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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

OPTIMIZATION OF ANTITUMOR AND ANTIVIRAL THERAPY OF BREAST CANCER PATIENTS INFECTED WITH HEPATITIS C VIRUS

Specialty: 3224.01-«Oncology»

Field of science: medicine

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INTRODUCTION

The relevance of the topic. Breast cancer (BC) is one of the five most common oncological diseases in the world, which takes the 1st place in the frequency of registration among women. According to World Health Organization, at least 1.5 million cases of breast cancer and about 500 thousand deaths from it are registered annually in the world. Moreover, breast cancer is often registered not only among the elderly, but also among people of working age. [1, 2]

In Azerbaijan, breast cancer steadily ranks the first place among all oncological diseases of women and is one of the 4 most common oncological diseases in the country [3]

In 95% of cases, breast cancer can be cured if it is diagnosed early. However, many patients seek medical help already in the late stages of breast cancer[4].

As a result, significant financial and other material resources are inevitably spent on the treatment of breast cancer especially, in developing countries[5].

High rates of breast cancer incidence and mortality, as well as their steady growth against the background of insufficiently high efficiency of existing methods of treating this disease, allow us to consider the fight against it and its social and individual prevention as one of the important problems of oncology both in Azerbaijan and in the world as a whole. On the other side, the hepatitis C virus (HCV) identified in 1989 turned out to be the causative agent of a widespread disease - hepatitis C (HS), which often acquires a chronic course and causes the development of liver cirrhosis [6].

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[1] Pomello A., Smith B., Alt A. Geographical patterns and time trends of cancer incidence. // Neoplasma, 2015, N.6. p.3-11.

[2] Parkin D., Bray F., Ferlay J. et al. Global cancer statistics. 2012 // Cancer. J. Clin., 2015, v. 65, p.74-108.

[3] Алиев Д.А., Мамедов М.К., Рагимзаде С.Э. Рак молочной железы и трансфузионные вирусные гепатиты. Баку: Элм,2013,304 с.

[4] Летягин В.П., Голикова А.А. Современные тенденции распространения рака молочной железы в России. / Тезисы докладов на 4-м съезде онкологов и радиологов России. Ростов-на-Дону. 2018, с.45.

[5] Федоров В.Э., Ласкано М., Чебуркаева М.Ю. Характеристика распространения рака молочной железы за рубежом. // Медицинские науки, 2016, N.4, с.3-9.

[6] Мамедов М К Вирусный гепаптит С. Баку: Сада, 2014, 172 с.

Infection caused by HCV (HCV infection) has a global spread, and the number of people with chronic HCV infection in the world is at least 200 million[7,8]

At the same time, the growth rate of the incidence of hepatitis C and mortality from hepatitis C over the past 20 years has increased, and in 2016 the number of newly infected persons reached 3 million people, and the number of deaths from hepatitis C and its complications amounted to about 600 thousand people [9,10].

Due to these circumstances, the fight against HCV infection is recognized as one of the priority tasks of modern medicine - in 2016, at the session of the World Health Assembly, the program "Global Strategy on Viral Hepatitis" designed for 2016-2021 was adopted and it aims to fundamentally change for the better the epidemiological and medical-social situation in relation to viral hepatitis and, including hepatitis C.

The clinical and pathogenetic similarity of HCV infection with HBV infection is also of interest to oncologists. It soon became clear that HCV infection has been implicated in the development of not only hepatocellular carcinoma (HCC), but also some types of lymphomas. In addition, it turned out that HCV infection is widespread among cancer patients. The latter raised question is that HCV infection may have clinical significance in such patients, that is, its presence may act as a factor that not only complicates the treatment of these patients, but also worsens its results.

These data initiated the study of the relevant oncological aspects of HCV infection. However, the first clinical and laboratory observations were carried out only with the help of serological (but without molecular genetic) methods of infection indication, and their

[7] Мамедов М.К., Дадашева А.Э., Кадырова А.А. Важнейшие достижения и перспективные пути дальнейшего развития современной инфекционной гепатологии. // Современные достижения азерб. медицины, 2016, N.2, с.3-11.

[8] Cooke G. et al. The global burden of viral hepatitis from 1990 to 2013.// Lancet, 2016, v.388, p.308-318.

[9] Worls Health Assembly. Global strategy on viral hepatitis. Geneve, 2016, 42 p.

[10] Əliyev C., Məmmədov M.G., Gudratov N.O. B tipli virus hepatitin onkoloji aspektləri. Bakı: Yazıcı, 2016, s.159-165.

results did not solve the issues related to the possible influence of this infection on the evolution of breast cancer.

