MEDICAL UNIVERSITY OF KARAGANDY

ANNOTATION

dissertation work for the degree of Doctor of Philosophy

Topic: "Influence of adjuvant chemotherapy on biochemical blood parameters in patients with breast cancer"

 Specialty: 6D110100 "Medicine"

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Karaganda, 2022

Relevance of the topic

The incidence of breast cancer (BC) today occupies a leading place in the structure of malignant neoplasms in women [1, 2].

Although most patients with localized breast cancer may be pain free, distant recurrence is common and is the leading cause of death from this disease. Adjuvant systemic therapy is effective in reducing the risk of distant and local recurrence, including endocrine therapy, anti-HER2 therapy, and chemotherapy, even in patients at low risk of relapse. The widespread use of adjuvant systemic therapy helps to reduce mortality from breast cancer [3].

The most important place in the treatment of early forms of breast cancer is occupied by adjuvant chemotherapy (ACT), which plays a decisive role in the prevention of distant metastases. The use of cytostatics or hormonal drugs after mastectomy contributes to an increase in relapse-free and overall survival of patients [4, 5].

In the adjuvant treatment of operable forms of breast cancer, the generally recognized standard is the CMF chemotherapy regimen. In order to achieve an additional therapeutic effect, some drugs are periodically replaced in the treatment regimen by others that are potentially more active. After the high efficacy of doxorubicin in metastatic breast cancer was proven, it began to be used as a replacement drug [6, 7].

ACT is the most significant achievement in the treatment of patients with breast cancer, the optimal use of which saves many lives every day. To date, there are standard chemotherapy regimens that have proven to be highly effective, relapse-free and stable survival rates. But, despite this, medicine does not stand still, and many scientists are trying to develop new chemotherapeutic drugs and their combinations with less toxicity, which will soon become a priority in adjuvant treatment.

Another side of polychemotherapy treatment is considered to be high toxicity, which manifests itself in the targeted destruction of tumor cells, as well as damage to healthy ones, which results in increasing metabolic disorders [8, 9].

One of the fundamental mechanisms of the normal development of the body is to maintain the balance of the state of the antioxidant defense of the body and the processes of free radical and peroxidation of various biomolecules [10]. In breast cancer, the reactions of lipid peroxidation have been studied quite well, but the range of protein oxidation products that have different biological activity has not been determined.

One of the endogenous sources of reactive oxygen species is the enhanced formation of intermediates of purine catabolism [11], which have been studied in sufficient detail in the neoadjuvant chemotherapy regimen for breast cancer, in combination treatment with the anticancer drug arglabin, and in the latter's mono regimen [12]. In addition, excessive formation of oxypurines induce endothelial damage.

Thus, at present, clinical oncology is of particular interest in the study of metabolites of oxidative stress and purine metabolism, since these indicators can be used as prognostic and predictive factors in planning both the overall treatment strategy and the choice of individual components of therapy.

Many scientists are trying to solve the problem of toxicity of chemotherapy drugs during treatment by including various cellular protectors and agents that have a restorative effect on metabolism [13].

Arglabin was experimentally studied at the Kazakh Research Institute of Oncology and Radiology [14, 15].

The mechanism of action was studied jointly with the laboratories of the MD Anderson clinic and Nu Oncology Labs (Houston, USA). It was found that Arglabin is a competitive inhibitor of farnesylation of RAS oncoproteins, reduces the expression of RAS genes and ATP content, and induces apoptosis of tumor cells [16, 17, 18].

Currently, arglabin is registered and used as an antitumor agent in the treatment of primary liver, ovarian, lung and breast cancer, both in monotherapy and in polychemotherapy.

Working hypothesis

Arglabin in the adjuvant mode increases relapse-free and cumulative survival rates in breast cancer patients and has a positive effect on biochemical processes in the body of breast cancer patients.

The purpose of the study was to evaluate the effect of adjuvant chemotherapy on the biochemical parameters of the blood of patients with breast cancer.

Research objectives:

1. Determine the toxicity of adjuvant polychemotherapy in breast cancer.

2. To study the state of oxidative metabolism in the blood of breast cancer patients on the background of adjuvant polychemotherapy (malonic dialdehyde, methylglyoxal, AOPP, carbonyl derivatives, membrane-bound hemoglobin).

3. To study the state of purine metabolism in the blood of breast cancer patients on the background of adjuvant polychemotherapy.

4. To study the effect of adjuvant chemotherapy with arglabin on overall and disease-free survival rates in patients with breast cancer.

