RESEARCH ARTICLE

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Assessment of Hematological Toxicity of Adjuvant Chemotherapy in the Complex Therapy of Breast Cancer

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Abstract

Within the framework of multicenter clinical studies of the original anticancer drug "Arglabin" in the complex therapy of breast cancer (BC) in an increased dose on the basis of the Regional Oncological Dispensary, Karaganda, 80 patients BC were examined and treated: 40 patients in the control group and 40 in the study group. The index of grade I anemia was higher in patients of the control group: in (15.6±6.42)% of patients with polychemotherapy (PCT) AC and in (6.9±4.7)% of patients with PCT according to the scheme AC+Arglabin ($p<0.05$). The inclusion of Arglabin to the AC regimen increases the rate of absence of toxicity to blood leukocytosis by 25.2% (69.0±8.6%) compared with the group of patients receiving APCT according to the AC regimen (43.8±8.8%); decrease in grade I leukopenia by 2.7 times (from 28.13±7.95% to 10.3±5.7%, $p\leq0.05$); 2-fold decrease in grade 2 leukopenia (from 28.1±7.95% to 13.8±6.4%). The inclusion of Arglabin to the AC regimen in APCT in BC patients increases the rate of absence of toxicity to blood granulocytosis by 14.8% (67.9±8.8%) compared to the group of patients who received APCT according to the AC regimen (53.1±8.8%); a decrease in grade 2 granulocytopenia by 3.9 times (from 28.1±7.95% to 7.14±4.9%, $p\leq0.05$). The inclusion of Arglabin to the adjuvant chemotherapy regimen eliminates the toxic effect of chemotherapy on erythrocytosis, leukocytosis and granulocytosis. No effect of arglabin on blood platelets indicators in breast cancer patients was revealed.

Keywords: Breast cancer- adjuvant chemotherapy- arglabin- toxicity of chemotherapy

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Introduction

In Kazakhstan, as in the rest of the world, breast cancer (BC) occupies the first rank in the structure of malignant tumors in women. At the same time, in the Republic of Kazakhstan, the standardized incidence rate of breast cancer in 2019 was 26.6%ooo per 100 thousand female populations, which in absolute numbers are 4955 new cases. Breast cancer ranks third in mortality after lung and stomach cancer (6.1%ooo).

The proportion of patients with stage II and III breast cancer among all newly diagnosed patients reaches 40%. These patients refer to patients with a locally advanced form of the disease, which requires an integrated approach to treatment, including adjuvant chemotherapy [1]. BC is one of the most highly heterogeneous tumors, the choice of treatment tactics depends on the biological properties of the tumor, which characterize the growth rate, the ability to invade and metastasize, and also affect the prognosis of the disease [2-4].

Chemotherapy is one of the main methods of cancer treatment, which allows not only to prolong the patient's life, but also to improve its quality. Hence, such an interest of clinicians is in the tolerability of chemotherapy, since the quality of life today is one of the main criteria for evaluating the results of treatment [5, 6].

This indicates the importance of searching for cytostatics with selective action, less toxic, with a high efficiency of action on the tumor. Currently, the use of phytopreparations is a fairly promising direction in the complex treatment of cancer patients. One of these agents is the original Kazakhstani anticancer drug "Arglabin", obtained on the basis of the eponymous sesquiterpene γ-lactone isolated from the endemic plant Artemisia glabella Kar. et Kir., which grows exclusively in Central Kazakhstan [7, 8]. The drug "Arglabin" is registered in the Republic of Kazakhstan (registration certificate RK-LS-5-No. 022733 dated January 30, 2017), as well as in the Russian Federation (registration certificate LS-001578 dated December 15, 2011).

In an in vitro study, it was established that the effect of Arglabin on the viability and proliferation of tumor cells is several times stronger than that of intact cells, that is, there is a selectivity of the chemotherapeutic action [9,

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10]. The study of the mechanism of the antitumor action of Arglabin showed that it is a competitive inhibitor of protein pharnesyl transferase [11-13]. As an inhibitor of protein pharnesyl transferase, Arglabin is able to block the mitogenic signal emanating from both H-Ras and K-Ras oncogenic proteins containing a farnesyl group, and to induce reversion of transformed cells by blocking the mitogenic signal [14-16].

