Role of Exogenous Phosphocreatine in Chemotherapy-induced Cardiomyopathy

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The 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) regimen is widely used in the management of breast cancer. The common cardiotoxic effects of doxorubicin include congestive heart failure and left ventricular dysfunction, and those of cyclophosphamide include pericarditis, myocarditis, and congestive heart failure. It has been postulated that cardiotoxicity of 5-fluorouracil presents as coronary artery diseases (eg, angina). Cardiomyopathy is a common outcome following treatment with the FAC regimen. We report on a 52-year-old woman with cardiomyopathy following chemotherapy and radiation therapy. The patient did not respond well to β-blockers and angiotensin-converting enzyme inhibitors. After the addition of exogenous phosphocreatine, the patient's cardiac condition improved significantly.

[Rev Cardiovasc Med. *2017;18(2):82–87 doi: 10.3909/ricm0867*]

KEY WORDS

Breast neoplasms • Chemotherapy • Cardiotoxicity • Cardiomyopathy • Phosphocreatine

Breast cancer is the most common type of cancer in women worldwide.[1,2] Over the past few decades, the use of adjuvant chemotherapy has greatly improved the survival rates of women with breast cancer. Although advances in new chemotherapeutic agents continue, research on the management strategies of their side effects has largely been neglected. This is significant because, although these therapies increase the life expectancy, many cancer survivors report poor quality of life after chemotherapy.

The combination of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) is widely used for the treatment of breast cancer.[3-5] Chemotherapy-induced cardiomyopathy is one of the most common complications of the FAC regimen; disease presentation ranges from myocardial dysfunction to irreversible heart failure and even death.[6]

A 52-year-old woman was admitted to the Republican Clinical Hospital (Kazan, Russia) with chemotherapy-induced cardiomyopathy. Despite following the current management strategies, the patient failed to respond to treatment. However, the patient's condition significantly improved following the administration of exogenous phosphocreatine. This case report discusses the potential utility of exogenous phosphocreatine in patients with chemotherapy-induced cardiomyopathy.

Case Report

A 52-year-old woman was admitted to the hospital complaining of persistent dry cough with serous expectoration, which worsened at night; acute precordial chest pain, aggravated by inspiration and on changing position; inspiratory dyspnea on mild exertion; edema of the lower extremities; palpitations; and a blood pressure (BP) of up to 180/100 mm Hg. The patient had undergone radical resection of the right breast in May 2013, followed by six cycles of chemotherapy (FAC regimen) and external beam radiotherapy at a total dose of 46 Gy. The cumulative dose exposure of doxorubicin was 0.531 g (approximately 0.05 g/m^2 per cycle).

Physical examination revealed tachycardia (112 beats/min), muffled heart sounds with a rough systolic murmur heard at all points of auscultation, BP of 160/90 mm Hg, harsh breath sounds with equally decreased air entry in the basal areas on both sides, and moderate ascites. Results of a complete blood count demonstrated leukocytosis (total leukocyte count [TLC], 10.5 × 10^9/L) with neutrophilic predominance (85%) and anemia (hemoglobin, 108 g/L). Biochemistry demonstrated an abnormal liver function test result, with elevated alanine transaminase (ALT; 104 U/L) and aspartate transaminase (AST; 65 U/L), and hypoproteinemia (total protein, 59.8 g/L). Coagulation profiling demonstrated a prothrombin index of 63.3% and fibrinogen concentration of 5.7 g/L. Electrocardiography revealed sinus tachycardia, low-voltage QRS complexes, and nonspecific ST-T changes suggestive of anterolateral wall ischemia (Figure 1). Echocardiography revealed an ejection fraction (EF) of 13%, hypokinesia of the basal segments of the left ventricle (anterolateral and apical segments), and akinesia of other segments. The following findings were also noted: marked reduction in the global contractile function of the left ventricle,

