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Association of *CDKN2A/B* deletions with survival of patients with diffuse large B-cell lymphoma

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ABSTRACT

Aim. To define the association of *CDKN2A/B* deletions in the 9p21 locus with survival of patients with diffuse large B-cell lymphoma.

Materials and methods. The study included 105 patients with diffuse large B-cell lymphoma who received first-line therapy with R-CHOP. A deletion of 9p21 was detected by fluorescent in situ hybridization of tumor tissue biopsy samples. Deletions of *CDKN2A* and *CDKN2B* were determined by real-time quantitative polymerase chain reaction. The overall survival and the progression-free survival were calculated by the Kaplan – Meier method with plotting of survival curves (the log-rank test). The risk of event occurrence was determined by the Cox regression analysis with the calculation of the risk ratio (RR) and 95% confidence interval (CI). The differences between the variables were considered statistically significant at $p < 0.05$.

Results. The deletion of the chromosomal region 9p21 was detected in the biopsy samples in 16.2% of patients. The *CDKN2A* deletions were detected in 23.8% of patients and *CDKN2B* loss – in 28.6% of patients. The progression-free survival was significantly lower in patients with the 9p21 deletion than in those without this aberration: 29.4% vs. 62.5%, respectively ($p = 0.012$; RR = 2.26; 95% CI = 1.17–4.38). The risk of disease progression at low and low-intermediate values of the International Prognostic Index was 5.9 times higher in patients with the *CDKN2B* deletion than in patients without this abnormality.

Conclusion. Deletion of the chromosomal region 9p21 is associated with low progression-free survival in patients with diffuse large B-cell lymphoma. Loss of *CDKN2B* is associated with a high risk of disease progression in patients with low and low-intermediate risk according to the International Prognostic Index.

Keywords: deletion of the 9p21 locus, diffuse large B-cell lymphoma, *CDKN2A/B*

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Взаимосвязь делеций генов *CDKN2A* и *CDKN2B* с выживаемостью больных диффузной В-крупноклеточной лимфомой

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РЕЗЮМЕ

Цель. Определить взаимосвязь делеций генов *CDKN2A* и *CDKN2B* в локусе 9p21 с выживаемостью больных диффузной В-крупноклеточной лимфомой.

Материалы и методы. В исследование включены 105 пациентов с диффузной В-крупноклеточной лимфомой, получавших терапию первой линии по схеме R-CHOP. Делецию 9p21 выявляли с помощью флуоресцентной гибридизации *in situ* биопсийных образцов опухолевой ткани. Делеции в генах *CDKN2A* и *CDKN2B* устанавливали количественной полимеразной цепной реакцией в реальном времени. Общую и беспрогрессивную выживаемость рассчитывали по методу Каплана – Мейера с графическим построением кривых (log-rank тест). Риск наступления события вычисляли методом регрессионного анализа Кокса с расчетом отношения рисков (ОР) и 95%-го доверительного интервала (95%-й ДИ). Различия между показателями считали статистически значимыми при $p < 0,05$.

Результаты. Делеция хромосомного региона 9p21 обнаружена в биопсийных образцах 16,2% больных. Поломки в гене *CDKN2A* выявлены у 23,8% пациентов, утрата *CDKN2B* –у 28,6%. Беспрогрессивная выживаемость значимо ниже у обследованных с делецией 9p21, чем у лиц без данной аберрации: 29,4% против 62,5% соответственно ($p = 0,012$; ОР = 2,26; 95%-й ДИ = 1,17–4,38). Риск прогрессии заболевания при низком и низком промежуточном показателе международного прогностического индекса в 5,9 раза выше у пациентов с делецией гена *CDKN2B*, чем у больных без указанной аномалии.

Заключение. Делеция хромосомного региона 9p21 связана с низкой беспрогрессивной выживаемостью больных диффузной В-крупноклеточной лимфомой. Утрата гена *CDKN2B* ассоциирована с высоким риском прогрессии заболевания у пациентов низкого и низкого промежуточного риска согласно международному прогностическому индексу.