At present, the effectiveness of chemotherapy is evaluated not only from the point of view of direct cytotoxic effects, but also taking into account the immunomodifying effects, which, to varying degrees, are characteristic of many chemotherapy drugs. It has been shown that Arglabin has an immunomodulatory effect [17, 18], has low toxicity and is well tolerated by patients.

The aim of this study was to assess the hematological toxicity of adjuvant chemotherapy using the drug "Arglabin" in the complex therapy of breast cancer.

Materials and Methods

This study was carried out as part of the research work under the Protocol "Multicenter clinical studies of the original drug "Arglabin" in the complex therapy of breast cancer in an increased dose", approved by the Committee for Medical and Pharmaceutical Control Research Protocol of MH RK (Protocol No.269 dated August 27, 2018).

The clinical study was carried out in accordance with ethical principles based on the Declaration of Helsinki and in accordance with the requirements of the GCP and current legislation. Informed consent was taken from all patients to participate in the clinical study. The procedure for disclosing randomization codes was carried out by opening the envelopes in which sheets were attached indicating the group number.

The present study included 80 breast cancer patients with newly diagnosed nodular breast cancer StIIa (T1N1M0, T2N0M0), IIb (T2N1M0, T3N0M0), IIIa (T1N2M0, T2N2M0) with histological and immunohistochemical verification of luminal A and B types, treated in oncological dispensary in Karaganda. The age of the patients ranged from 35 to 75 years (predicted life expectancy of at least 3 years) and who agreed to participate in the study.

All patients were divided into 2 groups: 1 - study, 2 - control by randomization with a blind method.

In the control group, the treatment was carried out according to the following scheme

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

Stage 2 - adjuvant polychemotherapy (APCT) according to the AC scheme: doxorubicin - 60 mg/m2, cyclophosphamide - 600 mg/m2 every 21 day, a total of 6 cycles. In the presence of side effects, the periods between cycles can be lengthened up to 4 weeks, the dose of chemotherapy drugs can be reduced by 25%.

Stage 3 - a course of postoperative external-beam radiotherapy

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

The study group received 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/m^2, cyclophosphamide - 600 mg/m^2 every 21 day + Arglabin 450 mg/m2 №7 days, every 21 day, 6 cycles in total. In the presence of side effects, the periods between cycles can be extended to 4 weeks, the dose of chemotherapy drugs and arglabin can be reduced by 25%.

Stage 3 - a course of postoperative external-beam radiotherapy

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

Criteria for the inclusion of patients in the study

Patients with nodular breast cancer StIIa, IIb and IIIa with histological and immunohistochemical verification of luminal A and B types of breast cancer; lack of pronounced pathology from the cardiovascular, pulmonary and urinary system; patients who did not receive specific anticancer therapy before inclusion in the study; no history of oncological pathology of other localizations.

Assessment of hematological toxicity was carried out according to the WHO recommendations (Geneva, 1979, 1985). In the study, blood value were taken before the start of chemotherapy and before each new course, all patients underwent 6 courses.

The statistical analysis of the obtained research results includes the calculation of the means and their errors, the Student's t-test to assess the reliability of differences between the compared groups using the "STATISTICA 10" and EXCEL applications. In the study of the effect of chemotherapy on blood parameters, the Yates correction was used (which was considered 100/2*N), instead of 0%, the correction itself was used, and 100%, as a 100 correction. The result was considered statistically significant at $p < 0.05$.

Results

On the base of the oncological dispensary in Karaganda, in 2018-2020, 80 patients with breast cancer were treated according to the Protocol, 40 patients of the control group and 40 patients of the study group.