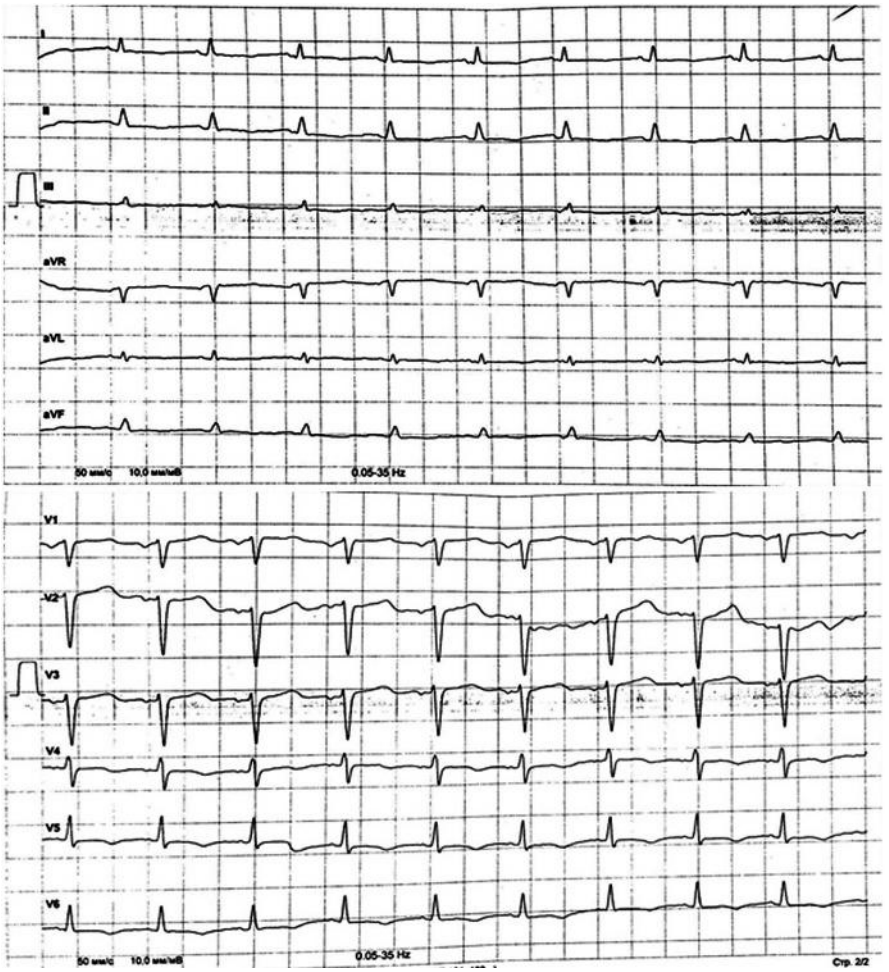

Figure 1. Electrocardiogram of the patient with chemotherapy-induced cardiomyopathy on admission.

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presence of thrombus in the left ventricle, left atrial enlargement, severe mitral regurgitation, severe tricuspid regurgitation, and pulmonary hypertension. The diagnosis of chemotherapy-induced cardiomyopathy was made accordingly. Treatment with perindopril, 1.25 mg/d, metoprolol, 25 mg twice daily, acetylsalicylic acid, 125 mg/d, furosemide, 40 mg/d, and spironolactone, 25 mg twice daily was immediately initiated.

Her cough worsened on the fourth day of admission, with an episode of ventricular tachycardia observed via electrocardiography (Figure 2). Amiodarone, 200 mg three times daily, meldonium, 500 mg twice daily (meldonium regulates the energy metabolism pathways resulting in inhibition of carnitine synthesis), and prenoxdiazine (peripherally acting cough suppressant), 100 mg four times daily, were initiated accordingly. The next day, cough intensity and dyspnea worsened. A computed tomography scan of the chest revealed a pulmonary embolism with pulmonary infarction (Figure 3); heparin, 5000 U four times daily was prescribed accordingly. Acetylsalicylic acid and oral furosemide were discontinued and replaced with intravenous (IV) furosemide, 80 mg daily, with an infusion of a polarizing solution (a mix of potassium-magnesium-isotonic and hypertonic saline). The patient became febrile (37.3°C) on the sixth day of admission. Laboratory testing demonstrated leukocytosis (TLC, 13.6 × 10^9/L) with neutrophilic predominance (84%) and markedly elevated liver function (ALT, 491 U/L; AST, 654 U/L). Chest ultrasonography revealed the presence of pleural effusions of 60 and 57 mm in the right and left pleural cavities, respectively. It was decided to discontinue amiodarone, administer ivabradine, 7.5 mg twice daily, and IV ademetionine, 400 mL (ademetionine works as a hepatoprotector by serving as a vital precursor to various reactions such as transmethylation, aminopropylation, and transsulfuration pathways), and increase the dose of furosemide to 140 mg/d and that of IV spironolactone to 50 mg twice daily.