This fact directly indicated that the available information about the features of HCV infection in patients with breast cancer is not enough to make an objective judgment about the clinical significance of infection in these patients. Accordingly, a number of issues in this problem, which have no small scientific and practical significance, needed special study.

The purpose of the study

The purpose of this study is to determine the current extent of the spread and features of HCV infection among with different clinical stages of breast cancer who were in the oncological hospital, as well as an objective assessment of the clinical significance of the infection, based on the development of optimized algorithm for managing this contingent of patients.

Research objectives:

1. To determine the spread of HCV infection in patients with different clinical stages of breast cancer and to assess the epidemiological significance of breast cancer patients as patients with breast cancer, as a high-risk group for HCV infection.

2. To determine the frequency of registration of various clinical pathogenetic forms of HCV infection in patients with different stages of breast cancer.

3. To assess impact of HCV infection on the course of breast cancer and on the course of the postoperative period, as well as on the toxic side effects of chemotherapy and common radiation reactions after radiation therapy.

4. To develop an algorithm for a differentiated approach to antitumor treatment of breast cancer patients with different clinical and pathogenetic variants of the course of HCV infection and to evaluate the possibilities of antiviral therapy for these patients as a means that can positively affect the course and prognosis of this disease.

Research methods

The study determined the prevalence of HCV infection and the features of its development among breast cancer patients, as well as a comprehensive assessment of the clinical significance of the infection

among such cancer patients. The prospective observation involved 217 breast cancer patients in whom specific markers of HCV infection were identified. İt was also analyzed and summarized the results of a serological study carried out using the immunenzyme techniques for the presence of antibodies to HCV (anti-HCV) in blood serum samples, obtained from 2682 patients with breast cancer and 218 patients with benign breast tumors (BBT) - the control group.

Main provisions of the defended dissertation

1. BC patients are still one of the high-risk groups of HCV infection. Moreover, a feature of such patients is a certain peculiarity of the forms and the nature of their HCV infection.

2. The clinical significance of subclinical HCV infection in breast cancer patients is mainly determined by the presence of laboratory signs of subclinical liver dysfunction (SLD). This fact should be taken into account when choosing and prescribing antitumor treatment to breast cancer patients and monitoring its results.

3. Patients with breast cancer with reproductive HCV infection, accompanied by signs of SLD, it is advisable to carry out anti-viral therapy, which can weaken the negative effect of infection on the results of anti-tumor treatment of breast cancer.

Scientific novelty of the obtained results

For the first time, it was shown that among breast cancer patients, reproductive HCV infection with a high viral load was detected more often than in infected individuals from the control group. At the same time, the frequency of spontaneous elimination of HCV among breast cancer patients was lower than that among infected individuals from the control group.

For the first time, the ratio of 4 main clinicopathogenetic forms of HCV infections in patients with different stages of breast cancer was determined and it was found that the frequency of registration of the inapparent form of infection increased as the stage of breast cancer increased.

The influence of subclinical HCV infection on the prognosis of breast cancer was retrospectively assessed and the main mechanisms capable of implementing such an influence are considered. For the first time, the effect of subclinical infection, occurring with labora-

tory signs of subclinical liver dysfunction and without these signs, on toxic side effects of chemotherapy was evaluated.

Finally, for the first time the appropriateness of antiviral therapy of Hepatitis C in patients with breast cancer has been demonstrated, the effectiveness and tolerability of different programs of such therapy are compared.

The results of this study complement and deepen the existing views of the pathogenetic features and clinical significance of HCV infection in cancer patients.

Practical significance of the study

The data obtained on the prevalence of infection among breast cancer patients can become the basis for further improvement of preventive measures in oncological hospitals, carried out in order to prevent infection of both intact patients and medical personnel.

The obtained information about the influence of subclinical HCV infection on the frequency and severity of complications of antitumor treatment of breast cancer patients can be taken into account when choosing individualized methods of antitumor treatment.

Based on the data obtained in the study, an algorithm for antitumor therapy of breast cancer patients with HCV infection was developed and proposed for use in the clinic.

Publication and implementation of research results in practice

The most important theoretical provisions of the dissertation and the main results of the research are reflected in 35 scientific works (28 articles, 6 theses and 1 methodical recommendation). Of these, 20 articles, 5 theses, 1 methodological recommendation were published in Azerbaijan, 8 articles and 1 thesis in foreign scientific journals, including 2 journals at the base of the PubMed system.