When studying the effect of APCT according to the AC scheme on hemoglobin indicators, no pronounced toxic manifestation of chemotherapy was noted. Grade 1 anemia was observed before the 1st course of APCT AC in (13.2±5.5)% of patients, this hemoglobin indicator either fell or rose; before the 6th course it was observed in (15.6±6.4)% of patients. In general, grade 1 anemia varied from (8.57±4.7)% to (20.0±6.8)% of patients receiving chemotherapy according to the AC regimen, and there was no statistically significant increase in this indicator by the 6th course. Grade 2 anemia was observed only before the 3rd course in (2.9±2.8)% of cases (Table 1).

A similar picture is observed in breast cancer patients

Table 1. The Incidence of Breast Cancer Patients by the Degree of Toxicity to Hemoglobin against the Background of adjuvant Chemotherapy (M%±m; 95% C.I.)

APCT	Toxicity degree					
	0 degree	1 degree	2 degree	0 degree	1 degree	2 degree
	Group with AC			Group with AC+Arglabin		
1 course	86.8±5.5	13.2±5.5		86.1±5.8	13.9±5.8	
	85.0:88.6	11.4:14.99		84.1:88.0	12.0:15.9	
2 course	98.7±1.8*	1.3±1.8*		85.7±5.9	14.3±5.9#	
	98.0:99.2	0.78:1.95		83.7:87.7	12.3:16.3	
3 course	77.1±7.1*	20.0±6.8*	2.9±2.8	76.5±7.3*	20,6±6,9*	2.9±2.9
	74.6:79.6	17.7:22.4	1.96:3.9	73.9:78.9	18.3:23.0	2.03:4.02
4 course	91.43±4.7*	8.57±4.7*		81.25±6.9*	15.6±6.4#	3.1±3.1
	89.8:92.96	7.04:10.3		78.8:83.6	13.4:17.96	2.1:4.3
5 course	90.9±5.0*	9.09±5.0*		90.0±5.48*	10.0±5.48*	
	89.1:92.6	7.42:10.9		87.9:91.9	8.09:12.0	
6 course	84.4±6.42	15.6±6.4*		93.1±4.7*	6.9±4.7*#	
	82:86.6	13.4:17.96		91.3:94.75	5.25:8.75	

*, reliability of differences with the initial indicators according to Student, p<0.05; #, reliability of differences between indicators of groups, p<0.05

who received APCT according to the AC+Arglabin scheme. The majority of patients did not have a toxic manifestation of chemotherapy. Grade 1 anemia in patients receiving chemotherapy according to the AC+Arglabin scheme decreased by the 6th course by 2 times from the initial indicator: from (13.9±5.8)% to (6.9±4.7)% of cases (p ≤0.05). Grade 2 anemia was observed before the 3rd course in (2.9±2.9)% of cases and the 4th course in (3.1±3.1)% of cases (Table 1).

Thus, the inclusion of Arglabin to the AC regimen helps to reduce the rate of grade 1 anemia by the 6th course by 2 times; from (15.6±6.4)% of patients receiving APCT according to the AC regimen to (6.9±4.7)% of patients receiving AC+Arglabin. A study of the parameters of leukocytes, granulocytes and blood platelets in patients who received APCT according to the AC and AC+Arglabin regimens was carried out.

Table 2 shows the incidence of breast cancer patients by the degree of toxicity to leukocytosis in the blood of breast cancer patients on the background of APCT.

The indicator of the absence of toxicity in relation to blood leukocytes in breast cancer patients on the background of APCT according to the AC scheme decreased with each course of chemotherapy, by the 6th course, the absence of leukopenia was observed only in (43.8 ± 8.8)% of patients. Grade 1 leukopenia increased from the 2nd course (21.1±6.6%) to (28.1±7.95)% of patients (p≤0.05) by the 6th course of chemotherapy. Grade 2 leukopenia also increased from (15.8±5.9)% of patients after the first course of chemotherapy according to the AC scheme to (28.1±7.95)% of cases by the 6th course (p≤0.05). Grade 3 leukopenia after 1 course of AC was observed in (10.5±5.0)% of patients and decreased by the 5th course to (6.1±4.2)% of patients, (p≤0.05).