On the seventh day, her temperature was 36.1°C, cough had decreased, and her general condition had improved on a background of forced diuresis. Heparin was discontinued, rivaroxaban, 20 mg/d was administered, and the dose of furosemide was increased to 180 mg/d. The next day, the patient's temperature was 36.3°C, dyspnea had decreased, and laboratory test results had improved (TLC, 11.4 × 10^9/L; ALT, 248 U/L; AST, 115 U/L).

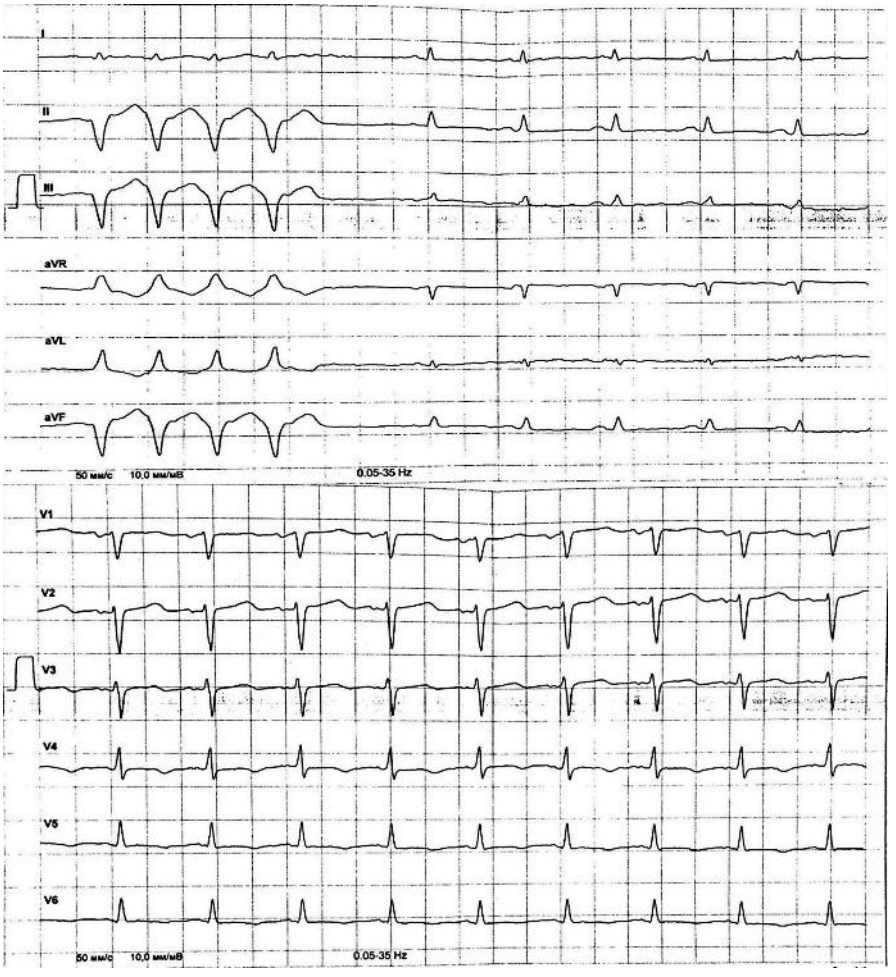

Figure 2. Electrocardiogram of a patient with chemotherapy-induced cardiomyopathy showing episodes of ventricular tachycardia.