Scientific novelty:

1. For the first time, a study of the use of arglabin in the adjuvant regimen in combination with chemotherapy according to the AC regimen in patients with breast cancer was conducted: a study of the hematological toxicity of adjuvant polychemotherapy was carried out and a decrease in toxicity was shown when the combination of the AC chemotherapy regimen with Arglabin was shown.

2. For the first time in the blood of patients with breast cancer, the effect of adjuvant chemotherapy with and without arglabin on the level of malondialdehyde, reactive carbonyl derivatives of proteins, methylglyoxal and membrane-bound hemoglobin was studied, and it was shown that APCT AS + Arglabin leads to a decrease in oxidative stress.

3. For the first time in the blood of patients with breast cancer, the effect of adjuvant chemotherapy with and without arglabin on the level of free purine bases was studied and it was proved that after APCT AS + Arglabin, in comparison with APCT AS, a statistically significant decrease in guanine levels was observed in erythrocytes ( from 720 to 512), hypoxanthine (from 783 to 585) and adenine (from 691 to 517).

4. For the first time, it has been proven that the addition of arglabin to the standard adjuvant treatment regimen for AS in patients with breast cancer increases disease-free survival by 9.5%.

Theoretical significance of the study

The results obtained made it possible to identify the advantages of using Arglabin with adjuvant polychemotherapy of AS in breast cancer.

practical value. The combination of adjuvant polychemotherapy according to the AS scheme with Arglabin in breast cancer eliminates hematological toxic manifestations of chemotherapy, reduces the level of oxidative stress and normalizes purine metabolism, increases the 3-year relapse-free survival rate by 9.5%. This scheme of adjuvant polychemotherapy can be recommended for clinical practice at an oncological dispensary.

The main provisions for defense:

1. Manifestations of hematological toxicity of adjuvant polychemotherapy according to the AC scheme are more pronounced compared to polychemotherapy according to the AC + Arglabin scheme.

2. In the blood plasma of patients with breast cancer, there is an increase in oxidative metabolism due to an increase in the levels of malondialdehyde, reactive carbonyl derivatives of proteins, methylglyoxal and membrane-bound hemoglobin.

3. Scheme APHT AS+Arglabin leads to a decrease in the level of methylglyoxal and membrane-bound hemoglobin in the blood plasma of patients with breast cancer when compared with the scheme APHT AS.

4. Scheme APHT AS + Arglabin in comparison with APHT AS normalizes the parameters of purine metabolism in the blood of patients with breast cancer.

5. The APHT regimen AC+Arglabin increases relapse-free survival rates in patients with breast cancer.Materials and methods of research

A prospective study that will include 80 breast cancer patients after surgery and receiving adjuvant chemotherapy.

Patients will be divided into 2 groups - 1 study, one control.

In the control group, treatment will be carried out according to the following scheme:

Stage 1 - surgical treatment in the amount of radical resection or radical mastectomy.

Stage 2 - adjuvant chemotherapy according to the AC scheme: doxorubicin - 60 mg / m2 (doxolec, doxorubicin-teva, doxorubicin-lance, adriablastin, farmorubicin - active ingredient - doxorubicin), cyclophosphamide - 600 mg / m2 (endoxan, cytoxan, cyclophosphamide-lance , cyclophosphamide - the active substance is cyclophosphamide) every 21 days, for a total of 6 cycles. In the presence of side effects, the periods between cycles can be extended up to 4 weeks, the dose of chemotherapy drugs can be reduced by 25%.

Stage 3 - a course of postoperative remote radiation therapy

Stage 4 - adjuvant hormone therapy for 3 years of observation.

In the study group, patients receive treatment according to the scheme:

Stage 1 - surgical treatment in the amount of radical resection or radical mastectomy.

Stage 2 - adjuvant chemotherapy according to the AC + Arglabin scheme: doxorubicin - 60 mg / m2 (doxolec, doxorubicin-teva, doxorubicin-lance, adriablastin, farmorubicin - the active substance is doxorubicin), cyclophosphamide - 600 mg / m2 (endoxan, cytoxan, cyclophosphamide -lance, cyclophosphamide - active substance - cyclophosphamide) every 21 days + Arglabin 450 mg / m2 No. 7 days, every 21 days, 6 cycles in total. In the presence of side effects, the periods between cycles can be extended to 4 weeks, the dose of chemotherapy and arglabin can be reduced by 25%.

Stage 3 - a course of postoperative remote radiation therapy

Stage 4 - adjuvant hormone therapy for 3 years of observation.

Inclusion Criteria:

1. Patients with nodular breast cancer (BC) St IIa (T1N1M0, T2N0M0), IIb (T2N1M0, T3N0M0), IIIa (T1N2M0, T2N2M0,) with histological and immunohistochemical verification of Luminal A and B types.