Ключевые слова: делеция локуса 9p21, диффузная В-крупноклеточная лимфома, *CDKN2A/B*

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a group of heterogeneous tumors with different clinical manifestations, morphological characteristics, genetic aberrations, and different responses to therapy and prognosis [1]. More than half of patients with DLBCL respond well to the standard R-CHOP chemotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone). However, relapses or refractory forms of the disease leading in most cases to death develop in 30–40% of cases [2]. Currently,

the international prognostic index (IPI) and its modifications are considered to be a simple and reproducible tool for estimating the individual risk of early disease progression. However, according to some authors, its practical application does not always accurately estimate the individual risk of therapy failure, since IPI is mainly based on clinical characteristics, so it is necessary to search for new markers associated with an unfavorable course of the disease [3].

Some of the reasons for the heterogeneity of clinical manifestations in DLBCL are molecular biological features of tumor cells [4, 5]. Extensive data on genetic disorders associated with the development of the disease and (or) neoplastic progression have been obtained using the next-generation sequencing methods [6, 7].

Some of the most frequently mutated genes in various malignant neoplasms are genes encoding inhibitors of cyclin-dependent kinases 2A/B (*CDKN2A* and *CDKN2B*), localized in the chromosomal region 9p21. They belong to the tumor suppressor family. *CDKN2A* and *CDKN2B* encode the corresponding proteins p16INK4a and p15INK4B, which are almost identical in structure and biochemical properties. Both proteins play an important role in the cell cycle control, blocking it during the G1 to S-phase transition by binding cyclin-dependent kinases 4 and 6 (CDK4/6). According to the literature, G1/S checkpoint dysfunction leads to uncontrolled proliferation of tumor cells [8].

Deletions of *CDKN2A/B* (9p21) occur in 20–30% of DLBCL cases and, according to some foreign authors, are associated with an unfavorable course of the disease [9]. No information was found on the influence of genetic aberrations in the chromosomal region 9p21 on the prognosis of the disease in the domestic literature. Therefore, the study on the prognostic value of aberrations in the 9p21 locus in patients with DLBCL is relevant.

The aim of the study was to determine the relationship of *CDKN2A/B* deletions at the 9p21 locus with survival of patients with DLBCL.

MATERIALS AND METHODS

The retrospective study included 105 patients with newly diagnosed DLBCL who received treatment at the clinic of KRIHBT in 201–2019. The average age was 59 (49–67) years. Among them, 50.5% (53/105) were men, 49.5% (52/105) were women. Stages 1 and 2 of the disease were determined in 40% (42/105) of the examined patients (according to Ann Arbor staging classification), stages 3 and 4 were determined in 60% (63/105) of patients. Half of the patients (52/105) belonged to high and high-intermediate risk groups according to IPI. All patients received standard first-line R-CHOP induction immunochemotherapy. The immunohistochemical (IHC) subtype of the tumor was determined based on the IHC algorithm proposed by C.P. Hans [10]: GCB subtype was found in 27.6% (29/105) of cases, non-GCB subtype was detected in 72.4% (76/105) of cases. A complete response to R-CHOP therapy was achieved in 64.8% (68/105) of those examined, a partial response was noted in 18.1% (19/105) of cases. Stabilization of the process and refractoriness to treatment were noted in 17.1% (18/105) of patients. Five-year overall survival (OS) was 64.8%, five-year progression-free survival (PFS) was 57.1%. The median follow-up of patients was 48 (20–60) months.

The deletion of the chromosomal region 9p21 was determined using fluorescent *in situ* hybridization (FISH) of biopsy samples of tumor tissue using the Kreatech CDKN2A (9p21) / 9q21 FISH probe according to the standard method in accordance with the manufacturer's protocol. The deletions of exons 1α, 2 in the *CDKN2A* gene and exon 1 in the *CDKN2B* gene were determined by quantitative real-time polymerase chain reaction (PCR) [11].

Statistical data processing was performed using the STADIA software. The frequency of occurrence of nominal independent variables in the groups, divided according to the characteristics under study, was compared using the Pearson's chi-square test (χ^2). The five-year OS and PFS were calculated by plotting the Kaplan – Meier survival curves. The differences between survival rates in the groups of patients were determined using the log-rank test. The risk of disease progression was calculated using the Cox regression analysis with the calculation of the hazard ratio (HR) and 95% confidence interval (CI). The selection of variables was performed by backward elimination (Wald's test). The differences between the parameters were considered statistically significant at $p < 0.05$.