Approbation of research results

The results of study were reported and discussed at the materials of the conference dedicated to the anniversary of the birth of the national leader of Azerbaijan, H.A.Aliyev (Baku, 2016), scientific and practical conference dedicated to the 100th Anniversary of V.Y.Akhundov (2016), scientific and practical conference of young scientists of the National Center of Oncology (2017, 2018, 2019), materials of the 11th Congress of the All-Russian Society of Epidemiologists, Microbiolo-

gists and Parasiotologists "Ensuring epidemiological well-being: challenges and solutions "(Moscow 2017), at the interdepartmental conference of the NCO on May 05, 2021 (Protocol No. 1) and at the Scientific seminar at the dissertation council of the NCO on October 11, 2021 (Protocol No. 6).

The dissertation was performed at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The volume and structure of the dissertation

The dissertation is presented on 143 pages (236407 characters) of the typewritten text and consists of an introduction (12888 characters), 7 chapters of research (172260 characters), results (16237 characters), conclusions (2422 characters), practical recommendations (3634 characters) and literature list (23547 characters). The literature list includes 128 works, 76.5% of which refer to the last 5-10 years of observation. The dissertation is documented by 26 tables and illustrated by 5 figures.

MATERIALS AND METHODS

The study is based on the most important results of research conducted on the basis of the Department of diagnosis and treatment of precancerous breast diseases of the NCO in Baku. A prospective follow-up involved 217 breast cancer patients who had specific markers of HCV infection. These patients were selected according to the results of serological examination of 2682 breast cancer patients who were examined or treated in the clinical departments of the National Center of Oncology during the period 2012-2014. The results of a serological study conducted using the enzyme immunoassay method for the presence of HCV antibodies (anti-HCV) in blood serum samples obtained in 2682 breast cancer patients and 218 patients with benign breast tumors (PRE-MJ) - control group were also analyzed and summarized.

The diagnosis of breast cancer was carried out on the basis of modern recommendations for the examination of patients - it included the determination of the most important parameters of the disease, using the necessary clinical, laboratory and instrumental studies. The

diagnosis was confirmed by cytological examination of punctate from the tumor, and in patients undergoing surgery - by subsequent histological examination of the removed tumor. The rate of breast cancer prevalence was expressed in clinical stages (CS) of the disease (from I to IV), determined by the TNM tumor classification system.

The presence of HCV infection in patients and individuals from control groups was determined by serological examination of blood serum to detect antibodies to HCV (anti-HCV). Seropositive (containing anti-HCV) sera were re-examined for the presence of: a) anti-HCV related to IgM (IgM-ant-HCV) and b) viral RNA, i.e. HCV.

Serological studies were carried out by the enzyme immunoassay (EIA) technique based on the appropriate commercial kits for serodiagnostics of HC. EIA was also used to exclude the presence of HBV infection in the studied individuals- on the basis of commercial kits for hepatitis B serodiagnosis, the presence of HBV surface antigen - HBsAg was detected in blood serum.

The data on the concentration of bilirubin (BR) and the activity of the indicator "liver" enzyme: alanine-aminotransferase (ALAT) were used in the study. An increase in one of these indicators without clinical symptoms of liver damage was considered a laboratory sign of subclinical liver dysfunction (SLD) [11].

When conducting clinical and laboratory observations of breast cancer patients who received one or another treatment, we were guided by the traditional principles of clinical oncology. The assessment of the frequency and severity of side effects of anti-viral therapy, in general, chemotherapy, was carried out in accordance with the recommendations of the WHO (1976).

In addition to the results obtained in the course of examination of participation and prospective follow-up (2012-2014) of breast cancer patients and individuals from control groups with benign breast tumors, archival material provided to us by our scientific supervisors for retrospective analysis and generalization. The latter was partially processed data previously obtained by our colleagues during clinical

[11] Əliyev C., Məmmədov M.G., Gudratov N.O. B tipli virus hepatitin onkoloji aspektləri. Bakı: Yazıcı, 2016, s.159-165.

and laboratory observations of breast cancer patients infected and uninfected with HCV in the departments of the NCO. Thus, these studies included an analysis of the nature of the influence of subclinical HBV and HCV infections on the incidence of complications noted after surgical operations in 22 patients with breast cancer. These data reflected the effect of persistent HCV infection on the course and prognosis of breast cancer and on the side effects of antitumor treatment, as well as the results of antiviral treatment of breast cancer patients and individuals from control groups.

Mathematical processing of the results expressed in percentages used traditional statistical formulas. All calculations were performed on a personal computer using the program "Statistics 6".

