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New Method for the Combined Treatment Associated Virus Non-Hodgkin;s Lymphoma

Key words: *non-Hodgkin's lymphoma, the association of viral, p53, bcl-2, new method of treatment*

Annotation: *Implementation of patients with malignant lymphomas complex molecular genetic, immuno and immunohistochemical studies in patients for the presence of viral load (hepatitis C, HIV, human papilloma virus HPV, varicella-zoster virus, Epstein-Barr virus) and character the expression of tumor markers p53 and bcl-2 as well as the inclusion complex therapeutic antiviral treatment significantly increased the efficiency of the treatment, thus eliminating the phenomenon of drug resistance and suppress viral persistence in tumor cells and increase the duration of disease-free period and overall survival.*

Introduction

Understanding of the linkages between the immune status, disrupted viral contamination due to the body, and the risk of cancer is usually based on a comparison of two paradigms: the immune system protects the body by observing the appearance of tumor cells and oncogenic viruses (for example immune carcinogenesis model) and chronic inflammation may increase the tumor growth and metastasis (inflammatory model) (2). While these models support the role of the immune status in many types of cancer pathology, they are not sufficient to explain the disproportionate increase in the risk of B-cell lymphoma in a population of patients with chronic immunosuppression or inflammation (3).

The question of the mechanisms of viral carcinogenesis concentrates on study of oncogenic potency of known and newly discovered viruses and their genes, the key proteins signaling systems in virus-infected cells, identification of cofactors required for the implementation of the tumorigenic properties of the virus, identify the transforming viral proteins on the analysis of the relationship of virus the host immune system, finding a convenient and sensitive models in vivo and in vitro and other aspects (1). At the same time we can confidently say that the serological and molecular biological markers of a number of known

oncogenic viruses are very important for the diagnosis of human tumors and to evaluate the effectiveness of the therapy (4). Undoubtedly, the association of the virus in oncology and, in particular, in lymphomas, makes a significant contribution to the development and disease outcome, and the development of new methods to increase the effectiveness of therapy can not address the problem of accounting molecular genetics and immunological factors of prognosis (5).

The aim of research was to improve the results of treatment of lymphoma by examining the frequency of the virus infection in patients depending on the stage, histological type, immunological parameters, age and sex, as well as the practical application of the new method of combined treatment, including chemotherapy and antiviral therapy.

Materials and methods

The criteria for selecting patients were patients with morphologically verified diagnosis of various forms of lymphoma, II-IIIAB tumor stage, the lack of severe comorbidity; gender and age of the patients did not matter.

The main stages of the implementation of the study include additionally to standard - examination of patients to the virus infection, with positive results in conjunction with chemotherapy, in complex treatment included antiviral therapy, evaluation of the effectiveness of the treatment was carried out according to international standards (immediate and remote results, quality of life).

For the implementation and perform tasks in all patients with malignant lymphomas conducted a comprehensive survey. From the lymph nodes before treatment biopsy taken for molecular biological and immunohistochemical studies.

Results and Discussion

In our study, patients with non-Hodgkin's lymphoma (NHL) divided into 2 groups: Group I - patients with a set of virus; Group II - patients in the control group with the absence of virus infection.

Table 1 shows the distribution of patients by age and sex.

The allocation of patients by age decades of NHL found that leads to rejuvenation of virus diseases: peak incidence in Group I account for up to 30 years, while the corresponding figure for the group II is more than 50 years.

Table 1

The distribution of patients by age and sex

Age	Group I (virus carrying), n=23				Group II (control), n=18			
	Men		Women		Men		Women	
	abs	%	abs	%	abs	%	abs	%
< 30	11	47,8±7,8	4	17,3±5,9	-		2	11,1±4,9
31-40	1	4,3±2,2	-		1	5,5±2,7	1	5,5±2,7
41-50	2	8,6±4,4	1	4,3±2,2	-		1	5,5±2,7
51-60	1	4,3±2,2	-		5	27,7±6,9	3	16,6±5,8
61-70	2	8,6±4,4	-		1	5,5±2,7	-	
> 70	1	4,3±2,2	-		3	16,6±5,8	1	5,5±2,7

The average age of male patients during virus infection was 35,6±4,56 years among women - 27,2±5,24 years; in the control group, the average age of the men was 60,7±3,80 years,

women - 45,5±6.97 years. The proportion of women in the group I was 21,7±6,44%, men - 78,3±6,44%; in group II, women made up 44,4±7,75%, men - 55,6±7,75%.

