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# WAYS OF MEDICINAL PREVENTION AND TREATMENT OF DOXORUBICIN-INDUCED CARDIOMYOPATHY IN ONCOLOGICAL PATIENTS

The high incidence of malignant tumors is currently supported by the general ageing of the world population and unfavorable environmental factors. In 2018, 18.1 million new cases of cancer and 9.6 million deaths from them were registered in the world. At the same time, a significant increase in the life expectancy of these patients after the treatment noted over the past 20 years highlights the problem of side effects of the anticancer therapy. One of the most serious side effects is the development of doxorubicin-induced cardiomyopathy (DRIC). In all three distinct clinical forms (acute, early and late) DRIC can develop in 58 % of patients after using anticancer treatment regimens with the inclusion of doxorubicin. The review provides a detailed analysis of medicinal treatment regimens and preparations (ACE inhibitors, beta-blockers, statins, etc.) currently used, and evaluates their effectiveness and expected results. Currently, several therapeutic strategies have been proposed for the prevention and treatment of DRIC, each of them has certain positive results. At the same time, some therapeutic methods used in the clinic have some disadvantages.

**Conclusions.** The limitations of the results of DRIC prevention achieved by the existing therapeutic regimens, as well as the possibilities for their prediction, have been stated. The need for further research to improve the effectiveness of medicinal prevention and treatment of DRIC is emphasized.

***Key words:*** doxorubicin-induced cardiomyopathy; chemotherapy; malignant neoplasms; myocardial dysfunction and heart failure; drug side effects

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**Шляхи лікарської профілактики та лікування доксорубіцин-індукованої кардіоміопатії в онкологічних хворих**

Висока захворюваність на злоякісні пухлини на теперішній час підтримується загальним старінням населення світу і несприятливими факторами екології. У 2018 році в світі було зареєстровано 18,1 млн нових випадків онкологічних захворювань і 9,6 млн смертей від них. У той же час за останні 20 років відзначається істотне збільшення тривалості життя таких пацієнтів після лікування, що висуває на перший план проблему побічних ефектів протипухлинної терапії. Одним з найбільш серйозних з них є розвиток доксорубіцин-індукованої кардіоміопатії (ДРІК). У всіх трьох клінічних формах (гострій, ранній та пізній) ДРІК спроможна розвинутися у 58 % пацієнтів після використання схем протипухлинного лікування з включенням доксорубіцину. В огляді детально проаналізовані схеми лікарського лікування і препарати (інгібітори АПФ, бета-адреноблокатори, статини та ін.), що використовуються на теперішній час, оцінена їх ефективність і очікуваний результат. Натепер запропоновано декілька терапевтичних стратегій з профілактики та лікування ДРІК, кожна з яких має визначені позитивні результати. У той же час деякі використовувані в клініці терапевтичні методи мають і цілий ряд недоліків.

**Висновки.** Констатовано обмеженість досяжних результатів профілактики ДРІК існуючими терапевтичними схемами, а також можливостей для їх індивідуального прогнозування. Підкреслюється необхідність подальших досліджень з метою підвищення ефективності лікарської профілактики і лікування ДРІК.

***Ключові слова:*** доксорубіцин-індукована кардіоміопатія; хіміотерапія; злоякісні новоутворення; дисфункція міокарда та серцева недостатність; побічна дія ліків

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**Пути лекарственной профилактики и лечения доксорубицин-индуцированной кардиомиопатии у онкологических больных**

Высокая заболеваемость злокачественными опухолями в настоящее время объясняется общим старением мирового населения и неблагоприятными факторами экологии. В 2018 году в мире было зарегистрировано 18,1 млн новых случаев онкологических заболеваний и 9,6 млн смертей от них. В то же время отмечаемое за последние 20 лет существенное увеличение продолжительности жизни таких пациентов после лечения выдвигает на первый план проблему побочных эффектов противоопухолевой терапии. Одним из наиболее серьезных является развитие доксорубицин-индуцированной кардиомиопатии (ДРИК). Во всех трех различаемых клинических формах (острой, ранней и поздней) ДРИК может развиться у 58 % пациентов после использования схем противоопухолевого лечения с включением доксорубицина. В обзоре детально проанализированы

используемые в настоящее время схемы лекарственного лечения и препараты (ингибиторы АПФ, бета-адреноблокаторы, статины и др.), оценена их эффективность и ожидаемый результат. В настоящее время предложено несколько терапевтических стратегий по профилактике и лечению ДРИК, каждая из которых дает определенные положительные результаты. В то же время некоторые используемые в клинике терапевтические методы обладают и целым рядом недостатков.

