
# Mechanisms of the Development of Cardiotoxicity in Breast Cancer Chemirterapy

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**ABSTRACT**

Modern treatment of breast cancer is associated with risks of cardiotoxicity. The article presents the mechanisms of cardiotoxicity development on the example of drugs used in the treatment of breast cancer (anthracyclines and a targeted drug - trastuzumab). Diagnostic methods, their advantages and disadvantages, the algorithm of diagnosis and continuation of therapy of patients receiving cardiotoxic therapy of breast cancer are presented.

**Keywords:** chemotherapy, targeted therapy, cardiotoxicity, echocardiography, doxorubicin, trastuzumab, cardiomyopathy, cardiovascular complications.

One of the most common oncological diseases among women is breast cancer (BC), which accounts for about 20% in the structure of oncological morbidity in women [2]. The nature and mechanisms of dynamic shifts in the blood cytokine profile at various stages of the spread of neoplasia in breast cancer are of great theoretical and practical significance, since it is cytokines that are the regulators of the most important processes of intercellular interaction in the lymphoid tissue, in the monocyte-macrophage system, have pronounced local and remote polymodal pro- and anti-oncogenic effects [1].

Chemotherapy is one of the main treatments for common forms of breast cancer. With the improvement and the emergence of new methods of treatment (chemotherapy, targeted therapy), good results and an increase in survival and relapse-free periods are observed. One of the most common side effects of some breast cancer chemotherapy treatments is cardiotoxicity.

Cardiotoxicity is a decrease in the contractile function of the heart that occurs during cancer therapy. Cardiovascular disease (CVD) is one of the most common manifestations of chemotherapy toxicity, which may be the result of a direct effect of cancer chemotherapy on the function and structure of the heart, especially if the patient already has cardiovascular risk factors [5, 6].

Anthracyclines and the targeted drug trastuzumab are often used in the treatment of breast cancer. Anthracyclines are an integral component of many effective neoadjuvant, adjuvant, and palliative chemotherapy regimens. In patients after breast cancer, the risk of developing cardiovascular diseases was approximately 2.4 times higher. These data point to the need to control CVD risk factors and develop strategies to reduce the risk of CVD-related mortality when they occur [7]. The frequency of cardiotoxicity of modern chemotherapy, using anthracycline and anthracycline-trastuzumab, is usually less than 5%. Anthracyclines cause irreversible death of cardiomyocyte cells with characteristic ultrastructural changes, including vacuole degeneration and loss of myofibrils [10, 11].

Anthracycline-induced cardiotoxicity is also based on an indirect effect, which consists in the increased formation of reactive oxygen species that cause peroxidation of myocyte membranes and the so-called "oxidative stress" [12,13].

It has been determined that in most patients there is an asymptomatic decrease in the left ventricular ejection fraction (LVEF) (> 5-15%), being within the reference values > 50% [8].

Most researchers define cardiotoxicity as a decrease in LV EF by 10 absolute percent to values less than 53% associated with chemotherapy, regardless of the presence or absence of clinical symptoms of heart failure. At the same time, other causes of a decrease in LV EF should be excluded. A decrease in LVEF should be confirmed by a repeat study after 2-3 weeks. With an improvement in EF by 5% or more, they speak of reversible LV dysfunction.

The main mechanisms of chemotherapy-induced cardiotoxicity include:

• impact on the coagulation system;

• arrhythmogenic effect (more often - by prolonging the QT interval);

• hypertensive action;

• nonspecific inflammation of the myocardium and/or pericardium [9].

Moreover, if anthracycline-related cardiac dysfunction is detected early and treated with heart failure drugs, patients often have good functional recovery. Conversely, if patients are diagnosed late after the onset of cardiac dysfunction, heart failure is usually difficult to treat [14]. Unlike anthracyclines, trastuzumab's cardiotoxicity usually occurs during treatment. Trastuzumab-associated cardiotoxicity is generally considered to be unrelated to cumulative dose, although a two-fold incidence of LV dysfunction has been reported when patients were treated for 24 months rather than the usual 12 months [15].

Trastuzumab-induced LV dysfunction and heart failure are usually reversible upon discontinuation of trastuzumab and/or treatment of heart failure [16].

Echocardiography is commonly used to assess the structure and function of the heart in cancer patients to detect and predict cardiomyopathy and heart failure [17-21]. The most commonly used parameter for monitoring left ventricular function with echocardiography is LV EF. To monitor cardiac function, it is recommended that the first follow-up echocardiography be performed at the end of chemotherapy, and not at the threshold cumulative anthracycline dose. If a patient develops clinical symptoms of cardiotoxicity during anthracycline treatment or is asymptomatic with an LVEF <45%, or a decrease to baseline of 15%, then treatment should be discontinued in order to adequately assess the patient's cardiac function and prescribe further treatment with caution [22] .

