USE OF NGS TECHNOLOGY IN DETERMINING THE PROGNOSIS OF AML FROM THE FAVORABLE RISK GROUP

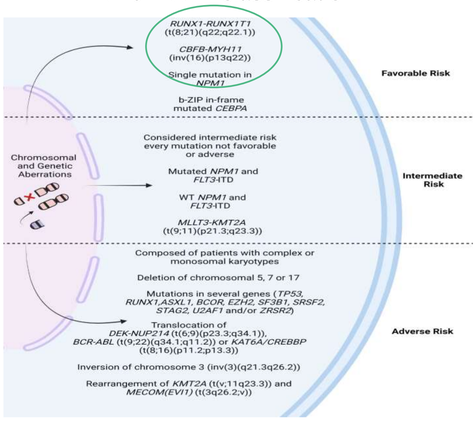
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Introduction

CBF and *NPM1*+ AML are categorized into a favorable-risk group according international classifications. However, certain patients who achieve CR eventually relapse or even die, suggesting clinical and biological heterogeneity. A more thorough genomic landscape study is required to select a therapeutic benefit.

ELN 2022 AML classification



Aim

Using high-throughput sequencing to identify factors of unfavorable course of the disease in patients from the favorable-risk AML.

Methods

86 patients with *CBF* (46pts) and *NPM1*+AML (40pts) were included in the analysis. Sequencing was performed on an Illumina platform (Illumina, US) with an average coverage depth of 2000

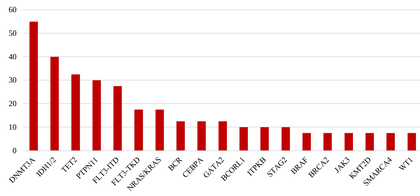
Custom gene NGS panel

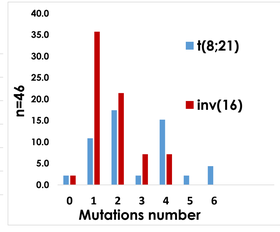
ABL1, AKT3, ALK, APC, ARID1A, ATM, ATRX, ASXL1, B2M, BCL2, BCOR, BCORL1, BCR, BIRC3, BRCA1, BRCA2, BRAF, BTK, CALR, CARD11, CBL, CCND1, CD79B, CD58, CDKN2A, CDX2, CEBPA, CIITA, CREBBP, CSF3R, CUX1, DDX3X, DEK, DIS3, DNMT3A, EP300, ETV6, EZH2, FAM46C, FAT1, FLT3, GATA1, GATA2, GNA13, GNAS, FBXW7, HIST1H1A, HRAS, ID3, IDH1, IDH2, IRF4, IKZF1, IKZF3, ITPKB, JAK2, JAK3, KDM6A, KDR, KIT, KLF2, KMT2A, KMT2C, KMT2D, KRAS, MAP2K1, MEF2B, MGA, MPL, MSN, MYC, MYD88, NF1, NOTCH1, NOTCH2, NPM1, NRAS, PDGFRA, PHF6, PIK3CB, PIM1, PLCG2, POT1, PRDM1, PTCH1, PTEN, PTPN11, PTPRD, RAD21, RB1, RHOA, RPS15, RUNX1, RYR1, SAMHD1, SETBP1, SF3B1, SH2B3, SMARCA4, SMC1A, SMC3, SOCS1, SRSF2, STAG2, STAT3, STAT6, SUZ12, SYK, TET2, TNFAIP3, TP53, U2AF1, WHSC1, WT1, XPO1, ZRSR2

Results

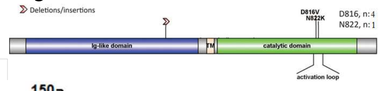
Patients with *CBF*-AML had a highly heterogeneous molecular genetic profile (at least 1 mutation was detected in 96%). The presence in 2 groups of *CBF*-AML - with t(8;21) and inv(16) their characteristic genetic features (the majority of patients with t(8;21) (74%) in contrast to AML with inv(16) (33%) had additional chromosomal aberrations (p=0.01); patients with t(8;21) had significantly more mutations than those with inv(16) (p=0.03); difference in morphology) made it reasonable to analyze them separately. The most frequent molecular events in both *CBF*-AML groups were mutations in *N/KRAS*, *KIT* and *FLT3* genes. Mutations in genes that activate signaling pathways negatively affected the relapse-free survival of *CBF*-AML patients. In addition to mutations in *NPM1* gene, mutations in genes of epigenetic regulators and genes activating intracellular signaling pathways were the most frequent. High allele ratio of mutations in *NPM1* gene (more than 43%) in the disease debut, presence of more than 2 additional mutations, myelodysplasia-associated mutations, *FLT3*-ITD and *FLT3*-ITD/*DNMT3A* mutations significantly reduced overall survival of *NPM1*+AML patients (p less than 0.05). In the *FLT3*-ITD-/*NPM1*+AML group leukocytosis and *NPM1*+/*DNMT3A*+/*IDH1/2*+ combination negatively affected patient survival.

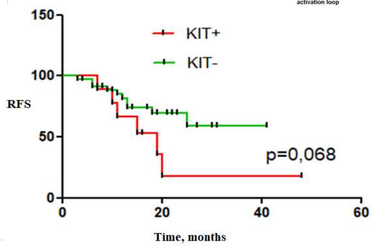
Frequency of mutations in *CBF*-AML



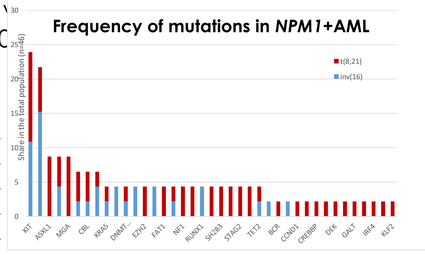


Prognostic significance of *KIT* mutations in *CBF*-AML

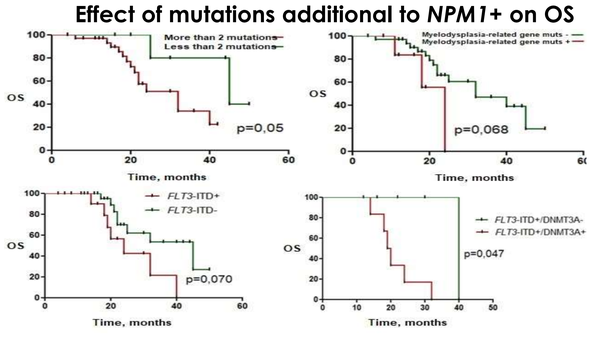




Frequency of mutations in *NPM1*+AML



Effect of mutations additional to *NPM1*+ on OS



References

Falini B, BNPM1-mutatedrunetti L, Sportoletti P, Martelli MP. acute myeloid leukemia: from bench to bedside. Blood. 2020 Oct 8;136(15):1707-1721.

Paschka P, Döhner K. Core-binding factor acute myeloid leukemia: can we improve on HiDAC consolidation? Hematology Am Soc Hematol Educ Program. 2013;2013:209-19.

Summary

The use of NGS method makes it possible to obtain a complete characterization of the mutational profile of the patient, which is critical for patients from the favorable group of AML, given the high frequency of mutations in them, their significant impact on the prognosis and the emergence of effective targeted therapy.