Table 2. The Incidence of Breast Cancer Patients by the Degree of Toxicity to Blood Leukocytosis in Breast Cancer Patients on the Background of adjuvant Chemotherapy (M%±m; 95% C.I.)

PCT	Toxicity degree							
	0 degree	1 degree	2 degree	3 degree	0 degree	1 degree	2 degree	3 degree
	Control group, AC				Study group, AC+Arglabin			
1	98.7±1.8	1.3±1.8			97.2±2.7	2.78±2.7		
	98:99.23	0.78:1.95			91.7:102.7	1.94:3.76		
2	52.6±8.1*	21.1±6.6*	15.8±5.9	10.5±5.0	65.7±8.0*	20.0±6.8*	8.6±4.7	5.7±3.9
	36.4:68.8	7.8:34.3	13.9:17.7	8.97:12.2	49.7:81.76	17.8:22.3	7.04:10.2	4.46:7.1
3	40.0±8.5*	28.6±7.6*	28.6±7.6	2.86±2.8*	52.9±8.6*	29.4±7.8*	14.7±6.1*	2.9±2.9*
	22.9:57.1	13.3:43.8	13.3:43.8	1.98:3.89	35.8:70.1	13.8:45.0	12.7:16.9	2.0:4.0
4	42.9±8.4*	25.7±7.4*	22.9±7.1*	8.57±4.7	68.8±8.2*	18.8±6.9*	12.5±5.9*	
	26.1:59.6	10.9:40.5	20.5:25.3	7.04:10.2	52.4:85.1	16.4:21.3	10.5:14.6	
5	60.6±8.5*	9.1±5.0*	24.2±7.5*	6.1±4.2*	98.3±2.4	1.7±2.4		
	43.6:77.6	7.4:10.9	21.7:26.9	4.7:7.59	97.3:99.1	0.95:2.7		
6	43.8±8.8*	28.1±7.95*	28.1±7.95		69.0±8.6*	10.3±5.7*	13.8±6.4*	6.9±4.7
	26.2:61.3	12.4:44.0	12.2:44.0		51.8:86.2	8.3:12.3#	11.5:16.3	5.3:8.8

*, reliability of differences with the initial indicators according to Student, p<0.05; #, reliability of differences between indicators of groups, p<0.05

Table 3. Frequency of Occurrence of Patients with Breast Cancer by the Degree of Toxicity to Blood Granulocytosis in Patients with Breast Cancer on the Background of adjuvant Chemotherapy according to the AC scheme (M%±m; 95% C.I.)

APCT	Toxicity degree				
	0 degree	1 degree	2 degree	3 degree	4 degree
1 course	98.7±1.8	1.3±1.8			
	98:99.2	0.77:1.96			
2 course	50.0±8.1*	7.9±4.4*	21.1±6.6	10.5±5.0	10.5±5.0
	33.8:66.2	6.5:9.4	18.9:23.2	8.97:12.2	8.97:12.2
3 course	42.9±8.4*	20.0±6.76*	5.7±3.9*	25.7±7.4	5.7±3.9*
	26.1:59.6	17.8:22.3	4.46:7.1	10.9:40.5	4.46:7.11
4 course	48.6±8.4*	17.1±6.4*	17.14±6.4	11.4±5.4	5.7±3.9*
	31.7:65.5	15.0:19.4	15.0:19.4	9.67:13.3	4.46:7.11
5 course	51.5±8.7*	12.1±5.7*	18.2±6.7	12.1±5.7	6.06±4.2*
	34.1:68.9	10.2:14.2	15.9:20.6	10.2:14.2	4.7:7.59
6 course	53.1±8.8*	9.4±5.2*	28.1±7.95*	9.4±5.2	
	35.5:70.8	7.6:11.3	25.4:30.98	7.63:11.3	

*, reliability of differences with the initial indicators according to Student, $p<0.05$