Discontinuation of doxorubicin therapy is recommended if LVEF decreases by ≥10% from baseline and reaches LVEF ≤50%. Patients with an abnormal baseline LVEF <50% are advised to conduct studies before each administration of doxorubicin [23,24].

For trastuzumab therapy, the manufacturers recommend baseline LVEF assessment followed by re-measurement of LVEF every 3 months (4 cycles) during treatment and every 6 months for the next 2-year period after completion of the regimen [25].

Serum cardiac biomarkers are increasingly being used to assess cardiotoxicity during and after chemotherapy. In patients with cancer receiving high-dose chemotherapy, an increase in troponin I was observed, which is a predictor of a subsequent decrease in LVEF and adverse cardiovascular events [26]. Patients with a persistent increase in troponin I after completion of chemotherapy are at high risk for subsequent events [27]. Patients with breast cancer treated with trastuzumab, who have an increase in troponin I, demonstrate insufficient recovery of LVEF, despite therapy for heart failure [28].

Thus, given the trend towards an increase in the incidence of malignant neoplasms and an increase in the patient's life expectancy after chemotherapy, the issue of parallel protection of the cardiovascular system, both during treatment and in the future, is relevant. To improve long-term outcomes and quality of life, it is necessary to balance the expected benefits of cancer treatment with the

risk of cardiovascular disease associated with the treatment and the individual patient, and determine strategies to prevent cardiotoxicity.

Numerous studies are currently underway to detect early damage to the heart and identify drugs that can protect against possible damaging effects. Increasing awareness of cardiovascular disorders associated with cardiotoxic cancer treatment has made it possible to move towards new interdisciplinary approaches to cardio-oncological care for patients with breast cancer. In all cases, it is necessary to adhere to the principle of "do no harm" and to patients who are undergoing or have already undergone chemotherapy treatment, it is recommended to visit a cardiologist, examination and treatment with drugs with proven efficacy.

The state of the patient's immune system and the ability of the treatment to influence the effector and suppressor components of immunity in many cases determine the prognosis of the disease and the success of various types of anticancer therapy, including targeted and chemotherapy [2]. It has been established that the clinical efficacy of various chemotherapy drugs in many cases depends not only on their direct cytostatic and/or cytotoxic effect on tumor cells, but also on their ability to modulate the tumor cell phenotype and influence the antitumor immune response. In this case, the initial state of the body's immune system and its response to the ongoing treatment is of decisive importance [1].

Analyzing the data of a number of lecturers, it should be concluded that the use of polychemotherapy in the complex traditional treatment of patients with breast cancer also exacerbated the development of an immunodeficiency state, as indicated by the above studies, a number of indicators of humoral and cellular immunity in the dynamics of the treatment of patients. Therefore, it is important to study the dynamics of immune system dysfunction during treatment and correct these changes in order to achieve good results of ongoing chemotherapy treatment. Identification of the relationship between the dynamic parameters of the cytokine system and the nature of their changes in the course of antitumor therapy with the effectiveness of the treatment can help in establishing prognostic and predictive immunological markers, developing individual approaches to the treatment of patients with breast cancer and increasing its effectiveness [1,2].

In connection with the foregoing, the expediency of further pathogenetic substantiation of the use of pharmacological preparations in the complex therapy of breast cancer, which simultaneously have the properties of immunomodulators, antioxidants, membrane protectors and detoxicants, is obvious.

It is also necessary in case of development of cardiotoxicity against the background of chemotherapy to carry out treatment in accordance with generally accepted recommendations for heart failure. The basic drugs should include ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists. It should be noted that the problem of finding a potential therapeutic drug remains open and needs to be resolved. Further research in this direction may contribute to the development of new effective tactics in the prevention and treatment of this complication of chemotherapeutic treatment of breast cancer.

Therefore, it is advisable to identify immunological disorders in patients with breast cancer, which, having improved prognostic information, can be the basis for developing an algorithm for the prevention and correction of immune dysfunction in complex therapy in order to prevent the development of cardiotoxicity during chemotherapy, which will significantly improve the results of treatment in patients with breast cancer. The foregoing convincingly testifies to the expediency of further study of the pathogenesis of breast cancer, the patterns of development of dysfunction of the immune and cytokine statuses at various stages of breast cancer development, which will expand the existing principles of diagnosis, predicting complications and increase the effectiveness of complex therapy for breast cancer.

