REPUBLIC OF AZERBAIJAN

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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

PATHOGENETIC AND CLINICAL ROLE OF VIRAL INFECTIONS AT LYMPHOMAS PATIENTS

Specialty: 3224.01 – "Oncology"

Field of science: medicine

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Baku – 2022

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INTRODUCTION

TOPICALITY. The problem of intercurrent infections is the most important and urgent for oncohematological hospitals, as these infections are most frequently detected in patients with chronic leukemia and lymphomas (LF).[1]

At the same time, among all intercurrent infections reported in cancer patients and, especially, in oncohematologi patients, viral infections are important, and first of all, those of them that are characterized by a global spread. These include infections caused by herpes simplex viruses (HSV), herpes zoster virus (VOG), cytomegalovirus (CMV), Epstein-Bap virus (EBV), lymphotropic retrovirus and HTLV-1 human hepatitis (HBV) and C (HCV)[2,3].

These infections are still among the leading causes of significant aggravation of the condition of these patients, and their presence can limit the possibilities of adequate therapy and adversely affect the clinical course of cancer[4,5].

Moreover, in some of situations, these infections can become the direct cause of the death of cancer patients. Therefore, it is not surprising that, according to the modern doctrine, the treatment and prevention of intercurrent infections should be considered as an integral part of the entire complex of therapeutic measures carried out by cancer patients [6,7,8]

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To this must be added the fact that these infections bring together three similar features.

Firstly, all of the mentioned viruses, which have a high potential for subclinical persistence in the body, are capable of causing not only acute, but also long-term (and including subclinical) chronic infections. Secondly, all these viruses have a marked tropism to the cells of the immune system and the ability to induce and sustain the development in the organism of immunosuppression, on the one hand, and a complex of immunopathological processes, on the other. Thirdly, some of these infections play the role as contributory factors in the emergence of cancer. In particular, HPV is associated with the occurrence of Kaposi sarcoma, EBV - Hodgkin LF (HLF) and Bepkitt`s LF, HTLV-1- adult T-cell leukemia and HCV - non-Hodgkin LF (NHL)[9,10,11]

From the point of view of clinical oncohematology, the importance of these infections in patients with lymphomas is demonstrated by 2 circumstances.

Firstly, by leaking in patients with LF, these infections can exacerbate the existing suppression of immunological reactivity, including anti-tumor resistance, in most of them. This indirectly suggests that these infections should be considered as a potential factor that can adversely affect the course and even the prognosis of LF. However, the significance of this possibility in the oncohematological clinic remains poorly understood, which prevent the development of a generally accepted algorithm for adaptive immunotherapy in these patients.

Secondly, there is reason to believe that the presence of these

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infections can, on the one hand, limit the possibilities of adequate anti-tumor therapy for patients with LF, and on the other hand, increase the frequency and severity of toxic side effects of such therapy and reduce the quality of life of patients during their treatment. However, this issue is still poorly researched, which hinders the targeted search for drugs and the development of methods capable of weakening the specified effect of these infections and, thus, improve the effectiveness of antitumor treatment.

Admittedly, many aspects of the wide spread of viral infections among patients with lymphomas have already been studied[3]. However, the scale of the spread of these infections among the specified contingent of patients living in Azerbaijan remains unknown. And finally, there are practically no data on the features of the spread among lymphomapatients of mixed infection caused by several viruses simultaneously.

The above considerations have prompted us to investigate, in a target way, a number of scientifically and practically important issues related to the spread of the above viral infections in patients with lymphomas.

PURPOSE AND OBJECTIVES OF THE STUDY. The aim of this study is to determine the prevalence and course of a number viral infections in LF patients and to assess the epidemiological and clinical significance of these infections as the basis of intercurrent diseases.

To achieve this goal, it was necessary to solve the following specific scientific problems:

1. To determine the frequency of detection of specific markers of infection with lymphotropic viruses in patients with LF and to compare these indicators with similar indicators determined in control groups of patients with solid malignant tumors (SMT) and individuals from the population of outwardly healthy adult residents in Baku.

2. To determine the frequency of detecting specific markers of infection with hepatotropic viruses in patients with LF and to compare these indicators with similar indicators determined in control groups of patients with SMT and individuals from the population of outwardly healthy adult residents in Baku.

3. To determine the predominant forms and variants of the course of lymph tropic and hepatotropic viral infections in patients with LF and compare the obtained data with similar data in relation to the same infections in patients with SMT and in healthy persons from the control group.

