Abstract: P578

Title: MUTATIONAL PATTERNS AND CLONAL HIERARCHY IN 430 PATIENTS WITH IDH1 MUTATED AML INDICATE PRACTICAL IMPLICATIONS FOR MOLECULAR TESTING AND TARGETED TREATMENT

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Clinical

Background:

Somatic mutations of isocitrate dehydrogenase 1 (*IDH1*) are found in 8-10% of patients with AML and alter the enzymatic function of IDH1 leading to the production of the oncometabolite 2-hydroxyglutarate which affects genome wide methylation patterns. The selective and orally available mutant IDH1 inhibitor ivosidenib is approved for combination treatment together with azacitidine in patients with newly diagnosed *IDH1* mutated AML that are not eligible for induction chemotherapy.

Aims:

Evaluate the pattern of co-mutations in a large cohort of*IDH1* mutated AML to decipher clonal hierarchies and evolution.

Methods:

4113 AML patients with a median age of 70 years and a female rate of 44% were examined including 422 patients with a documented history of MDS or MDS/MPN. Bone marrow samples were analyzed by cytomorphology, immunophenotyping, cytogenetics, and panel sequencing of 18 genes including *IDH1* with a limit of detection of 3% variant allele fraction (VAF). Patients were diagnosed according to the 5th edition of the WHO classification of 2022, and the results were stratified by age group (<65, 65-75, and >75 years).

Results:

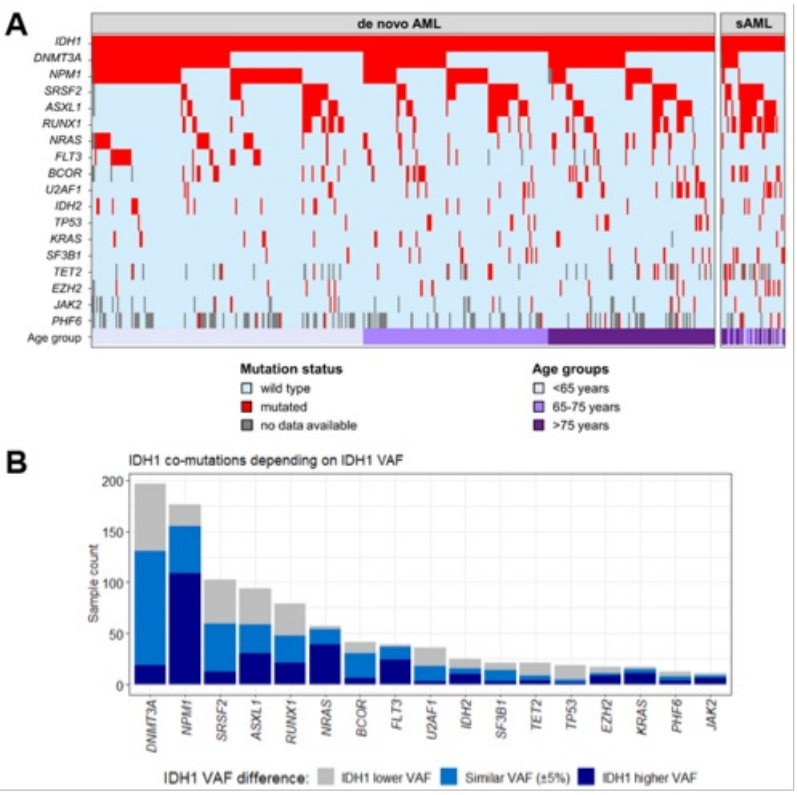
In total, 10.5% (430/4113) of patients harbored an*IDH1* mutation (10.6% in de novo AML; 9.5% in patients with a documented history of MDS or MDS/MPN). While the total frequency of *IDH1* mutations was rather consistent between age groups (range 8.4-11.6%), a trend towards higher frequency of p.Arg132Cys (39% to 66%) and lower frequency of p.Arg132His (45% to 20%) was observed in elderly patients. The most frequent co-mutations in a total of 430 cases with *IDH1* mutated AML were *DNMT3A* (46%) and *NPM1* (41%) followed by *SRSF2* (24%), *ASXL1* (22%), *RUNX1* (19%), *NRAS* (13%), and *FLT3* (9%). The co-mutational pattern clearly differed by age with a decrease of *NPM1*, *FLT3*, and *IDH2* mutations, and an increase of mutations in splicing factor genes and *TP53* in elderly patients (Figure 1A). According to WHO 2022 45% of*IDH1* mutated cases were classified as AML with defining genetic aberrations (90% AML with *NPM1* mutation), 45% as myelodysplasia related AML, and 10% as AML defined by differentiation.

When the clonal hierarchies were analyzed, the VAF of*IDH1* in individual patients was mainly similar or higher compared to *NPM1* and *FLT3* whereas a subclonal VAF of*IDH1* was typically observed in *TP53* mutated AML (Figure 1B). From a subset of 53 patients with *IDH1* mutated AML, a sample at relapse after therapy (not including ivosidenib containing treatment regiments) was analyzed. The *IDH1* mutation was present in only 51% but absent in 49% of patients at relapse. Patients with persistence of *IDH1* mutation at relapse showed a significantly higher VAF of the mutation at diagnosis compared to patients with loss of the mutation at relapse (median VAF 37.6% vs. 28.9%).

Summary/Conclusion:

The analysis of a very large real life cohort of AML including frail patients confirms a frequency of ~10% *IDH1* mutations. The trend towards lower fraction of p.Arg132His in elderly patients suggests further mechanistic studies. The co-mutational pattern and the underlying clonal hierarchy suggest that *IDH1* mutations are

present in the founder clone in some but not all patients. The loss of *IDH1* mutations at relapse in 50% of patients warrants a genetic re-analysis before considering targeted therapy at relapse. Both findings, relative *IDH1* clone size as well as loss of *IDH1* in relapse, have potential implications for targeted treatment decisions. Detailed analysis of molecular relapse patterns of *IDH1* mutated AML after treatment with ivosidenib or venetoclax containing treatment regiments is indicated.



Keywords: Clonality, AML, Ivosidenib