2. Female patients aged 30 - 70 years.

3. Consent of the patient to participate in the study.

4. The absence of severe pathology from the side of the cardiovascular, pulmonary and urinary systems.

5. Patients who did not receive specific antitumor therapy prior to inclusion in the study.

6. The absence of a history of oncological pathology of other localizations.

In these patients, it is planned to study the indicators of malondialdehyde, methiglyoxal, AOPP, carbonyl derivatives, membrane-bound hemoglobin, catalase, purines in the blood before, during and after adjuvant chemotherapy.

For statistical processing of the obtained results, the procedures of mathematical statistics will be used, implemented in the application programs "STATISTICA 10.0" and EXСEL. The processing of quantitative characteristics will be carried out by the method of descriptive statistics. Nonparametric methods will be applied. The significance of differences between groups of patients will be assessed using the fit test (χ2) at р˂0.05. Correlation analysis will be carried out using the Spearman test at р˂0.05.

Approbation of work

The main results of the dissertation work were reported and discussed at the international scientific conference "Cancer Research & Oncology and World Congress on Primary Health Care and Medicare Summit" May 20-21 2019 (Rome, Italy); "Membrane-bound hemoglobin in the erythrocytes of the blood of patients with breast cancer" collection of abstracts of the VII Congress of Radiologists and Oncologists of Kazakhstan with international participation October 17-18, 2019, Nur-Sultan.

The work was presented at an expanded meeting of the Department of Oncology and Radiation Diagnostics of the NAO MUK on April 21, 2022. (protocol No. 8).

Publications

On the topic of the dissertation, 9 printed works were published: in scientific publications recommended by the Committee - 4 (magazine "Medicine and Ecology" - 3, Modern problems of science and education -1), in an international scientific publication included in the Scopus database (magazine "Open Access Macedonian Journal of Medical Sciences") - 1, in conference proceedings, with international participation - 4, including a poster presentation. Certificates have been received on entering information into the state register of rights to objects protected by copyright No. 12094 dated September 22, 2020 Ministry of Justice of the Republic of Kazakhstan (Impact of adjuvant polychemotherapy with arglabin on indicators of oxidative metabolism in the blood in breast cancer), No. 12097 dated "22" September 2020 (Effect of adjuvant polychemotherapy with arglabin on blood purine metabolism in breast cancer) (Appendix A).

Work implementation

The results of the study were introduced into the work of the departments of the Multidisciplinary Hospital No. 3 in Karaganda, into the educational process of the Department of Oncology with Radiation Diagnostics and Biochemistry of NJSC "Medical University of Karaganda" (Appendix B). The dissertation work was written as part of a randomized multicenter clinical trial of the original drug "Arglabin" in the complex therapy of breast cancer at an increased dose, identification code AR 01/1.

The base for scientific research is MB No. 3 of Karaganda, the Department of Oncology and Radiation Diagnostics, the Department of Biological Chemistry of the NAO MUK.

Conclusions:

1. Indicators of hematological toxicity are significantly lower in patients with breast cancer who received adjuvant PCT according to the AC + Arglabin regimen. The indicator of the absence of toxicity to hemoglobin was statistically significant, which was (84.4±6.42)% in the group of patients treated with APC according to the AC regimen versus (93.1±4.7)% in the group of patients treated with AS + Arglabin. Statistically significant index of anemia I degree is higher in patients of the control group: (15.6±6.42)% in patients with PCT AS and (6.9±4.7)% in patients with PCT according to the AC + Arglabin scheme.

APCT AS + Arglabin contributes to a decrease in blood leukopenia by 25.5% (68.97±8.6%) compared with the group of patients who received APCT according to the AS scheme (43.75±8.8%); a 2.7-fold decrease in grade I leukopenia (from 28.13±7.95% to 10.34±5.7%, p≤0.05); a 2-fold decrease in grade II leukopenia (from 28.13±7.95% to 13.79±6.4%); a 3.9-fold decrease in grade II granulocytopenia (from 28.13±7.95% to 7.14±4.9%, p≤0.05).

2. In the blood plasma of patients with breast cancer, regardless of the stage of the disease, there is a simultaneous increase in malondialdehyde (at stage III from the norm 1.058 to 1.999, p≤0.001), reactive carbonyl derivatives of proteins (from 0.671 to 2.38, p≤0.001) and methylglyoxal ( from 0.32 to 29.4, p≤0.001). In the erythrocytes of women with breast cancer, regardless of the stage of the disease, there is a statistically significant decrease in RCPB (from 21.346 to 6.004) with a significant increase in methylglyoxal (from 0.582 to 22.4).