4. To determine the impact of the most common infections among LF patients on their treatment outcomes the toxic side effects of their chemotherapy and to evaluate these infections as potential factors that can reduce the effectiveness of treatment of these patients and limit their antitumor therapy options.

RESEARCH METHODS.

The basis of the clinical material was prospective data on 250 patients with HLF and 250 patients with NHL who were treated at the National Center of Oncology for the period from 2014 to 2019. In research work distribution and development characteristics of SHV1, SHV2, KHV, SMV, EBV, HTLV, HAV, HEV, HBV and HCV infections were determined among patients with lymphoma, as well as the clinical significance of the infection among this contingent of cancer patients was assessed as complex.

THE MAIN POINTS MADE FOR PROTECTION:

1. The risk of infection with herpetic viruses, as well as with enteric hepatitis viruses, was not significantly different in LF patients compared to those with SMT. At the same time, LF patients had a higher degree permissiveness with regard to reactivation of all latent herpetic infections and differed from patients with SMT in a higher frequency of reproductive course of these infections.

2. Only reproductive forms of herpetic infections had a moderately pronounced effect on some indices of innate immunity in LF patients. At the same time, the presence of both persistent and reproductive forms of herpetic infections in LF patients was not accompanied by a noticeable change in the frequency and severity of side effects against tumor therapy.

3. LF patients again manifested themselves as a group of individuals with a high risk of parenteral infection with transfusion hepatitis viruses. At the same time, the these hepatotropic infections in LF patients proceeded only in a subclinical form and in some cases were

accompanied by the appearance of laboratory signs of subclinical liver dysfunction (SLD).

4. Subclinical forms of transfusion viral hepatitis occurring in LF patients with laboratory signs of SLD had a more pronounced effect on the side effects of antitumor therapy in these patients than in LF patients without these laboratory signs.

SCIENTIFIC NOVELTY OF THE STUDY. For the first time in our country, a purposeful serological and, in some cases, molecular-genetic study of the blood of LF patients in Azerbaijan has been carried out for the presence of specific markers of HSV1, HSV2, VOG, CMV, EBV, HTLV, HAV, HVE, HBV infection in it.

These studies have for the first time provided data on the shield and patterns of the spread among patients with LF of the above 10 specific viral infections.

In addition, frequency ratios of the different pathogenetic and clinical forms of these viral infections in patients with LF have been determined and the predominant pathogenetic and clinical forms of these infections in these patients have been identified.

Practical value of the study. The results obtained on the breadth and features of the spread of the above viral infections among patients with LF can further serve as a very useful theoretical basis for further improvement of preventive measures carried out in hospitals of the oncohematological profile and, in particular, improving the quality of work on improving the efficiency of methods to control the virological safety of transfused blood.

In addition, the same results can stimulate the further study of the clinical and pathogenetic significance of these viral infections in patients with LF and the solution of questions related to the ability of these infections to provide clinically significant impact on the course of LF and the state of immunological reactivity of patients. Finally, these data will be able to supplement the existing ideas on these issues and facilitate further improvement of approaches to the treatment of patients with LF with the indicated viral infections, which will increase the effectiveness of treatment of this population of patients.

APPROBATION OF THE RESEARCH AND PUBLISHED WORKS.

The main materials of the dissertation were presented at the scientific-practical conference dedicated to the birthday of the national leader H. Aliyev (Baku, 2015, 2018, 2022), at the scientific-practical conference of young scientists and specialists of the NCO dedicated to the National Revival Day (Baku, 2017), at the 11th Congress of the All-Russian Society of Epidemiologists, Microbiologists and Parasitologists (Moscow, 2017), at the interdepartmental conference of the NCO (Baku, May 26, 2022, protocol №1) Report and discussed at the meeting of the Scientific Seminar of the Dissertation Council FD 1.02 (Baku, June 24, 2022, protocol № 2).

The main theoretical and practical provisions of the dissertation are reflected in 31 published scientific works (20 articles, 9 theses and 2 methodical recommendations).

APPLICATION OF RESEARCH.

