SOHO ANNUAL MEETING 2024

MOLECULAR-GENETIC PROFILING OF *NPM1*-MUTATED ACUTE MYELOID LEUKEMIA AND ITS PROGNOSTIC VALUE

E. Motyko[1], A. Kirienko[1], D. Kustova[1], T. Gert[1], I. Leppyanen[1], A. Radjabova[1], E. Karyagina[2], E. Ukrainchenko[3], I. Zyuzgin[4], S. Sidorkevich[1], I. Martynkevich[1]

[1]Russian Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [2]Municipal Clinical Hospital No. 15, St. Petersburg, Russia; [3]St. Petersburg State Budgetary Healthcare Institution "Alexandrovskaya Hospital", St. Petersburg, Russia; [4]NMRC of Oncology named after N.N.Petrov of MoH of Russia, St. Petersburg, Russia

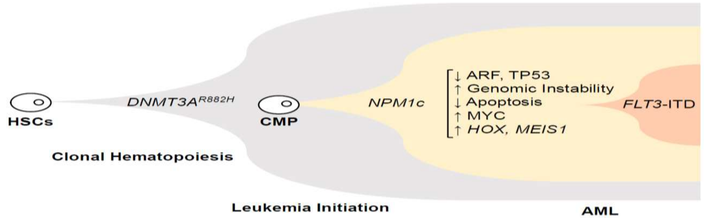
ФГБУ РосНИИГТ ФМБА России

ЦЕНТР КЛЕТОЧНОЙ И МОЛЕКУЛЯРНОЙ ПАТОЛОГИИ ФГБУ РНИИГТ

INTRODUCTION

Nucleophosmin (*NPM1*) is a multifunctional protein with both proliferative and growth suppressive roles in the cell. In humans, *NPM1* is involved in tumorigenesis via chromosomal translocations, deletions, or mutation. Acute myeloid leukemia (AML) with mutated *NPM1*, a distinct diagnostic entity by the current WHO Classification of myeloid neoplasm, represents the most common diagnostic subtype in AML and is associated with a favorable prognosis. Despite this, 30–50% of them experience relapse, and the factors that drive relapse are still not fully understood.

***NPM1* gene mutations in tumor transformation**



AIM

To analyze the genomic heterogeneity of AML with *NPM1* mutations using NGS and assess the impact of the most frequent aberrations on prognosis.

METHOD

40 *NPM1*+ AML patients: all patients with de novo AML

13 (32.5%) males and 27 (67.5%) females, median age 56 years (18-69)

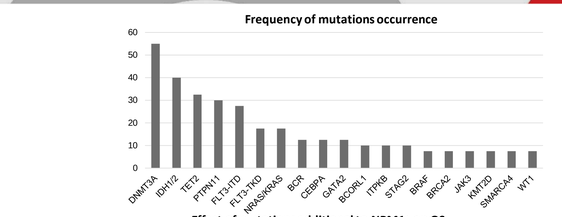
Cytogenetic study: normal karyotype was observed in all patients at the debut of AML

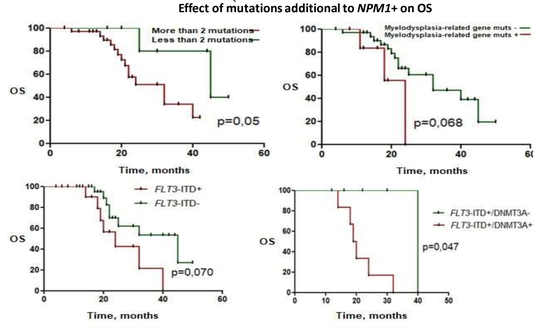
Samples were analyzed by high-throughput sequencing using a custom panel consisting of 118 genes.

