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ACUTE MYELOID LEUKEMIA WITH MUTATIONS IN EPIGENETIC MODIFIERS: KEY CHARACTERISTICS AND PROGNOSIS

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INTRODUCTION

The disruption in epigenetic regulation plays a critical role in AML pathogenesis. Nevertheless, **prognostic significance** of ***DNMT3A, IDH1/2*** **and** ***ASXL1*** mutations in predicting patient outcomes **remains controversial**, particularly when they interact with other molecular anomalies.

AIM

To determine the **characteristics and prognosis** of newly diagnosed **AML with mutations in epigenetic modifiers**.

DESIGN

We analysed the retrospective cohort:

- 147 patients (74 males and 73 females);
- Median age of 51 years.

Inclusion criteria:

- Patients with newly diagnosed AML who fulfill the WHO criteria;
- Age >18 years;
- Molecular genetic tests were performed to detect *DNMT3A, IDH1/2* and *ASXL1* mutations before initiating antileukemic therapy.

Exclusion criteria:

- Patients with APL (FAB M3);
- Relapsed AML.

✓ All patients received standard, high, or low-intensity chemotherapy.

✓ Mutations in *IDH1* (R132), *IDH2* (R140/R172), *DNMT3A* (R882) and *ASXL1* (exon12) were checked using droplet digital PCR and Sanger sequencing on whole-genome DNA.

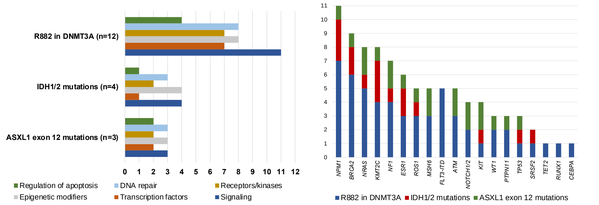
✓ Among them with mutations in epigenetic modifiers we performed NGS to investigate concomitant genetic abnormalities.

RESULTS

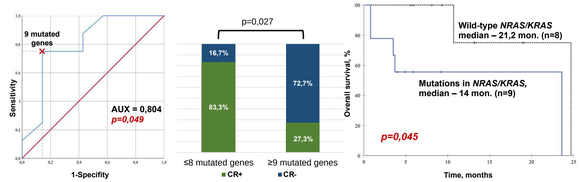
Characteristics of AML with mutations in epigenetic regulators

- **Overall frequency** of mutations in *DNMT3A/IDH1/IDH2/ASXL1* was **35,4%** (n=52): *IDH1*-R140 - 9,6%, *IDH2*-R132 - 6,1%, *DNMT3A*-R882 - 17,7%, *ASXL1* (exon 12) - 9,6%
- **Mutation in *DNMT3A*** was associated with higher blasts in bone marrow (78% vs. 56%, p=0.048) and mutations in *NPM1* (40,6% vs. 13%, p=0.002).
- **Patients with *IDH1/2* mutations** tended to have normal karyotype (26,8% vs. 7,5%, p=0,009), lower neutrophils count (median 0,5x10^9/l vs. 2,4x10^9/l, p=0.008), higher platelets (median 83x10^9/l vs. 45x10^9/l, p=0.006), losing of CD34 (54,1% vs. 30,1%, p=0.025), mutations in *NPM1* (31,3% vs. 11,7%, p=0.015) and in *DNMT3A* (30,8% vs. 12,4%, p=0.02).
- **Exon 12 mutations in *ASXL1*** were related to CD56 expression (63,6% vs. 23,4%, p=0.005), worse OS in patients with *NPM1* mutations (0,8 mon. vs. 23.2 mon., p=0.036), and lower complete remission rates (CRR) in patients with t(8;21)(q22;q22) (50% vs. 94,7%, p=0.01).