Scientific conclusions and practical recommendations have been introduced into the clinical practice of the Department of Oncohematology of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan, and are also used in the educational process of the Azerbaijan State Institute for the Improvement of Physicians named after A.Aliyev,

NAME OF THE ORGANIZATION WHERE THE DISSERTATION WORK IS CARRIED OUT:

The dissertation work was carried out 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 145 pages (235.219 characters) of the typewritten text and consists of an introduction (13.868 characters), 1st and 2nd chapters of the literature review (45.708 characters), 4 chapters of research (115.560 characters), results (23.965 characters), conclusions (2314 characters), practical recommendations (3634characters) and literature list (26.522 characters). The literature list includes 141works, to the last 5-10 years of observation. The dissertation is documented by 27 tables and illustrated by 2 figures.

PRESENT STUDIES AND ITS RESULTS. MATERIALS AND METHODS

Clinical observations, the results of which formed the basis of this dissertation work, were carried out at the Department of Onco-hematology of the NCO. The basis of the clinical material was based on prospective data on 250 patients with HLF and 250 patients with NHLF who were in the NCO for the period from 2014 to 2019.

LF diagnostics in all patients was made in accordance with the current guidelines for the examination of patients. All the necessary clinical, laboratory and instrumental examinations were used to solve the above tasks.

Clinical observations and clinical and laboratory studies were carried out in two directions: 1) determination of the spread of viral lymph tropic and hepatotropic infections in LF patients, as well as determining their predominant forms and features of their course among this patient population; 2) objectively assessing the clinical significance of viral lymphotropic and hepatotropic infections in LF patients and the developing optimal tactics for the management and treatment of LF patients infected with viral pathogens.

The spread of infections among patients with LF was determined by laboratory (serological) identification of these infections. For this, a solid-phase enzyme immunoassay reproduced on the basis of commercial reagents specially designed for the serological diagnosis of the respective infections was used.

In addition to LF patients, 300 patientswith SMT were examined for comparison, who were presented by patients with lung and gastric cancer. As a control group, 500 formally healthy adults from the pool of non-reimbursed blood donors were examined.

Initially, total antibodies to these viruses were detected: anti-HSV (antibodies to HSV), anti-HZV (antibodies to WHO), anti-CMV (antibodies to cytomegalovirus), anti-EBV (antibodies to EBV), anti-HTLV-1 (antibodies to HTLV1), anti-HCV (antibodies toHCV), anti-HAV (antibodies to HAV) and anti-HEV (antibodies to HEV). In the case of HBV, HBsAg was determined in sera.

Subsequently, serous sera (containing common antibodies to lymphotropic viruses) were examined to identify relevant antibodies

to these viruses, but related to IgM: IgM- anti-HSV, IgM -anti-HZV, IgM-anti-CMV IgM-anti and -EBV and etc.

The clinical significance of subclinical viral infections in LF patients was assessed on the basis of the nature of: 1) the effect of these infections on the incidence and stability of positive immediate patient outcomes; 2) their impact on long-term results of treatment of patients with these infections; 3) their impact on indicators of innate immunity (IUI); 4) their impact on the incidence and the severity of toxic side effects (ATTs) of chemotherapy (CT)given to these patients; and 5) their impact on the well-being of patients.

NHL patients were treated with first-line chemotherapy (CHOP +/- Rituximab or CHOP + Bl +/- Rituximab or CHOEP +/- Rituximab) or 2nd line chemotherapy (GDP +/- Rituximab or DHAP +/- Rituximab or "ICE + / - Rituximab).

Evaluation of the treatment effectiveness assessed on the basis of 2 criteria: 1) immediate result, assessed at the time of completion of treatment and 2) long-term outcome, determined by the duration of the achieved remission.

The frequency and severity of adverse toxic side effects of antiviral therapy were assessed using the WHO (1976) 5-point scale, according to their severity.

In most cases, the average incidence of four types of adverse toxic side effects of CT were compared: 1. Hematological toxicity (anemia, leucopenia, thrombocytopenia); 2. Gastrointestinal toxicity (nausea, vomiting, diarrhea); 3. Hepatic toxicity (increased activity of ALT and the level of bilirubin in the blood) and 4. Nephrotoxicity (proteinuria and increased creatinine in the blood).

In addition to the above, we note that, using the above approaches, we retrospectively analyzed the archived clinical material on the contingent of LF patients who were in the NCO from 2000 to 2011. Since these materials included data on several cases, the number of patients involved in each of these cases, as well as the details of the observations made, we have given in the relevant sections of the paper.

