Mutational profile of Diffuse Large B-cell Lymphoma with central nervous system relapse: analysis of CBioPortal for Cancer Genomics database

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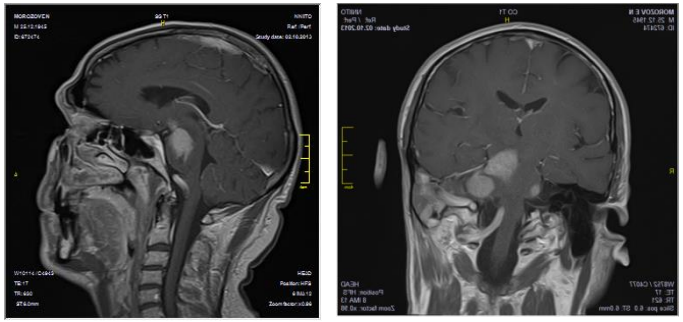
The high mortality of patients with central nervous system (CNS) involvement in Diffuse Large B-Cell Lymphoma (DLBCL) and the invasiveness/toxicity of CNS relapse prevention require the reliable selection of patients with a high risk of secondary CNS involvement (Fig. 1).

It is assumed that the development of molecular genetic approaches will allow improving the patient distribution into subgroups of CNS relapse risk. And understanding of the molecular genetic basis of the disease can help develop approaches for targeted tumor therapy.



The aim of the study was to identify the mutational features associated with high risk of CNS relapse in DLBCL.

Figure 1. *CNS relapse of DLBCL with damage to the subcortical structures of the left brain hemisphere*.

Methods.

High-throughput sequencing data of 1200 DLBCL from the cBioPortal for Cancer Genomics database were analyzed. DLBCL cases with (n=48) and without (n=355) CNS relapse were selected.

Results. According to the cBioPortal for Cancer Genomics database the significant differences in frequencies of MYD88 mutations and MYD88 p.L265P were detected in two clinical groups of patients: with CNS relapse and without CNS involvement (p=0.016 and p<0.001, respectively) (Tab. 1).

Table 1. *MYD88 gene mutations according to the cBioPortal for Cancer Genomics database*

Gene	CNS relapse (n=48) abs. (%)	DLBCL (n=355) abs. (%)	p-value $\chi 2$
***MYD88* mutants**	14 (29.2)	54 (15.2)	0.016
***MYD88* p.L265P**	12 (25.0)	32 (9.0)	<0.001

Thus, CNS relapse developed in 12/44 (27.3%) *MYD88* p.L265P carriers and only in 36/359 (10.0%) patients without this mutation (p<0.001). The CNS relapse risk in mutation *MYD88* p.L265P carriers was OR=3.365, 95% CI (1.59; 7.11).

The *MYD88* mutations were often combined with *PIM1* and *CD79B* genes aberrations in DLBCL with CNS relapse (Tab. 2). In total 19/48 (39.6%) of patients with CNS relapse DLBCL had the *MYD88*, *PIM1* and *CD79B* genes mutations versus 89/355 (25.1%) in DLBCL cases without CNS involvement (p=0.033).

Table 2. *MYD88, PIM1 and CD79B genes mutations combinations in DLBCL with CNS relapse according to the cBioPortal for Cancer Genomics database*

Gene 1	Gene 2	Log2 Odds Ratio	p-Value	q-Value	Tendency
MYD88	***PIM1***	>3	<0.001	0.003	Combination
MYD88	***CD79B***	>3	0.012	0.060	Combination
PIM1	***CD79B***	>3	0.019	0.064	Combination

Discussion.

Based on information presented in CBioPortal for Cancer Genomics database the DLBCL mutation profile have been analyzed. The *MYD88* L265P mutant DLBCL cases were significantly more likely to experience CNS relapse. This fact confirms the data of studies showing that in DLBCL cases with *MYD88* mutations tumor cells can penetrate and adapt to immune-privileged sites.

MYD88 is the canonical adaptor for inflammatory signaling pathways downstream of members of the Toll-like receptor and interleukin-1receptor families. Recurrent gain-of function *MYD88* L265P mutation leading to constitutive NF-kB pathway activation and imparting a proliferative and surviving advantage to cells.

The combination of mutations in the *MYD88*, *PIM1*, and *CD79B* genes is significant. The *MYD88* L265P mutation has good not only diagnostic but and therapeutic potential. The associated mutations *CD79B* and *MYD88* L265P have been shown to act synergistically. In cases with mutations in the *CD79B* and *MYD88* genes, the effective use of ibrutinib (selective Bruton-tyrosine kinase inhibitor) can be expected.