**Выводы.** Констатирована ограниченность достигаемых результатов профилактики ДРИК существующими терапевтическими схемами, а также возможностей для их индивидуального прогнозирования. Подчеркивается необходимость дальнейших исследований с целью повышения эффективности лекарственной профилактики и лечения ДРИК.

***Ключевые слова:*** доксорубицин-индуцированная кардиомиопатия; химиотерапия; злокачественные новообразования; дисфункция миокарда и сердечная недостаточность; побочное действие лекарств

The ageing processes of the world population and unfavorable environmental factors currently support the high incidence of malignant tumors. Thus, according to the well-known statistics, in 2018, 18.1 million new cases and 9.6 million deaths from oncological diseases were registered in the world. At the same time, through the joint efforts of practical medicine and scientists from various fields of knowledge in the last two decades, it was possible to achieve a significant increase in the life expectancy of these patients. Now the five-year survival rate after the treatment of malignant neoplasms as a whole reaches 64 %, and the ten-year survival rate – 41 %; it is almost twice as high as the similar indicators of 20 years ago. Against this relatively favorable background, the side effects of the anticancer therapy, which make a significant contribution to the morbidity and mortality of former cancer patients, have become a noticeable problem [1, 2].

Doxorubicin-induced cardiomyopathy (DRIC) is a very serious side effect of the complex and chemotherapeutic treatment of malignant tumors. And this effect is especially significant if we take into account the widespread use of doxorubicin (DR) in the treatment of leukaemia, several solid tumors, soft tissue sarcomas, and breast cancer. In particular, in the USA, DR is used in the treatment of oncological processes in more than half of patients with malignant neoplasms. And its replacement in most cases is not equivalent, as well as prevention methods based on reducing the dose of this drug or suppression it. All this significantly reduces the effectiveness of the anticancer treatment in general [3-5].

The clinically significant degree of the DRIC development in all three distinct clinical forms (acute, early and late) can reach 58 % of patients, and the mortality rate from it is 8.2 times higher than in patients without the use of the antitumor treatment regimens with the inclusion of DR. In 50 % of cases, death occurs as a result of the development of severe congestive heart failure at different periods of observation. In the literature, it is noted that DRIC has a significantly worse prognosis compared to cardiomyopathies of other etiologies [1, 6]. The negatory consequences of the negative impact of DR on the myocardium persist, most likely, throughout the patient's life. It was shown in detail in children who underwent the chemotherapy treatment in the past [7, 8]. Various authors provide heterogeneous data on both the incidence of DRIC and the survival rate of patients in its presence, indicating the individual tolerance of DR by each patient. But, in general, it is known that DRIC in the form of congestive heart failure develops, on average, in 5 % of cases when the cumulative dose of the preparation reaches 400 mg/m$^2$, while at 700 mg/m$^2$ the risk of developing this complication reaches 48 % and higher, i.e. there is an exponential increase in cardiotoxicity with an increase in the total dose of the preparation [9, 10].

In the clinical sense, DRIC, as noted above, is divided into acute, early and late. Acute DRIC develops immediately after infusion of DR and manifests itself in the form of transient left ventricular (LV) dysfunction, supraventricular tachycardia and various ECG changes and is most often reversible. At the same time, it is not known in detail how the acute form of cardiomyopathy will behave further since it can turn into an early or late form of DRIC or remain reversible. In turn, the early form of the pathology manifests itself within the first year of the treatment, and the late one – in several years. Some informed authors note that subclinical changes in heart functions during the DR treatment to a certain extent predict the possibility of DRIC in the future. In most patients, early symptoms of cardiotoxicity are manifested by a progressive decrease in left ventricular ejection fraction (LVEF) and other symptoms of the myocardial dysfunction. It is known that with the timely initiation of the DRIC treatment at this stage, good recovery of patients is noted. However, with the pathology detected late, the treatment is very difficult [7, 9, 11]. The mechanism of the toxic effect of DR on the myocardium and the pathophysiology of the DRIC development are currently not completely clear. Most researchers imply the possibility of multiple mechanisms, each of them has limited experimental evidence. This includes the mitochondrial or membrane dysfunction of the myocardium, as well as damage of sarcomere structures due to oxidative stress, iron metabolism disorders, calcium-mediated dysregulation of the cardiomyocyte homeostasis and their apoptosis. Ultimately, DRIC develops, which, according to the definition of the European Society of Cardiology,

represents "type 1 cardiotoxicity" – the irreversible dysfunction due to the death of cardiomyocytes. In its pure form, this process is irreversible and is characterized by their destructive-necrotic lesion. And clinically, the pathology manifests itself in the form of rapidly progressive congestive heart failure [3, 12, 13].