RESULTS

A deletion of the 9p21 chromosomal region was found in 16.2% (17/105) of the examined patients. All the results of the FISH analysis were confirmed by PCR, deletions were detected in 31.4% (33/105) of patients with DLBCL. On the one hand, the obtained data are due to higher sensitivity of PCR compared

to FISH in assessing copy number aberrations in histologic specimens. On the other hand, in some cases, a significantly smaller DNA area is deleted compared to the area covered by a commercial DNA probe. It does not lead to attenuation of the fluorescent signal. The deletions of exons 1α and (or) 2 in the *CDKN2A* gene were found in the formalin-fixed paraffin-embedded (FFPE) samples in 23.8% (25/105) of patients, the deletion of exon 1 in *CDKN2B* was found in 28.6% (30/105) of cases. All patients were divided into groups depending on the presence or absence of deletions of the chromosomal region 9p21 in the *CDKN2A* and *CDKN2B* genes.

There were no significant associations of the 9p21 deletions with clinical and laboratory characteristics of patients (age, disease stage, IHC subtype, IPI risk group) (data not shown).

The relationship between deletions of *CDKN2A/B* (9p21) and OS of patients has not been established (data not shown). The five-year PFS of patients with del9p21 was significantly lower compared to that of patients without this aberration: 29.4% (*Me* = 19 months) versus 62.5% (*Me* was not reached), respectively ($p = 0.012$; Fig. 1, *a*). The risk of disease progression in the patients with the 9p21 deletion in the FFPE samples was 2.26 times higher than in patients without genetic damage (HR = 2.26; 95% CI = 1.17–4.38). Associations between the presence or absence of *CDKN2A* deletions and PFS were not found (data not shown).

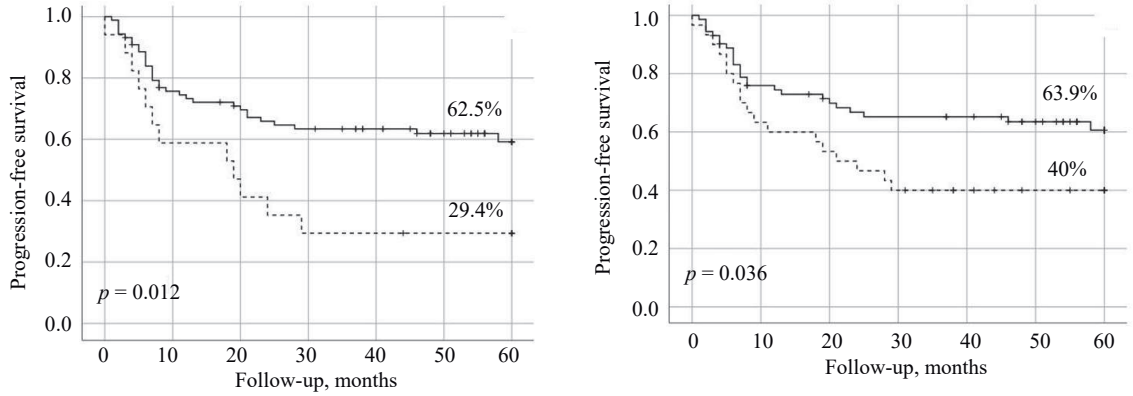

Fig. 1: Progression-free survival of patients: *a* – with a deletion of the chromosomal region 9p21 ($n = 17$, dotted line) and without aberrations ($n = 88$, solid line); *b* – with *CDKN2B* deletion ($n = 30$, dotted line) and without aberrations ($n = 75$, solid line)

The five-year PFS in patients with a *CDKN2B* deletion was lower than in patients without this anomaly: 40% (*Me* = 21 months) versus 63.9% (*Me* was not reached), respectively ($p = 0.036$; Fig.1, *b*). The risk of disease progression in patients with del*CDKN2B* was 1.9 times higher than in patients without the deletion (HR = 1.87; 95% CI = 1.03–3.42).

According to the results of the univariate Cox regression analysis, predictors of low PFS in patients with DLBCL were IPI > 2 ($p < 0.001$; HR = 6.22; 95% CI = 3.05–12.68), non-GCB subtype ($p = 0.058$; HR = 2.10; 95% CI = 0.98–4.51), deletion of the chromosomal region 9p21 ($p = 0.016$; HR = 2.26; 95% CI = 1.17–4.38) or *CDKN2B* deletion ($p = 0.041$; HR = 1.87; 95% CI = 1.03–3.42).