## References

1. Belyaeva N.N., et al., Immunoregulatory cells as potential cancer biomarkers. Bulletin of the Kazan NMU - 2016. - No. 3. pp. 185-191.
2. Seliverstova D.V., Evsina O.V. Cardiotoxicity of chemotherapy // Heart: a journal for practitioners. - 2016. - V. 5, No. 1. - P. 50-57.
3. Chazova I.E., Oshchepkova E.V., Kirillova M.Yu., et al. The risk of developing arterial hypertension in patients with cancer during antitumor treatment // Consilium Medicum. - 2016. - V. 18, No. 1. - P. 16-20.
4. Chazova I.E., Oshchepkova E.V., Kirillova M.Yu., et al. Cardiovascular and oncological diseases: the search for solutions to new problems // Systemic hypertension. - 2015. - V. 12, No. 2. - P. 6-7.
5. Ewer M., Ewer S. Cardiotoxicity of anticancer treatments // Nat. Rev. cardiol. - 2015. - Vol. 12. - P. 547-558.
6. Armstrong G.T., Oeffinger K.C., Chen Y., et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer // J. Clin. oncol. - 2013. - Vol. 31, no. 29. - P. 3673-3680.
7. Priorities in the Cardiovascular Care of Breast Cancer Survivors, Bonnie Ky, Show More // J. of Oncology Practice. - 2018. - Vol. 14, no. 4. - P. 205-211.
8. Khouri M.G., Douglas P.S., Mackey J.R., et al. Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues // Circulation. - 2012. - Vol. 126, No. 23. - P. 2749-2763.
9. Maria Florescu et al. Chemotherapy-induced Cardiotoxicity // J. Clin. Medical. - 2013. - Vol. 8, #1. - P. 59-67.
10. Billingham M.E., Mason J.W., Bristow M.R., Daniels J.R. Anthracycline cardiomyopathy monitored by morphologic changes // Cancer Treat Rep. - 1978. - Vol. 62, no.6. - P. 865-872.
11. Mackay B., Ewer M.S., Carrasco C.H., Benjamin R.S. Assessment of anthracycline cardiomyopathy by endomyocardial biopsy // Ultrastruct Pathol. - 1994. - Vol. 18, #1-2. - P. 203-211.
12. Elzbieta Sadurska. Current Views on Anthracycline Cardiotoxicity in Childhood Cancer Survivors // Pediatr Cardiol. - 2015. - Vol. 36. - P. 1112-1119.
13. Maria Florescu et al. Chemotherapy-induced Cardiotoxicity // J. Clin. Medical. - 2013. - Vol. 8, #1. - P. 59-67.
14. Cardinale D., Colombo A., Lamantia G., et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacological therapy // J. Am. Coll Cardiol. - 2010. - Vol. 55. - P. 213-220.
15. de Azambuja E., Procter M.J., van Veldhuisen D.J., et al. Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01) // J. Clin. Oncol. — 2014. — Vol. 32. — P. 2159-2165.
16. Suter T.M., Procter M., van Veldhuisen D.J., et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial // J. Clin. Onco. — 2007. — Vol. 25. — P. 3859-3865.
17. Zamorano J.L., Lancellotti P., Rodriguez Muñoz D., et al.: 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC) // Eur. Heart J. — 2016. — Vol. 37. — P. 2768-2801.
18. Armenian S.H., Lacchetti C., Barac A., et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline // J. Clin. Oncol. — 2017. — Vol. 35. — P. 893-911.
19. Yeh E.T., Bickford C.L. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management // J. Am. Coll Cardiol. — 2009. — Vol. 53. — P. 2231-2247.
20. Daher I.N., Kim C., Saleh R.R. et al. Prevalence of abnormal

echocardiographic findings in cancer patients: a retrospective evaluation of echocardiography for identifying cardiac abnormalities in cancer patients // Echocardiography. — 2011. —Vol. 28. — P. 1061-1067.
21. Cheitlin M.D., Armstrong W.F., Aurigemma G.P., et al. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography) // J. Am. Soc. Echocardiogr. — 2003. — Vol. 16. — P. 1091-1110.
22. Cai F., Luis MAF, Lin X., et al. Anthracycline-induced cardiotoxicity in the chemotherapy treatment of breast cancer: Preventive strategies and treatment // Mol Clin. Oncol. — 2019. — Vol. 11, №1. — P. 15-23.
23. Choi B.W., Berger H.J., Schwartz P.E., et al. Serial radionuclide assessment of doxorubicin cardiotoxicity in cancer patients with abnormal baseline resting left ventricular performance // J. Am. Heart. — 1983. — Vol. 106, №4, Pt 1. — P. 638-43.
24. Mitani I., Jain D., Joska T.M., et al. Doxorubicin cardiotoxicity: prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiography in the current era // J. Nucl Cardiol. — 2003. — Vol. 10, №2. — P. 132-139.
25. Avelar E., Strickland C.R., Rosito G. Role of Imaging in Cardio-Oncology // J. Curr Treat Options Cardiovasc Med. — 2017. — Vol. 19, №6. — P. 46.
26. Cardinale D., Sandri M.T., Martinoni A., et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy // J. Annal Oncol. — 2002. — Vol. 13. — P. 710-715.
27. Cardinale D., Sandri M.T., Colombo A., et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy // Circulation. — 2004. — 109. –– P. 2749-2754.
28. Cardinale D., Colombo A., Torrisi R., et al. Trastuzumab-induced cardiotoxicity: Clinical and prognostic implications of troponin I evaluation // J. Clin. Oncol. — 2010. — Vol. 28. — P. 3910-3916.