At all patients the diagnosis was made based on the data and the results of complex research (clinical and biochemical, X-ray, ultrasound, CT, myelogram, morphological) (Table. 2).

Affected areas in the non-Hodgkin's lymphoma in patients with viral infection (group I) most often in the cervical and axillary l units (50%), followed by mediastinal, supraclavicular, retroperitoneal and inguinal (25-45%), the least mentioned defeat iliac lymph nodes, spleen, Valdeyera (20% or less).

In the control group II pattern of lymph node different from the experimental group - patients with lesions of cervical lymph nodes was 70%, while the rest of the affected areas were less common: axillary, supraclavicular, inguinal lymph nodes malignantly transformed in 30-40% of cases; mediastinal, retroperitoneal, iliac - at least 20% of the cases; Valdeyera defeat rings observed in 60% of patients.

So a viral infection changes the picture of lymph node involvement in patients with NHL, compared with patients without viral load: Group I often malignantly transformed axillary, mediastinal, supraclavicular, retroperitoneal and inguinal lymph nodes (25-45%).

Table 3 shows the viral infection and immunological status in patients with non-Hodgkin lymphoma. Group I patients often have been infected with herpes simplex virus HSV and Epstein-Barr virus (65-80%). Cytomegalovirus infection, human papilloma virus, and varicella-zoster occurred in 43,4±7,7% of patients, hepatitis C and HIV - from 26,0±6,8% and 8,6±4,4%, respectively. Viral load influenced the immunological status in patients with NHL - interferon status was lower than that of patients' in-group II, and immunological status suppressed at 100%.

All the patients of Group II was carried out by 2 cycles of CHOP chemotherapy (Vincristine 1.4 mg/m^2/1 day, cyclophosphamide 750 mg/m^2/1 day, doxorubicin 50 mg/m^2/1 th day Prednisolone 40 mg/m^2 inwardly 1-5 days).

Table 2

Distribution of patients with NHL, depending on the viral infection and immunological status

Groups	Infection with a virus,% (absolute value)							interferon status, % (absolute value)			immunological status, % (abs)	
	HSV	EBV	CMV	HPV	Hepatitis C	HIV	VZV	interferon alpha	anti-interferon-alpha	interferon gamma	norm	depressed
Group I (virus carrying), n=23	65,2±7,4 (15)	78,2±6,4 (18)	43,4±7,7 (10)	43,4±7,7 (10)	26,0±6,8 (6)	8,6±4,4 (2)	43,4±7,7 (10)	8,6±4,4 (2)	8,6±4,4 (2)	8,6±4,4 (2)	0	100 (23)
Group II (control), n=18	-	-	-	-	-	-	-	16,6±5,8 (3)	11,1±4,9 (2)	11,1±4,9 (2)	44,4±7,7 (8)	55,6±7,7 (10)

Between courses of chemotherapy, patients received antiviral immunotherapy - altevir (interferon alpha-2b at a dose of 3 million IU three times per week).

Prior to initiation of treatment and after two courses of chemotherapy conducted virological and immunological research.

Table. 3 shows the results of immunohistochemical determination of tumor markers p53 and bcl-2 in patients with non-Hodgkin lymphomas.

Table 3

The results of immunohistochemical determination of tumor markers p53 and bcl-2 in patients with non-Hodgkin's lymphoma.