THE RESULTS OF SEROLOGICAL AND VIROLOGICAL STUDIES

To assess the current prevalence of HCV infection among the above-mentioned contingent of cancer patients, the results of serological examination for the presence of anti-HCV blood serum selected by simple randomization of 2682 patients with breast cancer (BC) and 218 patients with benign breast tumors were analyzed and summarized.

It turned out that anti-HCV was detected in 217 serums from breast cancer patients (8.1%) and 8 serums from patients with benign breast tumors (3.7%). We compared these data with the results of an anti-HCV tests of about 275 thousand adult healthy residents in Azerbaijan, according to which the average frequency of anti-HCV detection among the country's population was only 2.0%. [12]

This meant that the detection rate of anti-HCV among breast cancer patients in the $p < 0.01$ interval was statistically consistently higher than healthy adults living on the same territory. At the same time, we drew attention to the fact that the same indicator, previously determined in 1994 and 2004, was 9.0% and 10.2%, respectively: and did not differ significantly from the above.

[12] Əliyev C., Məmmədov M.G., Gudratov N.O. B tipli virus hepatitin onkoloji aspektləri. Bakı: Yazıcı, 2016, s.159-165.

This fact made it possible to believe that breast cancer patients, as before, should be considered as one of the groups with a high risk of parenteral HCV infection and in this respect do not differ from patients with other oncological diseases [Aliev J.A., Mamedov, 2008].

We compared the frequency of detection of anti-HCV in breast cancer patients with different clinical stages (CS) of the disease and found that detection rates of these antibodies were: 4.5% - at I CS, 6.1% - at II CS, 10.8% - at III CS and 11.9% - at IV CS. At the same time, the frequency of detection of anti-HCV in the general group of patients with III-IV CS exceeded the frequency of their detection in the general group of patients with I-II CS, and the difference between them remained statistically stable in the interval $p < 0.01$.(Table 1).

It followed from this that the frequency of detection of anti-HCV in the blood serum of breast cancer patients increased noticeably, as the CS of this disease increased.

Finally, after analyzing the results of a study of seropositive blood serum for the presence of IgM-anti-HCV in them, we found that the latter were present only in 13.8% of the serum, while they were not detected in 86.1% of serum (including 5.5% of serum belonging to reconvalescents HC) (Table 1).

Table 1

Frequency of detection of anti-HCV in patients with various clinical stages of breast cancer and detection of HCV RNA and IgM-anti-HCV

Clinical stages BC	Stage of BC patients	Frequency of detection of anti-HCV		Serums containing IgM-anti-HCV
		Abs.	M+m %	Abs.(%)
I	440	20	4,5+1,0%	1 / 5,0%
II	1054	64	6,1+0,7%	7 /10,9%
III	743	80	10,8+1,1%	12 /15,0%
IV	445	53	11,9+1,5%	10 /18,9%
Total	2682	217	8,1%	30 / 13,8%

This fact indicated that in breast cancer patients, the infection occurred in one of two pathogenetic forms: 1) in a reproductive form accompanied by the presence of IgM antibodies in the blood and

2) in a persistent form in which IgM antibodies were not detected.

Noted that the frequency of registration of infection cases in the reproductive form increased as the CS of the disease increased. At the same time, the average frequency of infection in the reproductive form in breast cancer patients was higher than in the control group of healthy individuals and patients with benign breast tumors.

The above data led to the conclusion that breast cancer patients form one of the groups with a high rate of infection with the HCV which increases as the length of their hospital stay prolonged. At the same time, in relation to a number of pathogenetic features of the development of infection, this risk group does not differ significantly from other high-risk groups of HCV infection.

THE RESULTS OF BIOCHEMICAL AND IMMUNOLOGICAL STUDIES

In no case did we notice visually detectable jaundice and the presence of any clinical and instrumental signs of inflammatory liver damage in BC patients. It showed that HCV infection remained subclinical in all cases. Also, without having the results of morphological examination of the liver of the above-mentioned BC patients with HCV infection and detailed clinical and instrumental examination of these patients, we could not thoroughly determine their clinical forms and identify variants of the course of HCV infection provided by the modern classification of chronic HC.

Furthermore, we had the results of determining the activity of the "main" liver enzyme - ALAT and the concentration of BR in the blood serum of BC patients and HCV-infected healthy individuals from control groups. By comparing these indicators in each individual, it made possible to retrospectively determine the pathogenetic (essentially laboratory) variant of the course of infection that the individual had at the time of taking blood for laboratory testing. This approach allowed us to identify 4 main typical variants of the course of HCV infection, which each of these individuals had at the time of taking their blood for research. The laboratory criteria for the selection of these variants are given in Table 2.