In selected observations, immunological tests were performed to assess the innate immunity (IME) of status of LF patients. For this,

we used a set of laboratory methods recommended by the Ministry of Health for use in preventive surveillance and clinical and experimental research. These studies were carried out on the basis of the Immunology laboratory of the B. Eyvazov Research Institute of Hematology and Transfusiology.

All numerical results were mathematically processed using the well-known formulas of variation statistics.

LYMPHOTROPIC VIRAL INFECTIONS IN LF PATIENTS

The blood serum of patients with LF, SMT and healthy individuals from the control group were examined for the presence of antibodies to 6 human lymphatic viruses: HSV1, HSV2, VOG, CMV, EBV and HTLV1. The results of this studies are presented in table 1.

In reviewing these results, we noted three facts. First, the frequency of detection of total antibodies to herpetic viruses (namely, to HSV, to VOG, to CMV and to EBV) in patients with LF had no statistically consistent difference from the frequencies of detecting the same antibodies in patients with SMT and in healthy control groups.

Table 1

Frequencies of detection of antibodies to lymphotropicviruses in patients with LF, SMT and healthy individuals from the control group

Type of infection	Revealed antibodies	patients with LF (n = 500)	patients with SMT (n = 300)	healthy faces (n = 500)
Lymphtropic infections	anti-HSV *	91.2%	92.0%	89.4%
	anti-HSV1	75.0%	75.0%	74.6%
	anti-HSV1	16.2%	17.0%	14.8%
	anti-HZV	83.2%	84.0%	81.2%
	anti-CMV	65.2%	61.0%	62.2%
	anti-EBV	87.6%	86.3%	85.0%
	anti-HTLV	2.8%	1.3%	0.8%
*overall frequency of anti-HSV detection				

Secondly, the frequency of detection of these antibodies in all three categories of examined individuals decreased in the series of

viruses: HSV, EBV, VOG, CMV, and HTLV. This meant that infections caused by HSV and VOG were the most common among LF patients.

Thirdly, the frequency of detecting antibodies to human retrovirus was highest in LF patients and lowest in healthy controls. The rate was intermediate in patients with SMT. It was clear that this infection is not widespread among LF patients.

Further, we examined the results of a repeated study of those sera in which total antibodies were detected for the presence of the corresponding IgM antibodies in them (except for the sera containing anti-HTLV). The results of this study are shown in Table 2.

The analysis of these data led us to the conclusion that, despite comparable rates of infection, the detection rates of IgM antibodies to HSV, to VOG, to CMV and to EBV in LF patients were statistically consistently higher than the detection rates of these same antibodies not only in healthy control group individuals, but also in patients with SMT.

Considering that IgM antibodies are a serological marker of reproductive herpetic infections, we assumed that LF patients were most permissive to the development of reproductive forms of these infections and were characterized by the highest risk of reactivation of latent herpetic infections.

Table 2

The frequency of detecting IgM antibodies to herpetic viruses in seropositive blood serum of patients with LF, patients with SMT and healthy controls

Type of infection	Detectable antibodies	in patients with LF	in patients with SZO	healthy controls
Lymphatic infections	IgM-anti-HSV	44.7%	17.8%	6 , 0%
	IgM-anti-HZV	15.2%	7.3%	3.8%
	IgM-anti-CMV	4.2%	3.3%	1.2%
	IgM-anti-EBV	26.8%	14.3%	3.8%

Thus, it was found that most frequent reproductive form in all the cohorts examined was HSV infection was observed: in more than 40% of patients with LF and almost 20% in patients with SMT. Other infections in the reproductive form were much less frequent.

HEPATOTROPIC INFECTIONS IN LF PATIENTS

A serological study of the blood serum of LF patients was carried out for the presence of specific markers of infection with hepatitis A (HAV), hepatitis E (HEV), hepatitis B (HBV) and hepatitis C (HCV) viruses.

The first two infections are combined into a group of "enteric hepatitis", and the last two infections into a group of "transfusional hepatitis". The results obtained are presented in tables 3 and 4.

As follows from Table 3, anti-HAV was detected in the vast majority (more than 95%) not only in LF patients, but also in patients with SMT and healthy individuals. However, IgM antibodies were not detected in seropositive individuals from among patients with LF, SMT and healthy individuals.

