SOHO ANNUAL MEETING 2024

ROLE OF TP53 ALTERATIONS IN MULTIPLE MYELOMA

E. NAGY[1], D. CSABAN[2], A. KOZMA[2], T. KRAHLING[2], Z. ORFI[2], N. KONDOR[2], A. TOMAN[2], L. VARGA[2], A. BORS[2], P. REMENYI[1], G. MIKALA[1], H. ANDRIKOVICS[2]
[1]Department of Hematology and Stem Cell Transplantation, Central Hospital of Southern Pest, National Institute of Hematology and Infectious Diseases
[2]Laboratory of Molecular Genetics, Central Hospital of Southern Pest, National Institute of Hematology and Infectious Diseases

INTRODUCTION

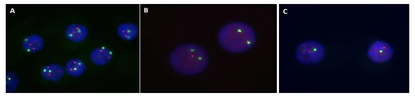
- Multiple myeloma is the second most common hematological malignancy. (1)
- Heterogeneous disease, prognosis depends on **cytogenetic abnormalities** (R2-ISS) (2, 4)
- TP53 abnormalities: **deletion of chromosome 17p** and/or **TP53 mutations** are associated with poor prognosis. (1-3)
- Based on literature data, **double hit** (heterozygous deletion and TP53 mutation) cases are associated with worse overall survival and progression free survival. (1, 3-5)

METHODS

- **Newly diagnosed** patients with MM, **2018-2023** at South Pest Central Hospital **(n=236).**
- Male/female: 134/102, first line VTD and VRD.
- Median age at diagnosis: 66,15 years.

Methods:

1. **CD138+** plasma cell selection. **(n=236)**
2. Fluorescence in situ hybridization: **del(17p) assay**, **(n=236)**, cut-off: >10% pos.

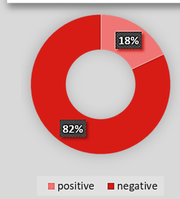


A) del(17p) negative B) del (17p) positive C) chr17del positive (17 monosomy)

3. Next Generation Sequencing: **TP53 mutation analysis**, **(n=140)** cut-off: VAF ≥ 4%.

RESULTS I

1. **Del(17p)** prevalence is higher [**18%** (43/236)] than published data (8-10%). (1, 3)

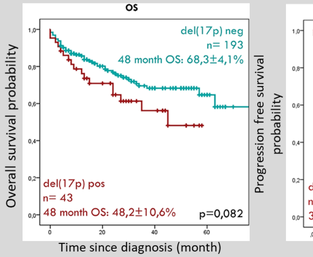


A) Del(17)p prevalence
43/236-18% positive
193/236-82% negative

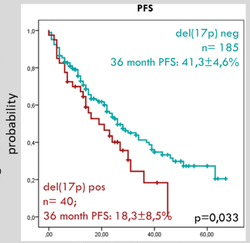
2. **Del(1p32**) is significantly more frequent in del(17p) positive patients (33%, [14/43] vs. 9%, [17/ 193] P=0.0002).

3. TP53 mutations occurred in 13% (17/128), mainly affecting the DNA Binding Domain. TP53 mutations alone occurred in 2% and the double hit cases occurrence was 10%.

4**. Del(17p) positivity** is associated with **unfavorable OS and PFS**.



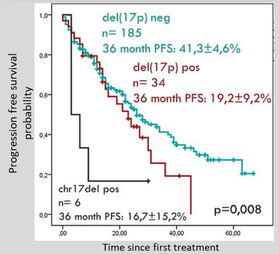
B) The effect of del(17)p on overall survival



C) The effect of del(17)p on progression-free survival

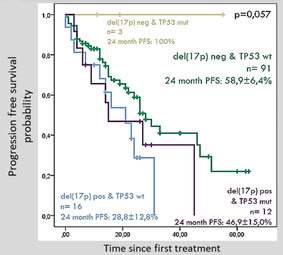
RESULTS II

5. **Chr17del (-17)** was associated with an even worse prognosis.



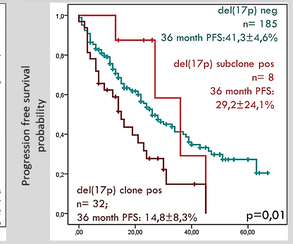
D) The effect of chr17del on progression free survival

6. **Double-hit** did not have a worse prognosis than single del(17p).



E) The effect of double-hit on progression free survival

7. **Subclonal TP53** deletion did not affect PFS and OS.



F) The effect of subclonal TP53 deletion on progression free survival

CONCLUSIONS

- The **frequency of del(17p) and TP53 mutations** in our study was **higher** than expected from the literature. (3, 4)
- Patients might be diagnosed at **later stage.**
- The **17p monosomy** may be characteristic of **hyperhaploid MM** with poor outcome.
- Low case numbers and the thresholds chosen may be responsible for the lack of prognostic relevance of subclonal and double hit cases.
- Crucial to continue to **detect TP53 mutations** using sensitive NGS technology and CNV analysis. (3, 5)

REFERENCES

1 **Sarah E. Clarke et al**. Chromosomal defects in multiple myeloma. Blood Reviews 2024; 64:101168.

2 **Kumar S. K. et al**. Current approaches to management of newly diagnosed multiple myeloma. Am J Hematol. 2022; 97:S3–S25.

3 **Martello M et al.** Clonal and subclonal TP53 molecular impairment is associated with prognosis and progression in multiple myeloma. Blood Cancer Journal 2022; 12:15.

4 **Liu E. et al.** Identifying novel mechanisms of biallelic TP53 loss refines poor outcome for patients with multiple myeloma. Blood Cancer Journal 2023; 13:144.

5 **Raimondi V et al**. A personalized molecular approach in multiple myeloma: the possible use of RAF/RAS/MEK/ERK and BCL-2 inhibitors. Explor Target Antitumor Ther. 2022; 3:463–79.

ACKNOWLEDGEMENTS

The presenter would like to thank the members of the Molecular Genetics Laboratory and the Hematology Department in the Central Hospital of Southern Pest.

CONTACT INFORMATION

Eszter Nagy MD - nagy.eszter@dpckorhaz.hu