Table 2

Laboratory criteria identifying various pathogenetic variants of HCV infections

N	Pathogenetic variants of the course of infections	The presence of a viral RNA	Increase in ALAT activity	increase in the level of BR < 50 mM/l	increase in the level of BR > 50 mM/l
1	Inapparent	+	-	-	-
2	Hyperfermentemic	+	+	-	-
3	Bilirubinemic	+	+	+	-
4	Hyperbilirubinemic	+	+	-	+
Abbreviations: ALAT - alanine aminotransferase; BR - bilirubin					

It is obvious that the inapparant variant of the course of infection was phenomenologically close to the latent form of HCV infection, and the hyperfermentemic variant - to its asymptomatic form, which was identified only by an increase in the activity of ALAT. The bilirubinemic variant, not accompanied by visually detectable jaundice, could be considered close to without jaundice form of infection, and the hyperbilirubinemic variant was pathogenetically close to the jaundice form of HCV infection.

Having identified these variants of infection in BC patients, it was determined the registration frequencies of these variants, as shown in Table 3.

Table 3

The frequency of detection of 4 pathogenetic variants of HCV infection in breast cancer patients with different clinical stages

Stages of BC patients	Number of patients	Inapparant abs., (%)	Hyperfermentemic abs., (%)	Bilirubinemic abs., (%)	Hyperbilirubinemic abs., (%)
I	17	3 (17,6%)	10 (58,8%)	3(17,6%)	1 (5,9%)
II	57	19 (33,3%)	34 (59,6%)	4 (7,0%)	-
III	78	46 (58,9%)	27 (34,6%)	5 (6,4%)	-
IV	53	34 (64,1%)	19 (35,8%)	-	-
Total	205	102 (49,8%)	90 (43,8%)	12(5,9%)	1 (0,5%)

As shown in the table 3, in BC patients infections most often occurred in the inapparant and hyperfermentemic variants, in which minimal "traumatization" of the liver was noted - the total frequency of their registration in these patients exceeded 90%.

As the clinical stage of the disease increased, on the one hand, there was an increase in the frequency of registration of the inapparant variant, and on the other hand, a noticeable decrease in the frequency of registration of hyper-enzymemic and bilirubinemic variants of infection. We considered the immune-mediated lysis of infected hepatocytes to be the probable cause of such a clinical and pathogenetic features of infection in breast cancer patients - with an increase in the clinical stage of breast cancer, the severity of immunosuppression increased, and the intensity of hepatocyte cytolysis decreased, which was expressed in an increase in the frequency of registration of the inapparant variant of infection.

ANALYSIS OF CLINICAL AND LABORATORY OBSERVATIONS RESULTS

A retrospective and prospective analysis of the clinical material was carried out.

The materials provided to us were subjected to a retrospective analysis, demonstrating various manifestations of the important clinical significance of HCV infection in BC patients. These materials were obtained during two independent clinical and laboratory observations previously conducted by the staff of the NCO.

In one observation conducted by M.K.Mammadov and et al. on 134 breast cancer patients with infection, it was shown that the 5-year survival rate of patients with clinical stage III breast cancer infected with HCV was lower than that in the control group of patients at $p < 0.05$. However, in this observation, the prognostic significance of the fact that these patients had signs of subclinical liver dysfunction was not evaluated. Therefore evaluation carried out and found that in infected breast cancer patients who had signs of subclinical liver dysfunction, the negative effect of infection on patient survival was more than in patients without these signs and remained in the range $p < 0.01$.

Observation conducted by our colleagues under the leadership

of S.E.Rahimzade (22 breast cancer patients who underwent radical mastectomy) was devoted to clarifying the influence of subclinical HBV and HCV infections on the incidence of complications noted after surgical operations in BC patients. Analyzing these results, we separated patients with HCV infection into an independent group and identified 2 subgroups of patients in it, differing in the presence of signs of subclinical liver dysfunction.The first subgroup included 10 patients with laboratory signs of SLD. The second subgroup included 12 patients without laboratory signs of SLD. The number of breast cancer patients who were free from infection and had no signs of SDP and forming a control group was 20 women. The volume of blood loss after surgery among patients with signs of SLD averaged 370 ml, and in patients without signs of SLD and the control group 290 ml and 280ml, respectively. Short-term and long-term lymphorrhea in the first group was 60% and 20%, and in the second and control groups 33.3%, 8.3% and 35.0%, 10%, respectively. Based on a comparison of the frequency of complications of masectomy noted in these subgroups (volume of blood loss, duration of lymphorrhea and development of moderate immunodepression), we came to the conclusion that the course of an increase in the frequency of complications of mastectomy was negatively influenced by the presence of signs of subclinical liver dysfunction in patients, and in patients who did not have these signs, the frequency of complications practically did not differ from that in the control group of non-infected patients.