Table 3

Frequencies of detection of total and IgM antibodies to HAV and HEV in patients with LF, SMT and healthy persons

antibodies	patients with LF	patients with SZO	healthy faces
anti-HAV	96.0%	98.0%	96.8%
IgM-anti-HAV	0	0	0
anti-HEV	9.0%	10.4%	*
IgM-anti-HEV	1.0%	1.2%	*
*research was not carried out			

At the same time, anti-HEV was detected at almost the same rate (about 10%) in patients with LF and SMT. A similar pattern emerged when serum-positive sera for the presence of IgM antibodies were detected at about the same rate (about 1.0%) in both LF patients and SMT groups.

These facts indicated, firstly, that patients with LF and SMT were involved in the spread of HAV infection in the same way as

people from other categories of the population, and secondly, that HEV infection among patients with LF, as well as among patients with SMT in our country is not widespread. Taking these findings into account, we further focused on HBV and HCV infections.

Prior to our studies, we consulted the relevant literature and received information that among the healthy population of Azerbaijan, HBV surface antigen (HBsAg) and antibodies to HCV (anti-HCV) are detected with a frequency of 2.1% and 2.0%, respectively. Table 4 shows the results of serum testing of LF and SMT patients for markers of HBV infection (HBsAg and anti-HBc) and HCV (anti-HCV).

Table 4

Frequencies of HBsAg and antibodies to HBV and HCV viruses in patients with LF and SMT

Type of infection	Revealed antibodies	LF patients (n = 500)	SMT patients (n = 300)
Hepatotropic infections	HBsAg	7.4%	5.3%
	anti-HBc	8.0%	6.6%
	anti-HCV	17.0%	7.7%

The table shows that HBsAg in LF patients was detected more than three times more often than in healthy individuals and almost one and a half times in SMT patients. Anti-HBc was detected almost with almost the same frequency as HBsAg, and, moreover, these antibodies were detected more often in patients with LF than in patients with SMT. And finally, the frequency of detection of HBsAg and anti-HBc in patients with NHLF patients slightly exceeded the frequency of their detection in patients with HLF patients.

At the same time, anti-HCV in LF patients was detected more than 8 times more frequently than in healthy individuals, and the frequency of its detection in LF patients was more than 2 times higher than in patients with SMT. Note that these antibodies were detected slightly more frequently in NHLF patients than HLF patients.

Thus, based on the results presented above, it could be said that HBsAg and anti-HCV detection rates were higher in LF patients than in SMT patients and significantly higher than in the healthy population of Azerbaijan. This circumstance again confirmed the validity of

the opinion that LF patients form an independent group of high risk of HBV and HCV infection.

Further, we tried to identify the prevailing forms of the course of subclinical HBV and HCV infections in patients with LF. Comparing the results of serological and biochemical blood tests, we were able to identify four main forms of the course of these infections: 1) the inapparent variant, in which there was no increase in ALaT activity in the blood; 2) the hyperenzymatic variant with a moderate increase in the activity of ALaT, but without an increase in the level of bilirubin; 3) the bilirubinemic variant, when together with an increase in ALaT activity, an increase in the bilirubin level to 50 mM / L was detected; and 4) the hyperbilirubinemic variant, in which an increase in the bilirubin level exceeding 50 mM / L was detected. These results are presented in Table 5.

It appeared that neither with HBV infection, nor with HCV infection were LF patients with hyperbilirubinemia variant of the course identified. At the same time, HBV infection in patients with LF most often lasted in the in apparent and hyperenzymatic variants.

Table 5

Frequency of pathogenetic variants of subclinical HBV infection and HCV infection in patients with LF

Pathogenetic variants of the course	in people with HBV infection	in people with HCV infection
1. İnapparent	67.6 + 8.3%	39.5 + 5.4%
2. Hyperenzymatic	26.5 + 7.6%	50.6 + 5.6%
3. Bilirubinemic	5.9 + 4.0%	9.9 + 3.3%
4. Hyperbilirubinemic	0	0

HCV infection in patients with LF most often revealed hyper enzymatic and inapparent variants of the course.

CLINICAL SIGNIFICANCE OF VIRAL INFECTIONS IN PATIENTS WITH LF.

So, patients with LF represent a population in which both herpetic infections and infections caused by viruses of transfusion hepatitis are widespread.

These two groups of infections fit with the notion that intercurrent infections regularly detected in cancer patients can be divided into opportunistic infections and true hospital-acquired infections.

The first group includes infections that develop as a result of the reactivation of viruses, which were latently persisting in the patient's body long before tumors developed. Herpes infections belong to them. Their more frequent development in patients with LF is associated with the presence of a set of conditions in their body, that increase permissiveness of the organism to its pathogens; they are expressed in the form of immunocompromise of these patients.