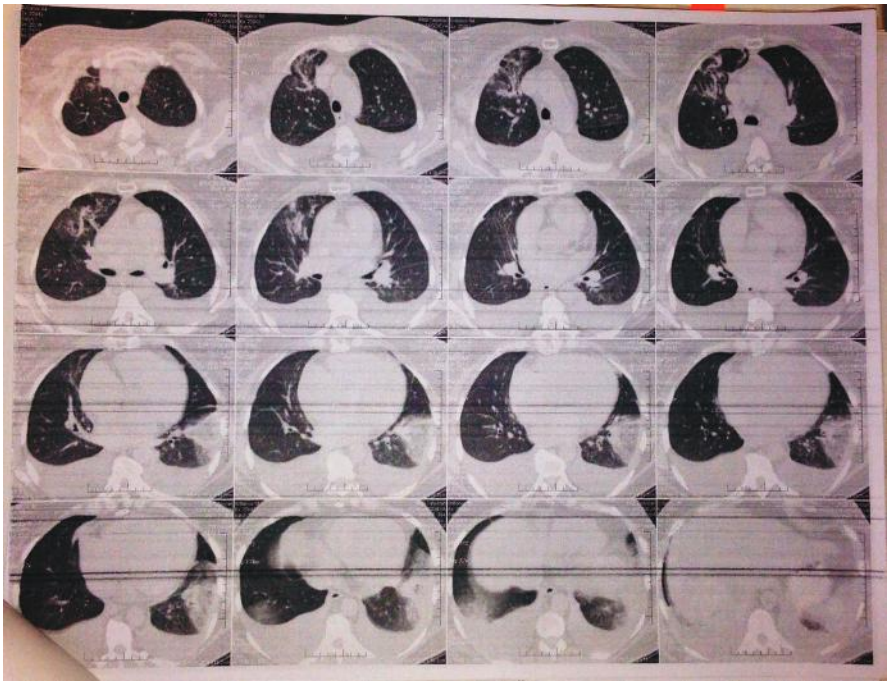

Figure 3. Computed tomography scan of the chest of a patient with chemotherapy-induced cardiomyopathy demonstrating pulmonary infarction.

Her EF remained at 13% and tachycardia persisted despite treatment. On the 11th day of admission, administration of 2 g/d of exogenous phosphocreatine was initiated. On the 13th day (3rd day of administration of exogenous phosphocreatine), EF increased dramatically to 29%. Thrombus was still present; Doppler ultrasonography demonstrated the presence of deep vein thrombosis in both lower extremities.

The patient was discharged a few days later. At discharge, the patient had mild dyspnea, mild edema, a TLC of 9.7 $\times$ 10^9/L, an ALT level of 46 U/L, an AST level of 46 U/L, and no evidence of pleural effusion. At follow-up, the patient had an EF of 42%, no evidence of pleural effusion, and no evidence of thrombus in the left ventricle.

Discussion

Chemotherapy-induced cardiotoxicity is defined as one or more of the following: (1) decline in left ventricular ejection fraction (LVEF), which is either global or very severe in the interventricular septum; (2) symptoms or signs associated with heart failure, including but not limited to dyspnea, third heart sound, pedal edema; (3) decline in LVEF of at least 5% to <55% from the baseline, accompanied with signs of heart failure or decline in LVEF of at least 10% to <55%, from the baseline without other signs of heart failure.[7] Based on the above criteria, this patient represents a classic case of chemotherapy-induced cardiotoxicity.

The cardiotoxic effects of chemotherapy depend on various risk factors, such as patient age, sex, previous cardiac disease, drug type and dose, cumulative dose, and administration route.[8] The reported cardiotoxic effects of doxorubicin include heart failure, left ventricular dysfunction, myocarditis, and arrhythmias. The underlying mechanism of cardiotoxicity is believed to be the production of free radicals leading to increased apoptosis and, at higher concentrations, necrosis of myocytes. Furthermore, it also affects the cellular membrane, induces mitochondrial damage, and negatively alters the adenosine triphosphate (ATP) production.[2,6,9] Cyclophosphamide does not cause any damage to the myocyte, but induces neurohumoral activation. Cardiotoxic effects of cyclophosphamide include congestive heart failure, hemorrhagic myocarditis, and pulmonary fibrosis.[2,6] 5-fluorouracil adversely affects the vascular endothelium, leading to vasoconstriction and vasospasm by activation of protein-kinase C.[10] The most commonly described cardiotoxic effect of 5-fluorouracil is angina-like chest pain.

Guidelines that are specific for the management of chemotherapy-induced cardiomyopathy are currently lacking and need to be

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developed. In 2009, the American College of Cardiology/American Heart Association guidelines for the diagnosis and management of heart failure in adults were updated with a minor focus on cancer patients, but they clearly state that patients with cancer may respond differently to conventional medications used to treat heart failure.[11] Almost all evaluated studies posited the use of β-blockers and angiotensin-converting enzyme (ACE) inhibitors, agents whose efficacy is well documented in heart failure. However, the use of these agents alone is not sufficient for heart failure management. A recent systematic review and meta-analysis by Kalam and Marwick[12] also concluded that use of cardioprotective agents such as β-blockers and ACE inhibitors prior to chemotherapy can prevent chemotherapy-induced cardiotoxicity; however, their use after chemotherapy requires more research.