The indicator of the absence of toxicity in relation to blood leukocytes in breast cancer patients on the background of APCT according to the AC+Arglabin scheme decreased at a slower rate with each course of chemotherapy (Table 2). By the 6th course, the absence of leukopenia was observed in (69.0±8.6)% of cases, which is 25.2% higher than in the group receiving APCT according to the AC scheme (43.8±8.8%). Grade 1 leukopenia in the group of patients receiving AC+Arglabin by the end of chemotherapy was observed 2.7 times less frequently (10.3±5.7%) than in the group of breast cancer patients receiving APCT according to the AC regimen (28.1±7.95%) ($p\leq0.05$). Grade 2 leukopenia in the group of patients receiving AC+Arglabin also increased from (8.6±4.7)% of patients after the first course of chemotherapy to (13.8±6.4)% of patients by the 6th course ($p\leq0.05$). But this indicator is two times lower than in patients receiving APCT according to the AC scheme (28.1±7.95%).

Thus, the inclusion of Arglabin to the AC regimen in APCT in breast cancer patients contributes to a decrease in the blood leukopenia rate by 25.2% (69.0±8.6%) compared with the group of patients receiving APCT according to the AC regimen (43.8±8.8%); decrease in grade 1 leukopenia by 2.7 times (from 28.1±7.95% to 10.3±5.7%, $p\leq0.05$); 2-fold decrease in grade 2 leukopenia (from 28.1±7.95% to 13.8±6.4%).

The indicator of the absence of toxicity in respect to blood granulocytes in breast cancer patients on the background of APCT according to the AC scheme decreased with each course of chemotherapy, by the 6th course, the absence of granulocytopenia was observed in (53.1±8.8)% of patients. Grade 1 granulocytopenia had an abrupt character, rose sharply from the 2nd course

Table 4. The Incidence of Breast Cancer Patients by the Degree of Toxicity to Blood Granulocytosis in Breast Cancer Patients on the Background of adjuvant Chemotherapy According to the AC+Arglabin scheme (M%±m; 95% C.I.)

APCT	Toxicity degree				
	0 degree	1 degree	2 degree	3 degree	4 degree
1 course	98.6±1.96	1.4±1.9			
	97.9:99.2	0.82:2.13			
2 course	71.4±7.6*	5.7±3.9*	8.57±4.7#	11.4±5.4	2.86±2.8#
	56.2:86.7	4.46:7.1	9.67:10.24	9.67:13.3	1.98:3.89
3 course	47.1±8.6*	35.4±8.2*	11.77±5.5#	5.88±4.0*#	
	29.9:64.2	18.9:51.7	9.94:13.72	4.58:7.34	
4 course	68.75±8.2*	9.37±5.2*#	12.5±5.9#	9.37±5.2	
	52.4:85.1	7.63:11.27	10.5:14.64	7.63:11.27	
5 course	63.3±8.8*	13.3±6.2*	10.0±5.5#	6.67±4.6*#	6.67±4.6*
	45.7:80.9	11.2:15.68	8.09:12.09	5.1:8.43	5.1:8.43
6 course	67.9±8.8*	14.3±6.6*#	7.14±4.9*#	7.14±4.9*	3.57±3.5
	50.2:85.5	11.9:16.87	5.41:9.09	5.41:9.09	2.37:5.01

*, reliability of differences with the initial indicators according to Student, $p<0.05$; #, reliability of differences between indicators of groups, $p<0.05$

(7.9±4.4%) to (20.0±6.76)% of cases (p≤0.05) by the 3rd course of chemotherapy, then gradually decreased, by the 6th course decreased to (9.4±5.2)% of cases.

Grade 2 granulocytopenia abruptly increased from (21.1±6.6)% after the first course of chemotherapy according to the AC scheme to (28.1±7.95)% of cases by the 6th course (p≤0.05). Grade 3 granulocytopenia after the 1st course of PCT AC was observed in (10.5±5.0)% of patients, sharply jumped after the 2nd course to (25.7±7.4)% (p≤0.05) and decreased by the 6th course up to (9.4±5.2)% of cases, (p≥0.05), that is, returned to the initial state of the 2nd course (Table 3).