The second group includes infections, the causative agents of which penetrate into the body after the appearance of LF - they manifest in the process of treating patients and are considered to be intercurrent. An example is viral hepatitis, which often develops in patients with LF due to the high risk of parenteral HBV and HCV infection during of diagnostic and treatment procedures.

By the clinical significance of intercurrent infections in patients with LF, we understood their ability to negatively affect the course and outcome of LF by worsening the results of LF treatment and /or increase the side effects of antitumor treatment and, in particular, chemotherapy.

CLINICAL SIGNIFICANCE OF HERPETIC INFECTION

Among LF patients, HSV infection was most often detected: anti-HSV was present in more than 90% of patients with LF and IgM-anti-HSV - in more than 40% of patients. For this reason, we recognized HSV infection as the most important in clinical attitude and was limited to assessing the clinical significance of HSV infection in patients with LF.

Assessing the significance of HSV infection, we took into account that, having tropism to both lymphoid cells and immunocytes, and epithelial cells, HSV can probably not only induce and maintain immunopathological processes, but also infect the epithelium of internal organs, causing pathology of surface and `barrier` tissues.

These features of HSV infection are important in patients with LF. So, it can exacerbate immunological reactivity and act as a poten-

tial factor adversely affecting the course and prognosis of LF. In addition, by altering the epithelium of the skin, it can impair the functioning of tissues most vulnerable to the effects of cytostatic drugs. This means that its presence can, on the one hand, reduce the effectiveness of chemotherapy in patients with LF, and on the other hand, increase the frequency and severity of its toxic side effects and reduce the quality of life of patients during the period of their treatment.

However, this features of HSV in patients with LF are still poorly understood, making it impossible to develop an algorithm for drug treatment these effects. That is why, believing that these features of the infection have an important utilitarian scientific and practical significance, we tried to assess their significance in patients with LF.

To assess in LF patients the nature of the effect of HSV infection on the immediate and long-term results of chemotherapy and the frequency and ATM of such chemotherapy, a prospective clinical and laboratory follow-up of 24-25years old primary HLF patients of the III clinical stage of both sexes in 2014-2015. Patients who had received 4-6 courses of chemotherapy according to the BEACHOPP program were selected from among those who hadanti-HSV in their blood. They were re-examined for IgM-anti-HSV as a serological marker of a reproductive infection.

As a result, three groups of patients were formed. The first group included 40 patients with a reproductive infection who had both anti-HSV and IgM-anti-HSV. Second group included 46 patients with persistent infection who had only anti-HSM. Third group included 50 patients who did not have either anti-HSV or IgM-anti-HSV (control group).

The immediate result of chemotherapy was assessed by defining the objective therapeutic effect as the sum of the percentages of complete and partial remissions obtained after chemotherapy.

The long-term result of chemotherapy was assessed using: 1) determination of the duration of the relapse-free period (calculation of the median of this period) in the patients who remained under observation with the achieved complete remission; 2) determination of the annual (5-year) survival rate of patients.

Comparison of immediate results of treatment of patients

showed that the maximum frequency of registration of the therapeutic effect of chemotherapy was observed in the control group of patients and amounted to 94.0 + 3.4%. It is in good agreement with the indicators reflecting the effectiveness of modern programs of chemotherapy for treatment of patients with HLF [Demina E.A. et al., 2017]. In the group of patients with persistent infection, the same effect was observed in 91.3 + 4.1% of patients, and in the group of patients with reproductive infection only in 77.5 + 6.6% of patients. This indicated that while persistent infection had no measurable effect on the immediate results of chemotherapy, reproductive infection was associated with lower treatment efficacy in the form of worsening of the immediate results of chemotherapy.

Comparison of the median of the recurrence-free period, expressed in months, showed that it was comparable in patients from the 2nd and 3rd groups, and in the group of patients with reproductive infection, it was noticeably less than in the first two groups; its difference from the first two remained stable in the interval $p < 0.05$.

5-year survival rates were: 77.5% in group 1; 91.1% in the 2nd group and 89.6% in the 3rd group. Although a stable difference between these rates persisted only in the $p < 0.07$ interval, we assumed that the presence of a reproductive infection negatively affected the survival of patients, whereas persistent infection did not have such an effect on survival. This meant that in our observation, a subclinical lingering reproductive infection played the role of a predictor of the lesser effectiveness of treatment of patients with LF.