Considering that the above materials were partially published, we did not reflect our results in the conclusions of the work, but only took them into account in the formation of our own opinion on the possible clinical significance of HCV infection.

In addition, the results of our prospective clinical and laboratory observation devoted to the study of the ability of HCV infection in breast cancer patients to act as a factor limiting the possibility of antitumor treatment and, especially, chemotherapy were summarized and analyzed.

In particular, during the observation of HCV-infected patients with clinical stages III breast cancer who received chemotherapy according to the standard AT program (doxorubicin and paclitaxel) in

2008-2014 in NCO, the effect of infection on the frequency and severity of toxic side effects of chemotherapy was evaluated. At the same time, 50 women had a hyperfermentemic variant, and 50 others had an inapparant variant of HCV infection. In the control group there were 50 women with breast cancer, but without infection. The frequency of side effects of chemotherapy in breast cancer patients is shown in Table 4.

Table 4

Frequency of registration of side effects of chemotherapy in patients with breast cancer with inappropriate and hyperfermentemic forms of infection

Side effects	Inap. form	Hyperf. form	Control
	-	2,0%	-
Hyporexia	2,0%	10,0%	2,0%
Nausea	-	2,0%	-
Vomit	10,0%	30,0%	14,0%
Diarrhea	16,0%	34,0%	18,0%
Stomatitis			
Increased BR	2,0%	8,0%	1,0%
Increase in ALT	12,0%	32,0%	11,0%
Increase in AST	8,0%	18,0%	6,0%
Hypercreatinemia	2,0%	10,0%	3,0%
Proteinuria	2,0%	4,0%	1,0%
Abbreviations: Inap. form - inappropriate form Hyperf. form * - hyperfermentemic form			

As shown in the table, the presence of infection in patients in an inappropriate form did not practically affect the frequency and severity of the majority of toxic side effects of chemotherapy. Also, in the presence of a hyperfermentemic form of infection in these patients, there was an increase and aggravation of such manifestations of the side effect of chemotherapy as nausea, diarrhea, stomatitis, as well as an increase in the activity of ALAT and ASAT and the level of BR in the blood.

Based on these results, we came to the conclusion that an important factor predetermining the increased risk of toxic effects of chemotherapy in patients with HCV infection was the presence of la-

boratory signs of subclinical liver dysfunction in them.

Therefore, the detection of HCV infection in breast cancer patients should not be considered as a contraindication to treatment or even as an indication of the need to limit the possibilities of applying chemotherapy. Detection of HCV infection (more precisely, antibodies to HCV) in breast cancer patients should prompt the doctor only to allocate such patients into a special clinical contingent that needs a more detailed laboratory examination to determine the presence or absence of signs of SLD and viraemia in these patients.

TREATMENT STRATEGIES IN PATIENTS WITH SUBCLINICAL HCV INFECTION

If the general treatment strategy of breast cancer patients with HCV infection does not differ from the treatment strategy of all other breast cancer patients, antitumor treatment tactics in such patients have certain characteristics and should be built differentially, depending on the results of in-depth laboratory analysis of patients. To provide this approach, among the seropositive (with anti-HCV) breast cancer patients with subclinical HCV infection we examined, 3 categories of unequal number of people were identified: 1) who had neither HCV RNA nor signs of SLD in their blood; 2) who had HCV RNA in their blood, but did not have signs of SLD; and 3) who had both HCV RNA and signs of SLD in their blood. We also accepted the fact that among such patients there could be persons with a manifest form of infection, who had clinical and instrumental signs of hepatitis (in our observation, we considered them such as people with a hypermentemic form of infection) - we allocated them into the 4th group. These categories are summarized in Table 5, in which the frequency of registration of individuals from these groups is noted.

It is obvious that in patients with a subclinical form of HCV infection, the question of prescribing treatment requires a differentiated approach and depends on the results of a blood test. So it is clear that patients from category I, being virtually free from infection, can receive antitumor treatment without any restrictions. Patients from category II, as they do not have signs of SLD, increasing the risk of side effects of therapy, can also receive the necessary treatment, but

liver function should be under more careful monitoring. Also, it is significant that patients from category I and II together accounted for half of all seropositive patients.