Groups	Expression of p53		expression bcl-2	
	negative or weakly positive	positive	negative or weakly positive	positive
Group I (virus carrying), n=23	78,2±6,4 (18)	21,7±6,4 (5)	26,0±6,8 (6)	73,9±6,8 (17)
Group II (control), n=18	66,6±7,3 (12)	33,3±7,3 (6)	22,2±6,4 (4)	77,7±6,5 (14)

At patients with non-Hodgkin's lymphomas (NHL) Group I observed a decrease in the p53 oncoprotein expressing tumor cell nuclei compared with the control group II. This allows you to ascertain the deterioration of the protective reaction of the body to the malignant transformation of immune cells during viral infection, ie viral load induces drug resistance of cancer cells.

Table. 4 shows the results of the treatment and shows the effectiveness of a new method of therapy of malignant lymphomas.

In the control group of patients with NHL overall effectiveness of treatment was 72,2±6,9%, while in 2 patients showed progression of neoplasms, in 3 - effect of the therapy were observed. In-group II, wherein patients weighed down by a viral infection and where to apply antiviral therapy, the rate of the overall efficiency was 100%, disease progression and treatment without result observed.

Table 4

The effectiveness of treatment in patients with non-Hodgkin's lymphoma

Groups	Regression 25%	Regression 50%	Regression 100%	without the effect	progression
Group I (virus carrying), n=23	43,4±7,7 (10)	56,5±7,7 (13)	0	0	0
Group II (control), n=18	27,7±6,9 (5)	44,4±7,7 (8)	0	16,6±5,8 (3)	11,1±4,9 (2)

Conclusion

Infection with the human body with the HIV virus, Epstein-Barr virus, a herpes-type 8, hepatitis B and C, and provokes the development of malignant lymphomas. The role of the virus in the induction of carcinogenesis to date not fully clarified, he can participate in genetic rearrangements lymphocytes, leading to malignant transformation of these cells and promote immunodeficiency states, against which there is increased proliferation of neoplasms. There is

no direct correlation between the already developed cancer pathology in a virus of association and the worst outcome of the disease, however, antiviral prophylaxis has a positive effect on the course of the treatment of lymphoma.

Implementation of patients with malignant lymphomas complex molecular genetic, immuno and immunohistochemical studies in patients for the presence of viral load (hepatitis C, HIV, human papilloma virus HPV, varicella-zoster virus, Epstein-Barr virus) and character the expression of tumor markers p53 and bcl-2 as well as the inclusion complex therapeutic antiviral treatment significantly increased the efficiency of the treatment, thus eliminating the phenomenon of drug resistance and suppress viral persistence in tumor cells and increase the duration of disease-free period and overall survival.

References

1. *Ha SY, Sung J, Ju H, Karube K, Kim SJ, Kim WS, Seto M, Ko YH. Epstein-Barr virus-positive nodal peripheral T cell lymphomas: Clinicopathologic and gene expression profiling study: Pathol Res Pract, 2013, 13 (3); 0344-S0338.*
2. *Hoffman AE, Liu R, Fu A, Zheng T, Slack F, Zhu Y. Targetome profiling, pathway analysis and genetic association study implicate miR-202 in lymphomagenesis: Cancer Epidemiol Biomarkers Prev, 2013, 22 (3); 327-336.*
3. *Kirk R. Haematological cancer: Hit the lymphoma, JAK: Nat Rev Clin Oncol, 2012, 9 (11); 608-612.*
4. *Shiels MS, Engels EA, Linet MS, Clarke CA, Li J, Hall HI, Hartge P, Morton LM. The Epidemic of Non-Hodgkin Lymphoma in the United States: Disentangling the Effect of HIV, 1992-2009: Cancer Epidemiol Biomarkers Prev, 2013, 22 (6); 1069-1078.*
5. *Smith N, Tierney R, Wei W, Vockerodt M, Murray PG, Woodman CB, Rowe M. Induction of Interferon-Stimulated Genes on the IL-4 Response Axis by Epstein-Barr Virus Infected Human B Cells; Relevance to Cellular Transformation: PLoS One, 2013, 8 (5); e64868.*