3. Application of the AS+Arglabin APHT scheme leads to a decrease in the level of MG (from 4.65 to 3.02, p≤0.001) and MSH (from 6.716 to 5.071, p≤0.01) in the blood plasma of patients with breast cancer when compared with APCT AS.

4. After APCT AS + Arglabin, in comparison with APCT AS, a statistically significant decrease in the indices of guanine (from 720 to 512), hypoxanthine (from 783 to 585) and adenine (from 691 to 517) is observed in blood erythrocytes; in blood plasma, there is a pronounced trend towards a decrease in these indicators.

5. When conducting adjuvant chemotherapy, the inclusion of arglabin in the AS regimen statistically significantly increases disease-free survival by 9.5%. One- and two-year relapse-free survival of the group of patients who received adjuvant chemotherapy according to the AC + arglabin regimen was 100%, three-year (96.5±2.9)% (Cox's F-Test (4.4)=1.0103 at p= 0.49615).

Bibliography:

1. Ferlay J., Soerjomataram I., Dikshit R., Eser S., Mathers C., Rebelo M. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012 // Int J Cancer. - 2015. - No. 36 (5). - R. 359-386.

2. Semiglazov V.F., Semiglazov V.V. Mammary cancer. Biology, local and systemic treatment. Moscow: SIMK; 2014.

3. BMC Med. 2015 Aug 17; 13:195. Progress in adjuvant chemotherapy for breast cancer: an overview. Anampa J1, Makower D2, Sparano JA3.

4. Lu WL, Jansen L, Post WJ, Bonnema J, van de Velde JC, de Bock GH (2009) Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis. Breast Cancer Res Treat 114:403–412.

5. Von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, Arahmani A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, Baselga J. New England Journal of Medicine, 2017, 377(2), 122-131 July 31, 2017 | 2017 issue 7.

6. J Clin Oncol. 2018 Oct 1;36(28):2826-2835. Epub 2018 Aug 14. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. Rimawi M1, Ferrero JM1, de la Haba-Rodriguez J1, Poole C1, De Placido S1, Osborne CK1, Hegg R1, Easton V1, Wohlfarth C1, Arpino G1; PERTAIN Study Group1.

7. Highlights of 2017(II)—Early Disease Professor Michael Gnant, MD, FACS Medical University of Vienna, Vienna, Austria 1st UK Interdisciplinary Breast Cancer Symposium—15th–16th January 2018.

8. Orlova R.V., Vaizyan R.I., Ivanova A.K., Tikhonova E.K., Zorina E.Yu. Chemotherapy of malignant tumors: problems and prospects. Issues of oncology. 2015;61(2):244-251. PMID: 26087606.

9. 3. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674-1685.

10. Pickersgill L, Litherland GJ, Greenberg AS, Walker M, Yeaman SJ. Key role for ceramides in mediating insulin resistance in human muscle cells. J Biol Chem. 2007;282(17):12583-12589. PMID: 17337731.

11. New insights into the regulation of purine metabolism: Purinosomes” Pedley, A. M., Benkovic, S.J. FEB 2017.

12. Zhumakaeva S.S., Muravleva L.E., Ponomareva O.A., Fomenko Yu.M., Kabildina N.A., Omarova I.M. Effect of arglabin on extracellular nucleic acids and metabolites of purine metabolism in patients with locally advanced breast cancer. Russian Biotherapeutic Journal Volume 15, - Number 1 2016. P. 38-39.

13. A.Yu. Yakovlev, D.N. Ulitin, A.S. Chichkanova, A.Yu. Vorontsova Prevention of metabolic complications of adjuvant chemotherapy for breast cancer oncology. Journal them. P.A. Herzen, 3, 2016.

14. Collection of scientific papers "Clinical aspects of the use of the antitumor drug" Arglabin "/ Ed. Academician of the National Academy of Sciences of the Republic of Kazakhstan S.M. Adekenova. - Karaganda, 2002. - 241s.

15. Omarova I.M. Clinical and pharmacological characteristics of the drug "Arglabin". - Karaganda, 2002. - 96 p.

16. Adekenov S.M. Artemisia glabella Kar. et Kir. – a source of the new antitumor preparation “Arglabin” // Phytomedicine -2000.- Vol. 7.-P.103.

17. Adekenov S.M. Arglabin - an antitumor agent from wormwood // Russian Journal of Biotherapy. - 2002. - No. 2. - T.1. - P.5-7.

18. Adekenov S.M. Prospects for the use of original herbal medicines in the clinic // Sat. scientific works "Innovative technologies in medicine and pharmacy". - Karaganda. - 2008. - S. 19 - 24.