Table 5

Clinical categories of breast cancer patients seropositive for HCV, taken into account when using the treatment algorithm

Clinical category	The presence of anti-HCV	Presence of HCV RNA	Signs of the SLD	Clinical signs	Frequency of registration
category I	+	-	-	-	5%
category II	+	+	-	-	45%
category III	+	+	+	-	44%
category IV	+	+	+	+	less than 1%

The question of prescribing treatment for group III should be resolved taking into account the fact that the presence of SLD increases the risk of side effects of treatment and should be considered a contraindication to chemotherapy. The significance of such a contraindication increased as the severity of the signs of SLD and, most importantly, the concentration of bilirubin increased.

Finally, in patients from category IV who have obvious clinical and instrumental symptoms of hepatitis and, including, signs of SLD, antitumor treatment, prescribed even for direct indications, due to the threat of liver failure, should always be postponed until full recovery of liver functions.

DRUGS AND TACTICS OF ANTIVIRAL THERAPY FOR PATIENTS

We believed that eliminating subclinical liver dysfunction makes possible to weaken the side effects of chemotherapy and thereby expand the possibilities of treating patients with HCV infection. Since infection is the cause of SLD in such patients, we considered that antiviral therapy (AVT) could be used to prevent the consequences of infection in cancer patients.

Until recently, interferon (IFN) preparations used in oncology were widely used in the treatment of chronic hepatitis C (CHC). Initially, we

summarized the data on the side effects of IFN and PEG-IFN obtained during the previous observation of a group of 27 breast cancer patients (from 2009 to 2015 during a 3-month follow-up) with HCV infection who received AVT in the form of IFN injections. It turned out that "early" toxic effects were observed in at least half of the patients, and "late" effects - in at least 10% of patients. At the same time, there was no significant difference between patients who received natural and pegylated IFN drugs (Table 6).

Table 6

Frequency of registration of "late" signs of side effects of IFN and PEG-IFN in treated breast cancer patients with CHC

"Late" signs of side effects of IFN preparations	Frequency of registration	
	a-IFN (n=19)	PEG-IFN (n=8)
Anemia	5,3%	-
Leukocytopenia	15,8%	12,5%
Thrombocytopenia	10,5%	12,5%
Hyporexia	5,3%	2,5%
Symptoms of depression	2,0%	2,5%

Tablet preparations with direct antiviral effect, the use of which began in 2015, turned out to be more attractive in the treatment of CHC in cancer patients. This fact prompted us to take part in a clinical and laboratory observation conducted to assess the effectiveness and tolerability of AVT with such drugs. For the period 2016-2018, 28 BC patients who had previously received antitumor treatment in the NCO and after it received AVT for 12 weeks using the drugs “sofosbuvir” and “daclatasvir” were under observation.

Upon completion of antiviral therapy, viremia was absent in all patients, that is, a full therapeutic effect was obtained. At the same time, none of the patients had any clinically significant signs of side effects of the drugs.

It meant that this approach to the treatment of CHC in BC patients allowed not only to get the maximum therapeutic effect, but also was not accompanied by side effects. It followed from this that the use of modern drugs for the treatment of CHC in cancer patients had

noticeable advantages over programs involving IFN preparations.

So, in the treatment of CHC in BC patients who have indications for AVT, preference should be given to antiviral drugs that have the greatest effectiveness and are better tolerated by patients.

Taking into account the obtained data that HCV infections in BC patients, occurring in an inapparant form does not play a significant negative prognostic role, it should be assumed that the detection of such an infection is not a reason for the immediate implementation of AVT to the patient, which can be either delayed until the completion of antitumor treatment, or at the discretion of the doctor carried out simultaneously with this treatment. Also, the issue of prescribing hepatotropic drugs to such patients should be resolved on a case-by-case basis.

CONCLUSIONS

1. Serological examination of the blood of patients with breast cancer (BC) who were in the clinic again confirmed the fact that some of them had an infection caused by the hepatitis C virus (HCV). In particular, the frequency of detection of antibodies to HCV (anti-HCV) in their blood was several times higher than the frequency of detection of the same antibodies to healthy adults in the country [7, 28].
2. The frequency of anti-HCV detection in breast cancer patients increased as the clinical stage of the disease increased and the development of HCV infection in these patients was characterized by the absolute predominance of subclinical forms of the course. All this made it possible to consider breast cancer patients as an independent group of persons with a high risk of infection, formed during the period of stay of these patients in an oncological clinic [16].
3. The group of HCV seropositive BC patients included both those with more rarely observed reproductive and those with more frequent persistent HCV infection. In addition, this group was heterogeneous in composition with respect to the variants of the course of this infection. Being subclinical, this infection occured in one of 4 pathogenetic variants, however, in more than 90% of cases, inap-

parant and hyperfermentemic variants were recorded, not accompanied by an increase in the level of bilirubin in the blood [2, 23].