We assumed that this effect was based on the ability of a reproductive infection to cause depression of immunological reactivity, especially since it is known that immunological disorders are important in the pathogenesis of LF. This was also indicated by the results of our study, in which we measured IIM parameters in HLF patients with different forms of the course of HSV infection. It appeared that patients with reproductive infection had changes in a number of indicators o IIM, while in patients with HLF with persistent infection these changes were not.

Evaluating the side effects of chemotherapy in HLF patients with various forms of HSV infection, we retrospectively summarized

the data reflecting the nature and intensity of ATM in patients from the above 3 groups of patients after receiving 4 courses of chemotherapy according to the above program.

It turned out that the signs of hematological toxicity in patients with persistent infection and uninfected patients were noted with approximately equal frequency. The same symptoms in patients with a reproductive infection were more frequent and more severe. However, the differences between the frequency of detection of these signs in patients with reproductive infection and in other patients remained stable over a fairly wide interval ($p < 0.1$).

Signs of gastrointestinal toxicity in patients with persistent infection and in patients with uninfected HSV were observed with almost the same frequency. At the same time, these signs in patients with reproductive infection were noted more often than in the two categories of patients with HLF mentioned above. However, these signs in all three groups of patients practically did not differ.

There were no significant differences in the frequency and severity of signs of hepatic and renal toxicity in patients of all three groups.

So, despite the small sample of HLF patients in whom we observed, we concluded that while persistent infection had no detectable adverse effect on both effectiveness of chemotherapy and its ATM, reproductive infection showed the ability to worsen the results of chemotherapy and aggravate its toxic side effects.

This suggested that the detection of persistent HSV infections in patients with LF should not be the basis for recommending special management and treatment. On the contrary, the detection of a reproductive HSV infection may indicate the appropriateness of distinguishing patients into a special clinical population, characterized, on the one hand, by increased risk of developing immunosuppression, and, on the other hand, a higher risk of increased frequency and increased side toxic manifestations of CT and its effectiveness.

CLINICAL SIGNIFICANCE OF HEPATOTROPIC INFECTIONS

Assessing the clinical significance of subclinical HBV and HCV infections from the point of view of an oncologist, we had in

mind that both HBV and HCV have pleiotropic (hepatotropic and lymph immunotropic) activity and are capable of causing pathology not only in the liver, but also in a number of other organs. Moreover, the development of these infections can be accompanied by the formation of not only a complex of metabolic changes, but also a number of immunological disorders and immunopathological reactions.

Importantly, these infections, which are common among patients with LF, are widespread, albeit less widely and among patients with SMT. Moreover, these infections, even in a subclinical course, were capable of adversely affecting the efficacy of breast cancer (BC) treatment: both infections were accompanied by both a reduction in the frequency of recording therapeutic effect and a reduction in the duration of the achieved remissions. In addition, these infections were capable of aggravating ATM of CT drugs in patients with breast cancer.[12]

At the same time, it was found that the realization of these effects in both infections was closely related to the presence of laboratory signs of subclinical liver disfunction (SLD) in breast cancer patients - the noted ability of both HBV and HCV infections to influence the results of chemotherapy and the frequency of its ATM appeared mainly only in patients with SLD. In patients who did not have the sign of SLD, the negative impact of both viral infections on the effectiveness of chemotherapy and its ATM was minimal.

Taking these considerations into account, we carried out observations that made it possible to objectively assess the influence of both infections, firstly, on the results of standard chemotherapy in patients with stage II LF (both HLF and NHLF), and secondly, on the side toxic effects of chemotherapy. These studies allowed us to establish and formulate three important points.

First, in a certain proportion of patients with LF, both subclinical HBV infection and subclinical HCV infection worsened the results of chemotherapy. At the same time, in the case of both infections, the deterioration of treatment outcomes took the form of a de-

[12] Михайлов М.И.: Мамедов М.К. Вирусные гепатиты В и С у онкологических больных. М.:ВК, 2012, 228 с.

crease in the frequency of treatment effect and a shortening of the duration of the achieved remissions.

Secondly, a more detailed analysis of the data obtained in the observations showed that the above-mentioned effect appeared only in those patients with LF, in whom laboratory signs of SLD were found. In LF patients who did not have this symptom, the negative effect of both viral infections on the effectiveness of chemotherapy was minimal.