Currently, several therapeutic strategies have been proposed for the prevention and treatment of DRIC, each of them has certain positive results. However, what they have in common is the limitedness of the results achieved and the possibilities of their prediction, and some of them, even the therapeutic methods used in the clinic, have several adverse effects. We deliberately leave out of this review the methods of preventing the DRIC development, which imply changes in the doses of DR, the rate and rhythm of administration, replacement of the drug with less cardiotoxic ones and others that worsen the results of the anticancer treatment, and, therefore, they cannot be considered, in our opinion, as a therapeutic strategy.

The most comprehensive approach to the DRIC prevention was proposed in 2017 by the American Society of Clinical Oncology. It was approved by the American Heart Association where it is recommended to consider a prevention strategy even before starting the treatment for a malignant neoplasm. The approach is based on the position of common pathogenesis and risk factors for the development of neoplasms and a cardiovascular pathology. In this regard, the patient is recommended to decrease the risk of developing DRIC by reducing excess weight, adhering to a diet, adequate exercise and smoking cessation [14].

At the same time, over 50 years of the use of DR in the clinic, many regimens for the prevention and medicinal treatment of DRIC have been proposed. Some of them, such as the use of adrenergic agonists during a DR infusion and with a range of adverse effects, have become history. However, an analysis of the existing ones in most cases shows that their evidence base, with a few exceptions, is rather limited. Undoubtedly, this is a direct consequence of the ambiguity regarding the pathogenesis of the DRIC development itself.

**ACE inhibitors.** There are studies limited in number and volume on the effectiveness of the use of ACE inhibitors for the prevention of DRIC. In six out of seven such works entered the databases, the role of enalapril was assessed positively to varying degrees, while five publications indicated a significant difference in the LVEF observed with its use, as well as in a decrease in the level of troponin in the blood. In 84 children with the hematological pathology, the use of enalapril made it possible to reduce the decrease in LVEF 6 months after the treatment with anthracyclines, and also to fourfold reduce the characteristic increase in specific blood biomarkers. The similar data are demonstrated by other publications where, under the influence of enalapril, a decrease in the increase in the LV end-systolic volume and the diameter of the left atrium, as well as other echo signs of DRIC, was recorded. There is a well-founded opinion that enalapril is effective in preserving the systolic and diastolic function in cancer patients received the DR treatment earlier [1, 15, 16].

Concerning the time of the required initiation of the DRIC drug prevention there were interesting data from a multicenter phase III study ICOS-ONE, which compared patients who were prescribed enalapril at the beginning of the chemotherapy with patients who received it only after increasing the concentration of troponin in the blood serum. The troponin concentration was the highest 1 month after the DR administration and was identical in both groups. However, in 12 months, DRIC defined as a 10 percentage point decrease in LVEF with the values <50 % developed only in 3 patients: 2 in the prevention group and 1 in the troponin increase group. Since the results obtained in these groups did not differ, the authors recommended the treatment strategy with the onset of increased troponin in the blood as more practical one [17].

**Beta-blockers** (BB) are widely used to treat heart failure of any genesis due to their ability to block its characteristic progressive neurohormonal cascade of development. The additional antioxidant activity of carvedilol and nebivolol naturally substantiates their use for the DRIC prevention. In a meta-analysis of the prophylactic use of carvedilol, which included 8 randomized clinical trials (RCT) and combined 633 patients, the incidence of significant decreases in LVEF was lower in patients in the carvedilol group (3.2 % vs 5.8 %). The authors concluded that the prophylactic use of carvedilol may reduce the incidence of a specific LV dysfunction. However, the studies in this work were short-term [18]. Several more studies on the similar use of carvedilol in groups of women with breast cancer have shown the similar results. However, they had insignificant differences in the cardiac function immediately after the treatment with DR. But already 6 months after it, the differences in LVEF, the rate of its deformation, and other signs of the LV dysfunction, including the concentration of biochemical markers in the blood, were significant [19, 20]. In another study involving 50 children with acute lymphoblastic leukaemia, the pre-administration of carvedilol for 5 days before each dose of DR caused a significant improvement in LV functions measured by the echographic examination one week after the last dose of the drug. It also prevented the increase in the concentration of specific biomarkers in the blood plasma observed in the control group, indicating the cardioprotective effect of carvedilol [21].