Molecular landscape of AML with mutations in epigenetic regulators

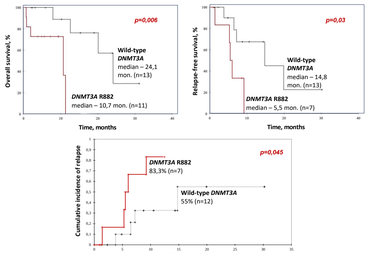


NF-1, NRAS/KRAS mutations led to inferior outcomes when accompanied by mutations in epigenetic modifiers (median OS – 14 mon. vs. 21,1 mon., p=0.045 and CRR – 40% vs. 87,5%, p=0.021).



DNMT3A, ASXL1, IDH1/2 mutations: prognostic impact

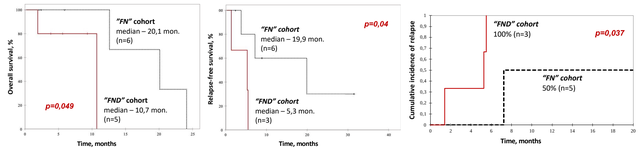
***DNMT3A*-R882** mutation **predicted worse prognosis** in case of cooperations with **normal karyotype** (OS – 11,3 mon. vs. 24,1mon., p=0.048), ***NPM1* mutations** (OS – 10,7 mon. vs. 24,1 mon., p=0,006; RFS – 5,5 mon. vs. 14,8 mon., p=0.03; CIR – 83,3% vs. 55%, p=0.045)., ***FLT3*-ITD mutation** (CIR – 100% vs. 60,8%, p=0.036).



Patients with NPM1-mutated AML

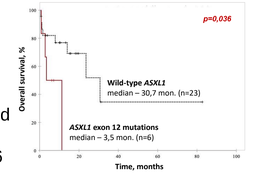
Patients with **three mutations** (*FLT3*-ITD+*NPM1*+*DNMT3A* - ***"FND"***) had significantly **inferior OS** (10,7 mon. vs. 20,1 mon., p=0.049), **RFS** (5,3 mon. vs. 19,9 mon., p=0.04) and **higher CIR** (100% vs. 50%, p=0.037) **in comparison with those without *DNMT3A*-R882 mutation.**

In multivariate analysis *"FND"* combination was independently associated with **worse OS** (HR 4,21, p=0.038) and **RFS** (HR 14,1, p=0.001) along with detection of unfavorable chromosomal aberrations (HR 3,22, p=0.022 and HR 3,753, p=0.047 respectively).

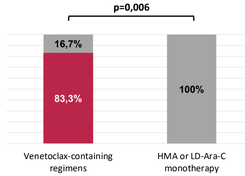


**cohort «FND»* – patients with *FLT3*-ITD mutation, mutated *NPM1* and mutation R882 in *DNMT3A*
**cohort «FN»* – patients with *FLT3*-ITD mutation, mutated *NPM1* but with wild-type *DNMT3A*

ASXL1* mutations** were associated with a **lower CRR** (50% vs. 94,7%, p=0,01) and **inferior OS** (3,5 mon. vs. 30,7 mon., p=0,036) among patients classified as ***ELN Favorable, and with **inferior OS among *NPM1*-mutated AML** (0,8 mon. vs. 23,6 mon., p=0,034).



Favorable genetic category (ELN-2022)



Patients with mutations in *IDH1/2* or *DNMT3A*, who were not suitable candidates for intensive treatment, experienced **improved rates of achieving CR** when they received venetoclax-containing low-intensity induction regimens (100% vs. 83,3%, p=0,006).

CONCLUSION

✓ Mutations in *DNMT3A, IDH1/2* and *ASXL1* associate with certain hematological and genetic features.

✓ These mutations don't possess independent prognostic value by themselves, but can predict negative outcomes within specific patient cohorts.

✓ Triple-mutated status (***"FND" cohort***) determines really bad prognosis with low overall survival, relapse-free survival and high cumulative incidence of relapse.

CONTACT INFORMATION

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