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TP53 GENE MUTATIONS IN RUSSIAN PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

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INTRODUCTION

TP53 gene mutations are involved in the pathogenesis of various human neoplasms. The role of *TP53* gene lesions is most studied for chronic lymphocytic leukemia (CLL) [1-2], while data for other lymphomas are scarce.

AIM

To study the frequency, diversity, and significance of *TP53* gene mutations in Russian patients with MCL.

METHOD

The study included 59 DNA samples from MCL patients. Patients without *TP53* mutations received treatment according to the R-BAC/R-HA+auto-HSCT regimen. For the cases with *TP53* mutations, enhanced treatment strategies (including various combinations of chemotherapy, targeted therapy, auto- and allo-HSCT, and CAR-T) were used. Mutations in the *TP53* gene (exons 4-10) were detected using NGS or Sanger sequencing [3]. The clinical significance of the detected variants was assessed using the Seshat online tool based on the UMD *TP53* Mutation Database [4].

RESULTS

TP53 gene mutations were detected in 24 patients (40%): 21 cases with missense variants (6 of them in “hotspot” positions – 4 p.R248 and 2 p.R273), 2 patients with splicing site variants, and 1 case with nonsense variant. 20 variants were identified as likely pathogenic, and 4 had unclear significance. Median event-free survival (EFS) in patients with *TP53* gene mutations was less than 10 months, while in the group without mutations, the median EFS was not reached.

In the group with *TP53* mutations, 50% of fatal outcomes were associated with disease progression and 50% with other causes. In the group without mutations, 25% of deaths were associated with treatment and disease progression and 75% with other causes. Median overall survival (OS) in patients with *TP53* mutations was 20 months, and in the group without mutations, the median OS was not reached.

exon	Variant, cDNA	Variant, protein	Signi-ficance	VAF	exon	Variant, cDNA	Variant, protein	Signi-ficance	VAF
4	c.C374G	p.T125R	path	80%	7	c.G743A*	p.R248Q*	path	>15%
5	c.A377G	p.Y126C	path	>15%	7	c.T764A	p.I255N	path	70%
5	c.G517A	p.V173M	path	14%	8	c.G811A	p.E271K	path	46%
5	c.T518G	p.V173G	path	52%	8	c.G818A*	p.R273H*	path	38%
6	c.560-2A>G	-	like path	>15%	8	c.G818A*	p.R273H*	path	8%
6	c.G638A	p.R213Q	path	25%	8	c.T831A	p.C277X	like path	84%
6	c.A641G	p.H214R	path	49%	8	c.C832T	p.P278S	path	>15%
6	c.T645G	p.S215R	path	74%	8	c.G856A	p.E286K	path	49%
6	c.672+1G>A	-	like path	58%	8	c.A860G	p.E287G	VUS	5%
7	c.C742T*	p.R248W*	path	>15%	8	c.G869A	p.R290H	VUS	4%
7	c.C742T*	p.R248W*	path	26%	8	c.C886T	p.H296Y	VUS	3%
7	c.C742T*	p.R248W*	path	>15%	9	c.A934G	p.T312A	VUS	12%

TP53 variants in Russian MCL patients (- “hotspot” variants)*

CONCLUSIONS

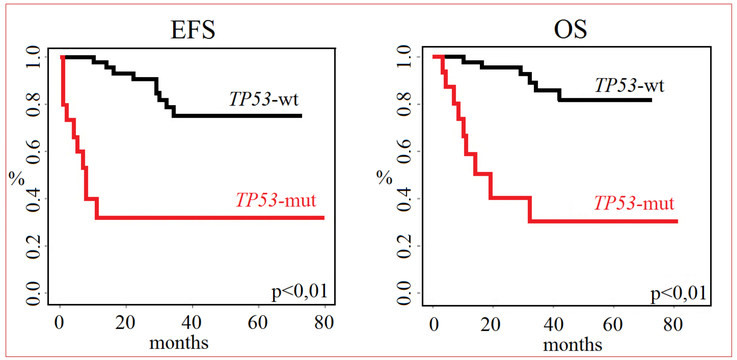
The frequency of *TP53* gene mutations in our cohort of patients with MCL was significantly higher than the mutation frequency reported for other MCL patient cohorts. One can explain this bias by patient selection. Our results show that the course of MCL in patients with *TP53* mutations is significantly worse despite enhanced treatment protocols. We are planning further correlation studies of the type of mutations, allelic load, and combinations with other chromosome 17 lesions with the disease course.

REFERENCES

1. **Malcikova J., et al.** Monoallelic and biallelic inactivation of TP53 gene in chronic lymphocytic leukemia: selection, impact on survival, and response to DNA damage. Blood. 2009; 114:5307–14.
2. **Stilgenbauer S., et al**. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014; 123:3247–54.
3. **Malcikova J., et al.** ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia—update on methodological approaches and results interpretation. Leukemia. 2018; 32:1070–1080.
4. http://vps338341.ovh.net

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Event-free and overall survival in MCL patients with or without TP53 mutations.