The indicator of the absence of toxicity in relation to blood granulocytes in breast cancer patients on the background of APCT according to the AC+Arglabin scheme (Table 4) decreased with each course of chemotherapy more slowly. By the 6th course, the absence of granulocytopenia was observed in (67.9±8.8)% of patients, which is 14.8% higher than in the group receiving APCT according to the AC regimen (53.1±8.8%). Grade 1 granulocytopenia also had an abrupt character, by the 6th course it was observed in (14.3±6.6)% of patients, which is 1.5 times more often than in the group of breast cancer patients who received APCT according to the AC scheme (9.4±5.2%) (p≤0.05). Grade 2 granulocytopenia was observed by the 6th course in (7.14±4.9)% of patients, this indicator is 3.9 times lower than in patients receiving APCT according to the AC regimen (28.1±7.95%).

Grade 3 granulocytopenia after 1 course of PCT AC+Arglabin was observed in (11.4 ± 5.4)% of patients, decreased by the 6th course to (7.14 ± 4.9)%, (p≤0.05). Indicators of grade 3 granulocytopenia in both groups are almost the same.

Thus, the inclusion of Arglabin to the AC regimen in APCT in breast cancer patients contributes to a decrease in the rate of absence of toxicity to blood granulocytopenia by 14.8% (67.9±8.8%) compared to the group of patients who received APCT according to the AC regimen (53.1±8.8%); a decrease in 2 grade granulocytopenia by 3.9 times (from 28.1±7.95% to 7.14±4.9%, p≤0.05). The effect of APCT on blood platelet indicators was not revealed, the inclusion of Arglabin to APCT according to the AC scheme in the adjuvant regime also did not affect the blood platelet indicators in breast cancer patients.

Discussion

It can be concluded that the drug "Arglabin" does not worsen the toxic effect of standard chemotherapy, but, on the contrary, levels the toxic manifestation of standard chemotherapy according to the AC scheme.

The selective action and immunomodulatory effect of Arglabin explains the leveling of the toxic effect of standard chemotherapy according to the AC scheme.

Arglabin in an increased dose of 450 mg/m^2 is tolerated by patients satisfactorily. The most pronounced toxicity of APCT was observed in patients with breast cancer of the control group who received the AC regimen, compared with patients who received PCT AC+Arglabin.

Statistically significant is the indicator of the absence of toxicity to hemoglobin, which was observed in the group of patients receiving APCT according to the AC regimen, in (84.4±6.42)% of patients versus (93.1±4.7)% of patients receiving AC+Arglabin.

The indicator of grade I anemia is higher in patients of the control group: in (15.6±6.42)% of patients with PCT AC and in (6.9±4.7)% of patients with PCT according to the scheme AC+Arglabin (p <0.05).

The inclusion of Arglabin to the AC regimen in APCT in breast cancer patients increases the rate of absence of toxicity to blood leukocytosis by 25.2% (69.0±8.6%) compared with the group of patients receiving APCT according to the AC regimen (43.8±8.8%); decrease in grade I leukopenia by 2.7 times (from 28.1±7.95% to 10.3±5.7%, p≤0.05); 2-fold decrease in grade 2 leukopenia (from 28.1±7.95% to 13.8±6.4%).

The inclusion of Arglabin to the AC regimen in APCT of breast cancer patients increases the rate of absence of toxicity to blood granulocytosis by 14.8% (67.9±8.8%) compared with the group of patients who received APCT according to the AC regimen (53.1±8.8%); a decrease in granulocytopenia of the 2nd degree by 3.9 times (from 28.1±7.95% to 7.14±4.9%, p≤0.05).

Thus, the inclusion of Arglabin to the adjuvant chemotherapy regimen eliminates the toxic effect of chemotherapy on erythrocytosis, leukocytosis, and granulocytosis. No effect of arglabin on blood platelet indicators in breast cancer patients was found.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

This study was carried out as part of the research work under the Protocol "Multicenter clinical studies of the original drug "Arglabin" in the complex therapy of breast cancer in an increased dose", approved by the Committee for Medical and Pharmaceutical Control Research Protocol of MH RK (Protocol No.269 dated August 27, 2018).

Conflict of interests

Authors have no conflict of interests.

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