RESULTS

All patients (40/40, 100%) had at least one mutation in addition to mutations in *NPM1*, with an average of 5 mutations per patient (1-9). The most frequently mutated genes were *DNMT3A* (55.0%), *IDH1/2* (40.0%), *TET2* (32.5%), *FLT3*-ITD (27.5%), *PTPN11*(30%), *FLT3*-TKD(17.5%), *N/KRAS* (17.5%), *RYR1* and *GATA2* (12.5%). Patients with *FLT3*-ITD mutations had a 5-year overall survival (OS) of 34%, compared to patients without *FLT3*-ITD, 55% (p=0.001). We found a trend toward lower OS in patients with *DNMT3A* R882 mutations (p=0.153). We identified a small group of patients who lived more than 5 years after the diagnosis of AML, where there was a trend toward a decreased presence of myelodysplasia-related gene mutations (p=0.211).

In the group of 29 patients without *FLT3*-ITD 14 patients (48.3%) had relapse after consolidation chemotherapy. We compared mutations at diagnosis and relapse in 10 patients - only 2 patients relapsed with exactly the same mutations. Mutations in *FLT3* and *IDH1/2* were both acquired and lost at relapse. Mutations in *NRAS* were more frequently lost at relapse. Various cytogenetic abnormalities were acquired at relapse (4/10,40%). The mean number of mutations at diagnosis in relapse group was 5.5, compared to 3.9 in patients without relapse (p = 0.041). Patients with *NPM1/DNMT3A/IDH1/2*mut combination showed a trend toward lower OS (p=0.09).

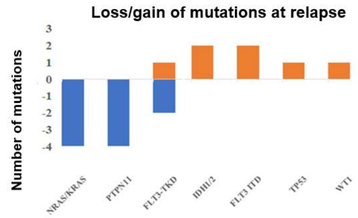


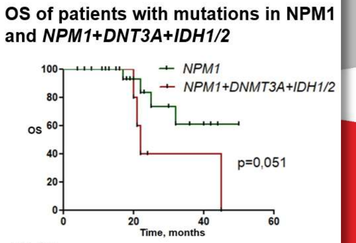


Characteristics of patients from the group *NPM1+/FLT3*-ITD- AML

Number of patients with *NPM1+/FLT3*-ITD- AML: 29

	Relapse (n=14)	No relapse (n=15)	p
Median age	56 (28-69)	57 (18-65)	>0,05
WBC (x 109/l)	53,7	31,2	<0,05
Gender male/female	5/9	5/10	>0,05
Number of mutations additional to NPM1 at disease debut	6,5	3	<0,05





Cytogenetic aberrations in relapse: t(3;4), t(5;12), t(6;19)

CONCLUSIONS

1. AML with mutations in *NPM1* gene represents a large genetic subgroup of AML and is characterized by significant heterogeneity.
2. In addition to mutations in *NPM1* gene, mutations in genes of epigenetic regulators and genes that activate intracellular signaling pathways are the most common.
3. High allele ratio of mutations in *NPM1* gene in the disease debut, presence of more than 2 additional mutations, mutations associated with myelodysplasia, *FLT3*-ITD+ and *FLT3*-ITD+/DNMT3A+ mutations significantly reduce the OS of *NPM1*+AML patients.
4. In the *FLT3*-ITD-/NPM1+AML group, high mutational ratio, leukocytosis and *NPM1*+/DNMT3A+/IDH1/2+ combination negatively affect patient survival.
5. The use of NGS method allows the most complete characterization of individual molecular nature for patients from the favorable prognostic group of *NPM1*+AML, identification of additional risk factors and selection of effective therapy.

REFERENCES

Zarka J, Short NJ, Kanagal-Shamanna R, Issa GC. Nucleophosmin 1 Mutations in Acute Myeloid Leukemia. Genes (Basel). 2020 Jun 12;11(6):649.

Falini B, Brunetti L, Sportoletti P, Martelli MP. NPM1-mutated acute myeloid leukemia: from bench to bedside. Blood. 2020 Oct 8;136(15):1707-1721.

CONTACT INFORMATION

Ekaterina Motyko PhD

katteerina@mail.ru