Another BB, nebivolol, was also studied in a small randomized clinical trial in women with breast cancer who received the DR chemotherapy; among them, 27 patients received nebivolol in the dose of 5 mg daily, and 18 women received placebo. In 6 months, there was a significant increase in LV size and a decrease in LVEF in the placebo group, and they were unchanged in the nebivolol group. In the subsequent follow-up, the serum natriuretic hormone (NT-proBNP) concentration did not change in the nebivolol group, but was significantly increased in the control group of patients [22].

The studies of metoprolol as a cardioprotective agent for DRIC as a whole have not yet given unambiguous results. And this is true not only for a few clinical observations, but also for a relatively large number of works in the experiment on animals [23-25].

Several studies have examined the effectiveness of combinations of an ACE inhibitor and BB for the DRIC prevention. For example, 90 patients with recurrent hematologic malignancies (OVERCOME study) received enalapril in combination with carvedilol. During 6 months of the follow-up after the chemotherapy, patients receiving this combination of drugs showed a significantly smaller decrease in LVEF than in control. The mean LVEF according to echocardiography decreased by 0.17 % and 3.11 %, respectively, and only 2 patients had symptoms of congestive heart failure [26].

**Angiotensin II receptor blockers.** In the study by Nakamae H. et al. [27], the potential cardioprotective effect of valsartan was studied in 40 patients with non-Hodgkin's lymphoma who received the chemotherapy in the CHOP regimen. Valsartan after the DR administration significantly inhibited LV dilation, the lengthening and dispersion of the QTc interval, and an increase in the concentration of specific biomarkers in the blood. Unfortunately, the patients were followed up for only one week after the chemotherapy. An RCT studying the efficacy of candesartan, metoprolol and their combination involving 120 women with breast cancer who received the DR postoperative adjuvant chemotherapy revealed a significantly lower decrease in LVEF in the candesartan group. Metoprolol did not show cardioprotective properties since the decrease in this indicator when taken was identical to the control group. However, the results of using these two preparations together were conflicting [23].

In a meta-analysis of 14 studies, the efficacy of several drugs for the primary prevention of the DRIC development was studied. It showed that antagonists of angiotensin II and BB reliably prevent the short-term cardiotoxicity of DR. However, as the authors note, a decrease in LVEF does not necessarily mean that these drugs prevented the primary damage to cardiomyocytes. This effect is most likely associated with a decrease in systemic vascular resistance. Unfortunately, the analysis data did not include data on the incidence of clinical complications (for example, hospitalizations or deaths from heart failure) and other side effects more than 1 year after the DR introduction. Only one study indicated that 3.2 years after the chemotherapy, 106 women with breast cancer who received BB throughout their treatment had an 80 % lower risk of hospitalization for heart failure than 212 women who received the similar chemotherapeutic regimens without using BB [28].

**Aldosterone antagonists.** It is known that blockade of mineralocorticoid receptors, for example, with potassium-sparing diuretics, suppresses the development of cardiosclerosis and improves the survival of patients with CHF after myocardial infarction, as well as optimizes the extrarenal effects of aldosterone. In this regard, the idea of using such an approach for the prevention and treatment of DRIC looks quite logical. Under experimental conditions on animal models, spironolactone prevented functional changes that were characteristic of DRIC – prolongation of the QTc interval, decrease in LVEF, as well as an increase in end-diastolic and systolic LV sizes [29]. A double-blind RCT of 83 women with breast cancer, some of them received spironolactone while taking DR, showed that it provided significant, albeit short-term, cardioprotection. According to echocardiography, the decrease in LVEF and diastolic parameters 3 weeks after the chemotherapy was significantly less in the spironolactone group than in the control group. Similarly, lower concentrations of cardiac biomarkers in the blood serum (creatine kinase-MB, troponin and NT-proBNP) were observed [30].

At the same time, it turned out that the overall potential and effectiveness of the use of preparations in this area is very different in studies on animals and humans. First of all, since DRIC under the effect of DR in the clinic develops over months or years, and on animals data due to acute trauma by the introduction of its high doses are obtained [10, 31].

