Mutation Status of *B2M* and *CD58* genes in Primary Mediastinal B-Cell Lymphoma

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Introduction

The b2m and cd58 proteins are involved in the immune recognition of tumor cells by cytotoxic T lymphocytes and NK cells. Defects in the genes encoding these proteins lead to the inability of the immune system to perform its normal protective functions. Along with other genetic abnormalities, this may play an important role in the pathogenesis of primary mediastinal large B-cell lymphoma (PMBCL).

Methods

A retrospective analysis included 49 tumor DNA samples from PMBCL patients. Mutations were determined by Sanger sequencing (n=49), analysis of STR loci closest *B2M* – by PCR and fragment analysis (n=4).

Aim

To determine the frequency of *B2M* and *CD58* mutations and their effect on disease pathogenesis and treatment response in PMBCL.

Results

B2M mutations were detected in tumor cells from 30 patients (61.2%), including obviously pathogenic variants (nonsense, frameshift, start codon alterations) in 27 cases (Figure 1). Analysis of STR showed a large-scale deletion of one allele of *B2M* in 4 patients. Figure 4 shows the results of a comprehensive study of one of these patients. Of the 13 patients for whom complete absence of normal allele was suspected, only three were diagnosed with disease progression. *CD58* mutations were detected in tumor cells from 18 patients (36.7%). In 11 cases, these were obviously pathogenic variants (Figure 1). The absence of normal allele was assumed for 5 patients, and disease progression was observed in three cases.

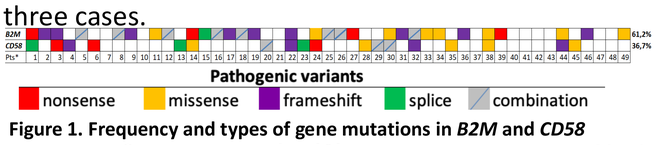


Figure 1. Frequency and types of gene mutations in *B2M* and *CD58*

There were 11 *B2M* and 4 *CD58* mutations at the ATG start codon with substitutions affecting any of its three positions (Figure 2). A similar pattern was observed for the donor splicing site of *CD58* (c.70+5G>N, n=6) (Figure 3).

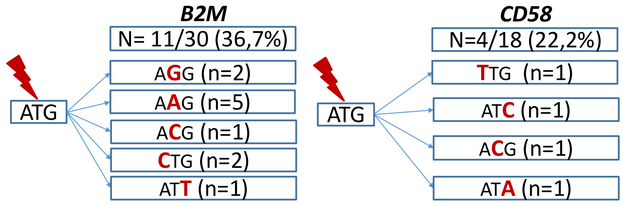
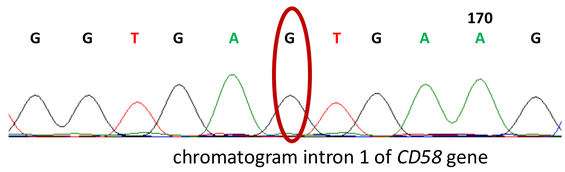


Figure 2. Mutations at the ATG start codon of *B2M*, *CD58*

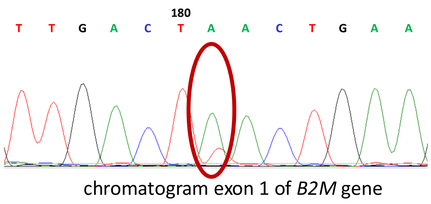
CD58 c.70+5G>N, N=6/18 (33,3%)



chromatogram intron 1 of *CD58* gene

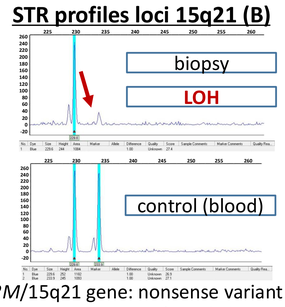
Figure 3. Mutations at the donor splicing site of *CD58*

Sanger sequencing (A)



chromatogram exon 1 of *B2M* gene

STR profiles loci 15q21 (B)



Chromosome microarray analysis (C)

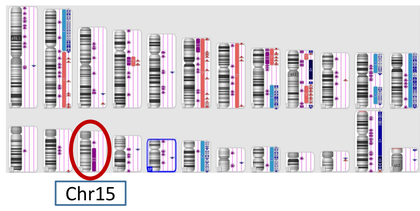


Figure 4. (A) Sanger sequencing analysis exon 1 of *B2M*/15q21 gene: nonsense variant c.176T>A (p.Leu59Ter); **(B)** STR profiles loci 15q21; **(C)** CMA result: copy-neutral loss of heterozygosity at 15q (purple bar – cnLOH; red bar – loss; blue bar – gain)

Summary

According to our (61.2% and 36.7%, respectively) and recently published data (36.4% and 36.4%, Donzel et al., 2023), mutation rates in *B2M* and *CD58* in PMBCL significantly exceed similar rates for DLBCL (8-17% for *B2M* and 4-5% for *CD58*, Cao et al., 2016; Qin et al., 2023). The high frequency of involvement of the start codons of both genes and the fifth position in intron 1 of *CD58* probably indicates the existence of a special mechanism of targeted mutagenesis *in vivo*. The absence of normal *CD58* allele should probably be considered as an unfavorable prognostic factor for patients with PMBCL.

References

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2. Cao Y. et al. Mutations or copy number losses of CD58 and TP53 genes in diffuse large B cell lymphoma are independent unfavorable prognostic factors. Oncotarget. 2016; 7(50): 83294-83307. doi: 10.18632/oncotarget.13065.
3. Qin Y. et al. Efficacy and safety of PD-1 monoclonal antibody plus rituximab in relapsed/refractory diffuse large B cell lymphoma patients. Eur J Haematol. 2023; 111(3): 356-364. doi: 10.1111/ejh.14013.