4. Even subclinical HCV infection in breast cancer patients had specific clinical significance. Thus, its presence directly correlated with a reduction in the 5-year survival rate of stage III BC patients, the frequency of some complications of surgical operations and the frequency of registration of side effects of chemotherapy and radiation reactions that developed after radiation therapy [34].
5. The solution of the issue of antitumor treatment for breast cancer patients with HCV infection requires a differentiated approach and consideration of the results of determining in patients not only the activity of liver enzymes and the concentration of bilirubin in the blood [17, 26, 29, 31].
6. BC patients with HCV infection who have indications for anti-viral therapy can be prescribed both alpha-interferon preparations and direct-acting antiviral drugs. At the same time, preference may be given to the latter due to the greater effectiveness of therapy, lower frequency of side effects and better patient tolerance [6, 20, 27].

PRACTICAL RECOMMENDATIONS

1. Considering the epidemiological risk to cancer patients and medical staff of breast cancer patients with HCV infection, as well as the potential ability of this infection to have an adverse effect on the immediate and long-term results of breast cancer treatment and toxic side effects of chemotherapy, it should be recognized that timely identification of such patients with breast cancer and their allocation to a special clinical group, regardless of whether they have clinical signs of liver dysfunction (i.e., viral hepatitis) is an important clinical task.

2. All breast cancer patients upon admission to the hospital should undergo a serological examination to detect antibodies to HCV (anti-HCV) in their blood.

Such patients must undergo biochemical examination to identify individuals with an increased concentration of bilirubin and, first

of all, the activity of liver enzymes (ALAT, ASAT, etc.) and virological (molecular genetic) examination to detect HCV RNA in their blood, i.e. HCV itself.

3. In order to maximize the individualization of approaches to the management and treatment of such breast cancer patients, depending on the results of these laboratory studies, all seropositive HCV-breast cancer patients should be assigned to one of the 4 clinical categories:

The first category includes patients who do not have clinical signs of liver dysfunction, but have only anti-HCV in their blood (without the presence of HCV RNA in it) and normal blood biochemical parameters.

The second category consists of patients who do not have clinical signs of liver dysfunction and laboratory signs of SLD, but have both anti-HCV and HCV RNA in their blood.

The third category consists of patients who do not have clinical signs of liver dysfunction, but have both anti-HCV and HCV RNA in the blood, and laboratory signs of SLD.

The fourth category includes patients with clinical signs of liver dysfunction, in whose blood anti-HCV, HCV RNA and an increase in the concentration of bilirubin or the activity of "liver" enzymes are detected.

4. The basis of tactics of antitumor treatment of BC patients with HCV infection should be on the principle of individualization, based on an assessment of the prospective, on the one hand, the prospects for the effectiveness of the planned treatment, and on the other hand, the degree of risk of complications and side effects of such treatment.

Patients from category 1 are considered HCV-free and therefore do not need antiviral therapy. They can receive antitumor treatment without any restrictions related to infection. These patients do not need antiviral therapy.

Patients in category 2 without laboratory signs of SLD can receive antitumor therapy fully, only if the liver status is regularly monitored. If there are indications, these patients can also receive AVT.

Patients from the 3rd category who have laboratory signs of

SLD are characterized by an increased risk of developing side effects of treatment and therefore can receive such treatment only in special situations - after correlating the chances of getting the expected therapeutic effect and the degree of risk of possible complications. Treatment is carried out only under the condition of constant careful monitoring of the liver condition, If there are indications, these patients can also receive AVT.

Patients from the 4th category, having clinical and instrumental signs of hepatitis, are contraindicated in antitumor treatment because of the serious risk of developing liver failure. The decision on their treatment should be postponed until the appearance of clear clinical, laboratory and laboratory signs of restoration of liver function. These patients can also undergo AVT.

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List of abbreviations:

BC - breast cancer

HC - hepatitis C

HCV - hepatitis C virus

HBV - hepatitis B virus

CT - chemotherapy

RT - radiation therapy

MT - malignant tumor

CHC - chronic hepatitis C

IFN - alpha interferon

EIA - enzyme immunoassay

AVT - antiviral therapy

ALAT - alanine aminotransferase

ASAT - aspartate aminotransferase

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