**Statins.** The pleiotropic effects of statins are their ability to reduce oxidative stress and inflammation. These two mechanisms directly counteract the negative effects of DR and potentially protect the patient from developing DRIC. In a cohort study of 67 women with breast cancer who received statins during the chemotherapy with DR, a significantly lower risk of heart failure was recorded compared to 134 patients in the control group. The follow-up lasted 2.6 years after the oncological diagnosis and treatment [12]. At the same time, an RCT of the prophylactic use of atorvastatin in 40 patients treated with DR did not find significant differences in a decrease in LVEF <50 % in 6 months of the treatment compared to control [32]. Most researchers of this

area of prevention of the DRIC development note that at the current level of knowledge it is practically impossible to differentiate the expected protective mechanisms of statins: whether they are associated with their pleiotropic effects or they are a consequence of a decrease in the manifestations of ischemic cardiomyopathy. Although the majority concludes that in any case, cancer patients with hypercholesterolemia or an increased risk of cardiovascular complications should receive the appropriate statin treatment when undergoing the chemotherapy with the inclusion of DR. At the same time, the advantages and risks of such an empirical approach remain unclear, and there are no long-term studies in this direction.

**Dexrazoxane**, an EDTA derivative, has been used to protect the heart from the cardiotoxic effects of chemotherapeutic drugs, including DR, for over 20 years. It is currently the only drug approved by the FDA and the European Medicines Agency (EMA) for the prevention of DRIC. The mechanism of action is based on the transfer of extra-complex iron into chelate compounds, and it reduces the number of metal ions in combination with DR *in vivo* and the formation of superoxide radicals. It is also assumed that dexrazoxane can intracellularly take the form with an open ring, blocking the generation of free radicals exactly here [4, 19]. Dexrazoxane has a proven cardioprotective capacity both on animal models and in human studies. There was decrease in subclinical forms of DRIC (asymptomatic LV dysfunctions) and fewer heart attacks than in patients who did not receive dexrazoxane during the treatment with DR [4, 33]. The meta-analysis of 10 RCTs of dexrazoxane, including more than 1,500 cancer patients, has shown that the preparation markedly reduces the incidence of heart failure. It is noted that the administration of dexrazoxane immediately before the DR infusion minimizes the decrease in LVEF and the concomitant increase in the concentration of cardiac troponin or NT-proBNP [34, 35].

At the same time, there were reports in the literature about the ability of dexrazoxane to potentiate secondary malignant neoplasms and the development of myelodysplastic syndrome in pediatric practice. And although more recent and large-scale studies of these and other patients with secondary malignant neoplasms did not reveal a direct relationship with the use of this preparation, the discussion on this matter is considered not closed [8, 36].

**Metabolic preparations**, for example, trimetazidine, normalize the energy balance in cardiomyocytes during hypoxia, preventing a decrease in the intracellular ATP content. The ability of a medicine to maintain cellular homeostasis and the functioning of membrane ion channels create the prerequisites for the prevention of the DRIC development. At the same time, the cumulation of the effect over time, being characteristic of this group of preparations, in this case, is not a disadvantage since the side effects of the DR action develop similarly over time. In the study by Vasyuk Yu. A. et al. [7], the cardioprotective effect of trimetazidine was investigated in 26 out of 50 patients with breast cancer who received DR in combination with cyclophosphamide and fluorouracil. After 6 months of the follow-up, the number of patients with clinical signs of HF increased in both groups. At the same time, against the background of the trimetazidine therapy, the left atrium size, like some other indicators of echocardiography, in contrast to the control group, remained stable. The study showed that trimetazidine did not significantly affect the main clinical parameters compared to the standard treatment. In another study of 73 patients with breast cancer, three months after the start of the chemotherapy using DR, there were significant differences between the two groups in LV velocity characteristics and both ventricular deformity indices, indicating the LV systolic dysfunction. In the trimetazidine group, these changes were minimal [37].

Another preparation of this group, ranolazine was actively studied on animal models where its ability to protect cardiomyocytes from oxidative stress caused by DR was confirmed. It is thought to be useful in treating the LV diastolic dysfunction due to its ability to reduce late sodium flow and counteract intracellular calcium accumulation. However, these results are still pending in the clinic [36, 38].

In experimental conditions, single studies of the cardioprotective potential of some other preparations and medicinal substances (ivabradine, coenzyme Q10, etc.) were also performed. For some of them, modest positive results have been obtained, but they are still little systematized [36, 39].

CONCLUSIONS

Thus, summarizing the above, we can conclude about the very modest positive results of the DRIC prevention achieved with the current therapeutic regimens. There is practically no convincing data on their reduction in the frequency of early and especially late forms of this complication, as well as the possibilities for their prediction. Practically, all the medicinal strategies currently used in the clinic, as well as those studied on animal models, can only counteract individual mechanisms of the DRIC development. However, today it is known that this pathology is a complication with many mechanisms of its development. And since we cannot refuse the use of DR as a highly effective antitumor antibiotic over the longer term, the risk of developing DRIC remains. Further research in the direction of increasing the effectiveness of its medicinal prevention remains necessary for practical medicine.

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