The multivariate Cox proportional hazard model (Table 1) includes parameters that have passed selection by the significance level (IPI > 2, non-GCB subtype, del9p21). A loss of the chromosomal region 9p21 was identified as an independent predictor of low PFS along with IPI > 2. The risk of disease progression was 1.95 times higher in patients with a 9p21 deletion than in those without aberrations at the study locus ($p = 0.031$; HR = 1.95; 95% CI = 1.07–3.56).

Table 1

Multivariate Cox regression analysis of predictors of progression-free survival in patients with diffuse large B-cell lymphoma, *n* = 105

Parameter	HR	95% CI	*p*
IPI >2	5.82	2.85–11.91	<0.001
del 9p21	1.95	1.07–3.56	0.031

The relationship between the presence of genetic aberrations at 9p21 and the survival rates of patients with low or low-intermediate risk (according to IPI) was studied. In patients with *CDKN2A* or *CDKN2B*

deletions, the PFS was lower than in those with an intact locus: 66.7 vs. 86.1% (p = 0.109; *Me* was not reached; Fig. 2, *a*) and 60 vs. 88.9%, respectively (p = 0.009; *Me* was not reached; Fig. 2, *b*).

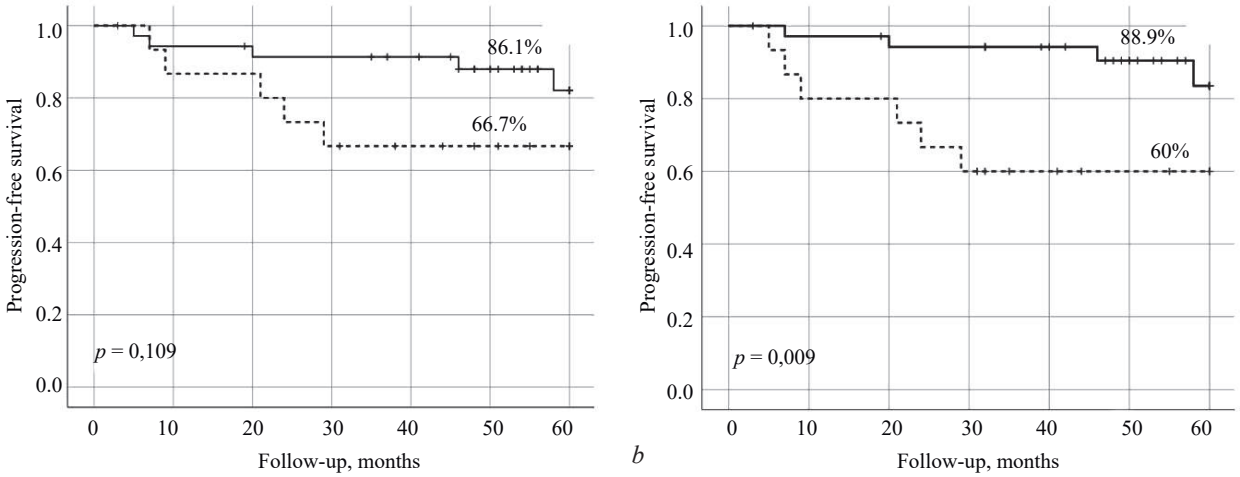

Fig. 2. The progression-free survival in patients with low or low-intermediate risk in the presence of a deletion: *a* – in the CDKN2A gene (n = 15, dotted line), *b* – CDKN2B (n = 15, dotted line) and without aberrations (n = 38, solid line)

Only *CDKN2B* deletion showed statistical significance in the univariate Cox regression analysis for PFS (p = 0.018; HR = 4.67; 95% CI = 1.30–16.81). Assessing the effect of several predictors on disease progression, such as age ≥ 60 years (p = 0.140; HR = 2.6; 95% CI = 0.73–9.21), del *CDKN2A* (p = 0.124; HR = 2. 65; 95% CI = 0.76–9.22), del *CDKN2B* (p = 0.018; HR = 4.67; 95% CI = 1.30–16.81), it was found (Table 2) that patients with del *CDKN2B* had a higher risk of disease progression (by 5.9 times) than those without the gene loss (p = 0.010; HR = 5.9; 95% CI = 1.54–22.61).