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Because the cardiotoxic changes discussed above are triggered by alterations in metabolism, metabolic therapy represents a promising new avenue for the treatment of heart failure, with suitable targets for therapy, including substrate utilization, oxidative phosphorylation, and the availability of high-energy phosphates.[13] ACE inhibitors and β-blockers prevent ventricular remodeling and may have indirect metabolic effects on the heart; however, they do not have any effect on its energy metabolism.[14-16]

Metabolic therapy has a direct effect on the energy metabolism of the heart, wherein the energy demand exceeds the energy supply in patients receiving chemotherapy. Creatine plays a crucial role in maintaining the essential levels of intracellular ATP.[17] The creatine kinase system in the mitochondrion catalyzes the transfer of high-energy phosphate in ATP to creatine to form phosphocreatine and adenosine diphosphate. The creatine kinase system also utilizes the phosphocreatine for the reformation of ATP. When the energy demand and supply balance is disrupted, phosphocreatine levels fall to keep ATP at a normal level. This resulting imbalance in the cardiac myocyte contributes to the failure of the heart's contraction mechanism.[18] Phosphorus magnetic resonance spectroscopy is a noninvasive method used to gain insight into cardiac metabolism. It allows quantification of metabolites such as phosphocreatine, ATP (α, β, and γ), phosphodiesters, and 2,3 diphosphoglycerate. Researchers have employed this technique in in vivo studies for calculating the phosphocreatine-to-ATP ratio; however, due to low spatial and temporal resolution, its use has been limited in clinical cardiology.[19,20]

Exogenous phosphocreatine is chemically similar to endogenous phosphocreatine and increases the metabolism of the myocardium and muscles. Administration of exogenous phosphocreatine has been shown to improve LVEF, lower rate of arrhythmias, and exert protective effects on the ischemic myocardium in both in vitro and in vivo studies.[17,21] Phosphocreatine also appears to be effective in protecting the myocardium by preserving intracellular high-energy phosphates, maintaining the structural integrity of the sarcolemma, and preventing peroxidative damage.[22] Further, administration of phosphocreatine also improves microcirculation, thereby reducing the extent of necrosis and ischemia.[21,23]

Our patient presented with the most severe form of chemotherapy-induced cardiomyopathy. Although we used the recommended treatment strategies, the patient's cardiac condition deteriorated until phosphocreatine was administered. Addition of phosphocreatine proved to be a game changer because it not only halted the worsening of LVEF, but it also improved it. Exogenous phosphocreatine was administered for a total of 10 days during hospitalization only. After administration of exogenous phosphocreatine, the patient's EF improved to 29%, and has been stable ever since. These findings were evident during her stay at the hospital and subsequent follow-ups. Currently the patient is being followed up every 6 months.

Conclusions

The chemotherapeutic agents discussed above trigger multiple changes at cellular and molecular levels, such as reduction in the levels of phosphocreatine and ATP, as well as the phosphocreatine-to-ATP ratio and endothelial damage.[24-26] Therefore, initiating a therapy targeted at improving the metabolism by administration of exogenous phosphocreatine

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proves to be of benefit. This results in increase in intracellular levels of phosphocreatine and ATP. Furthermore, benefits such as improvement of dyspnea, microcirculation, and short-term mortality give additional leverage to the use of phosphocreatine.

Many studies have evaluated the therapeutic use of exogenous phosphocreatine. Although results of large studies have yet to be reported, exogenous phosphocreatine appears to have utility as a metabolic therapy in conjunction with β-blockers and ACE inhibitors in the management of chemotherapy-induced cardiomyopathy. ■

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MAIN POINTS

- Breast cancer is the most common type of cancer in women worldwide. The combination of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) is widely used for the treatment of breast cancer; however, chemotherapy-induced cardiomyopathy is one of the most common complications of the FAC regimen.
- Chemotherapy-induced cardiotoxicity is defined as one or more of the following: (1) decline in left ventricular ejection fraction (LVEF), which is either global or very severe in the interventricular septum; (2) symptoms or signs associated with heart failure, including but not limited to dyspnea, third heart sound, pedal edema; (3) decline in LVEF of at least 5% to <55% from the baseline, accompanied with signs of heart failure or decline in LVEF of at least 10% to <55%, from the baseline without other signs of heart failure.
- Chemotherapeutic agents trigger multiple changes at the cellular and molecular level such as reduction in the levels of phosphocreatine and adenosine triphosphate (ATP), as well as the phosphocreatine-to-ATP ratio and endothelial damage. Therefore, initiating a therapy targeted at improving the metabolism by administration of exogenous phosphocreatine proves to be of benefit.
- Exogenous phosphocreatine is chemically similar to endogenous phosphocreatine and increases the metabolism of the myocardium and muscles. Administration of exogenous phosphocreatine has been shown to improve LVEF, lower rate of arrhythmias, and exert protective effects on the ischemic myocardium.