In both our cases, spironolactone was used with favorable results. One study on breast cancer patients found that administering spironolactone alongside anthracycline therapy resulted in a less significant decrease in LVEF and diastolic function [18]. The combination drug sacubitril + valsartan shows promise in treating patients with reduced LV systolic function resulting from cardiotoxic chemotherapy. With complete neurohumoral inhibition and a significant reduction in mortality and hospitalization for CHF, similar results can be expected in this patient group [19]. The PRADA II trial aimed to investigate the potential of preventing LV dysfunction and heart failure in breast cancer patients receiving adjuvant chemotherapy with anthracyclines and/or trastuzumab using metoprolol, candesartan, or a combination of both. However, the trial showed no significant differences in the effect of

these cardioprotective drugs on LVEF in a relatively small sample. However, the LV end-diastolic volume was smaller in the candesartan group after 2 years, and longitudinal myocardial deformation decreased to a lesser extent than in the comparison group. Furthermore, the metoprolol group showed a reduction in supersensitive troponin release.

The treatment of CHF syndrome involves prescribing drugs that have been clinically and prognostically effective (quadritherapy for CHF), using an implantable cardioverter–defibrillator and modern antiarrhythmic therapy (if required). These observations are noteworthy because sodium–glucose cotransporter type 2 inhibitors were used in both cancer patients. Patient K had type 2 diabetes mellitus, whereas patient I did not have any concomitant diabetes mellitus.

This group of drugs has not been extensively studied in patients with cancer. Recently, the first data on the use of type 2 sodium–glucose cotransporter inhibitors in patients with cancer and diabetes mellitus treated with anthracyclines were published [16]. The study found that patients receiving type 2 sodium–glucose cotransporter inhibitors had a lower incidence of cardiovascular events compared with the control group (3% vs. 20%; p=0.025). The main group of patients (32 patients) had a lower overall mortality rate than the control group (92 patients) (9% vs. 43%; p <0.001). Moreover, they had a lower incidence of sepsis and neutropenic fever (16% vs. 40%; p=0.013). In addition, sodium–glucose cotransporter type 2 inhibitors appeared to be completely safe.

CONCLUSIONS

Initial reports on the use of quadritherapy for CHF in cancer patients, particularly with sodium–glucose cotransporter type 2 inhibitors, are promising. However, further confirmation is warranted through randomized clinical trials designed specifically for patients with cancer and CHF, both with and without concomitant diabetes mellitus.

These clinical cases demonstrate the potential of a multidisciplinary team approach for treating complex patients, such as those with both CHF and active cancer. Modern cancer therapy can be successful in treating patients with severe heart failure.

INFORMED CONSENT

Written voluntary informed consentwas obtained from each, patient K. (06.06.2020) and patient I. (01.03.2021), for publication and description of clinical cases.

ADDITIONAL INFORMATION

Authors' contribution. *A.K. Peresada* — research design, text writing, search and analytical work; *N.V. Dupik* — research design, collection of material, treating patients; *D.P. Dundua* — collection of material, treating patients, writing and text editing; *S.V. Korolev*, *R.S. Chaikin* — treating patients, text editing; *A.G. Kedrova* — treating patients, discussion and text editing. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interests. The authors declare that they have no competing interests.

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