Table 2

Multivariate Cox regression analysis of predictors of progression-free survival in patients with low and low-intermediate risk, n = 53

Parameter	HR	95% CI	p
del *CDKN2B*	5.90	1.54–22.61	0.010
Age ≥60 years	3.25	0.87–12.08	0.079

DISCUSSION

DLBCL is a heterogeneous lymphoid neoplasm with variable gene expression patterns and genetic abnormalities that contribute to different clinical courses of the disease and responses to therapy. *CDKN2A/B* aberrations can disrupt various biological programs, in particular DNA damage response (via the p14-ARF/p53 pathway) and cell cycle regulation (via the RB/p16 tumor-suppressive pathway). When the latter is impaired, neoplastic cells accumulate additional mutations, contributing to clonal tumor evolution, genome instability, and, as a result, drug resistance and disease progression [8]. So, B. Chapuy et al. identified a subset of DLBCL variants with biallelic inactivation of *TP53* and a loss of *CDKN2A*, characterized by genomic instability and low survival rates, regardless of the gene expression profile [7].

According to the obtained data, the deletion of the chromosomal region 9p21, established by the FISH method, was found in 16.2% of patients. The results of molecular cytogenetic studies were confirmed by PCR. The loss of *CDKN2A* was found in 23.8% of patients, the loss of *CDKN2B* – in 28.6% of individuals. The obtained data generally correspond to the data mentioned in the literature [9]. The high frequency of genetic disorders determined by PCR is probably due to the high sensitivity of the applied analysis, in contrast to FISH. Although FISH does not detect deletions of smaller regions (microdeletions) and small subclones, the method is considered as specific and indicative. The simultaneous use of technologies is complementary and minimizes errors.

Several studies have shown the association of del9p21 with the prognostically unfavorable ABC subtype of DLBCL [12, 13]. In our study, no similar pattern was found. Perhaps the differences are due to the methods of determining the subtype: the analysis based on the gene expression profile and immunohistochemical methods.

It was found that the deletion of the chromosomal region 9p21, along with IPI > 2, was an independent

predictor of low PFS in patients with DLBCL. The risk of disease progression was two times higher in patients with the 9p21 deletion than in patients without aberrations at the locus under study. It was determined that the PFS of patients belonging to low or low-intermediate risk groups with a *CDKN2B* deletion was significantly shorter than in the individuals without the genetic damage. The risk of progression was more than five times higher in patients with IPI ≤ 2 with a deletion of *CDKN2B* compared to the same parameter in patients without the gene loss. The results are partially in line with the data obtained by F. Jardin et al., who found that *CDKN2A* and (or) *CDKN2B* deletions were associated with shorter overall and disease-free survival of patients [9]. At the same time, we did not reveal any differences in the OS of patients depending on the presence or absence of deletions of the chromosomal region 9p21 and (or) *CDKN2B*.

Associations between the presence of del *CDKN2A* and survival rates of patients with DLBCL were not found. The results are similar to those reported by C.R. Bolen et al. [12] and K. Karube et al. [13]. At the same time, researchers have shown that complex changes in the TP53/CDKN2A biological pathway are associated with low survival rates (OS and PFS), regardless of IPI and the molecular subtype of the disease [13].

CONCLUSION

The deletion of the chromosomal region 9p21 is associated with low PFS rate in patients with DLBCL. The deletion of the *CDKN2B* gene is associated with a high risk of disease progression in low- and low-intermediate risk patients (IPI). Aberrations in the chromosomal region 9p21 (del *CDKN2A/B*) are determined using both PCR and FISH. The obtained results can be used as additional molecular genetic criteria for assessing the unfavorable course of DLBCL.

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Authors' contribution

Sarpova M.V. – conception and design, analysis and interpretation of the data. Tregubova E.V. – analysis and interpretation of the data. Diakonov D.A. – conception and design, justification of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Vaneeva E.V. – analysis and interpretation of the data. Posin V.A. – justification of the manuscript and critical revision of the manuscript for important intellectual content. Samarina S.V. – collection of clinical data about patients. Nazarova E.L. – justification of the manuscript and critical revision of the manuscript for important intellectual content.

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