Thirdly, in patients with LF who had signs of SLD, both infections markedly increased the frequency of symptoms of all four types of toxicity mentioned above. In contrast, in patients who did not have signs of SLD, the presence of these infections was not accompanied by a marked increase in the frequency of ATM incidence.

These data suggest that the real clinical significance of HBV and HCV infections in patients with LF is determined not by the very fact of detection of these infections in patients, but by the presence or absence of a symptom of SLD in these patients.

In summary, we came to two conclusions reflecting the particular clinical significance of the above-mentioned hepatotropic infections.

First, subclinical HBV and HCV infections in patients with LF without signs of SLD have no significant adverse effect on treatment outcomes of patients and side effects of CT. Accordingly, patients with such infections do not need special treatment strategies.

Secondly, subclinical HBV and HCV infections in patients with LF, with a sign of SLD, can adversely affect the results of chemotherapy and its ATM. Such patients should be allocated to a special clinical population characterized by a higher risk of less effective chemotherapy and more frequent occurrence of ATM of such chemotherapy.

CONCLUSIONS

1. Of the 6 lymphatic viral infections identified among patients with LF, infections caused by herpes simplex viruses (HSV) and herpes zoster virus, which were detected in more than 90% of serologically examined patients, had the highest prevalence [20, 21].

2. The frequency of detection of total antibodies to HSV did not have statistically stable differences from the frequency of their detection in patients with solid malignant tumors (SMT) and healthy individuals from the control group. At the same time, in patients with LF, the frequency of detecting antibodies to HSV related to IgM and found in about 40% of patients with LF was almost 3 times higher than the same indicator in patients with SMT and more than 7 times in healthy individuals from the control group [10,24].
3. The presence of HSV infection in patients with LF who had IgM antibodies to HSV, i.e the presence of a reproductive infection in them was combined with the worst immediate and long-term results of treatment of these patients and more frequent registration of signs of the toxic effect of chemotherapy (CT). At the same time, in patients with LF, in whom the indicated antibodies were not detected, the above combination was not observed [20,23].
4. Of the 4 hepatotropic viral infections detected among patients with LF, only infections caused by hepatitis B (HBV) and hepatitis C (HCV) viruses, found in 7% and 17% of the examined patients with LF, had the highest prevalence among these patients, respectively. The frequency of detection of these infections in patients with LF was several times higher than the frequency of their detection in patients with SMT and in healthy individuals from the control group [2,3].
5. In patients with LF, HBV infection and HCV infection in 67.6% and 39.5% of cases, respectively, flowed in different forms, in which the activity in blood of alanine aminotransferase (ALaT) remained within the normal range [27].
6. The presence of HBV and HCV infections in LF patients with moderately increased blood ALT activity was combined with worse immediate and long-term results of treatment in these patients and more frequent registration of symptoms of the toxic effect of CT. At the same time, in patients with LF, in whom ALaT activity remained normal, the above combination was not observed [22, 28].

PRACTICAL GUIDANCE

1. Given the initially widespread occurrence of HSV infection in oncohematological hospitals and its potential ability to adversely affect the results of treatment of patients with LF and the side effect of chemotherapy, all patients admitted to such hospitals should be serologically tested for the presence of antibodies to HSV.

2. Patients with LF, who have been found to have anti-HSV antibodies during the examination, should be re-tested for IgM anti-HSV.

Patients in whom such antibodies are detected should be identified as a special group in which the efficacy of chemotherapy can be expected to decrease and its toxic effects to increase. In relation to such patients with LF, it is necessary to more carefully prevent the toxic side effects of chemotherapy.

3. Patients with subclinical HBV and HCV infections, with even a moderate increase in ALaT activity in the blood should be treated as a separate group, in which a decrease in efficacy of CT and an increase in its toxic effect can be expected. In such patients with LF, the decision to prescribe chemotherapy and the prevent its possible toxic effect requires special caution.

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The defense will be held on 23 september 2022 at 14^{00} at the meeting of the Dissertation council FD 1.02 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan

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Dissertation is accessible at the Library of National Center of Oncologyof the Ministry of Health of the Republic of Azerbaijan

Electronic versions of dissertation and its abstract are available on the www.aak.gov.az.

Abstract was sent to the relevant addresses on 26 July 2022.

Signed for printing: 30.06.2022

Paper format: 60x84$^{1/16}$

Volume: 36 066 characters

Number of hard copies: 20