Abstract: PB1770

Title: CHARACTERIZATION OF THE MUTATIONAL PROFILE OF PATIENTS WITH CBF-AML - HETEROGENEITY AND IMPACT ON THE PROGNOSIS

Abstract Type: Publication Only

Session Title: Acute myeloid leukemia - Biology & Translational Research

Background:

Core-binding factor (CBF) acute myeloid leukemia (AML) encompasses AML with inv(16) and t(8;21). Despite sharing a common pathogenic mechanism involving rearrangements of the CBF transcriptional complex, there is growing evidence for considerable genotypic heterogeneity.

Aims:

To analyze the genomic heterogeneity of CBF-AML using NGS and assess the impact of the most frequent aberrations on prognosis.

Methods:

The study included 46 CBF-AML pts - 22 pts with inv(16) and 24 pts with t(8;21). Samples were analyzed by high-throughput sequencing on MiSeq platform (Illumina, USA). A panel consisting of 118 genes was developed based on literature data.

Results:

97 mutations were found in 48 of 118 target genes: 60 mutations in AML pts with t(8;21) and 37 mutations in those with inv(16). In 21 genes, mutations were detected repeatedly (≥2 times). At least 1 mutation was detected in 95.8% of pts with t(8;21) and 95.5% of pts with inv(16). On average, significantly more mutations were found in AML pts with t(8;21) than in AML pts with inv(16), 2.6 versus 1.9 mutations, respectively (p=0.04). In AML pts with t(8;21), 41 different genes were mutated; with inv(16), 19 genes contained mutations. Of the 48 affected genes, mutations in 12 genes were common in both CBF-AML subgroups, whereas pts with t(8;21) had a higher proportion of private mutations (70.7% (29) versus 36.8% (7), respectively). Mutations in RTK/RAS signaling pathways were the most common events in the two types of CBF-AML, with the highest incidence in *NRAS+KRAS* (26.1%; t(8;21), 12.5%; inv(16), 40.9%), *KIT* (19.6%; t(8;21), 20.8%; inv(16), 18.2%) and *FLT3* (4.3%; t(8;21), 0%; inv(16), 9.1%).

Characterization of the molecular genetic profile of pts with t(8;21) AML: mutations in epigenetic regulation genes *ASXL1* (16.7%) and *EZH2* (4.2%), DNA methylation - *DNMT3A* (4.2%), cohesion complex - *RAD21* (8.3%) and SMC3 (8.3%), *MGA* (16.7%), involved in *MYC* signaling pathway, *SH2B3* (8.3%), *SETBP1* (8.3%) that were absent in AML with inv(16) were found. Molecular genetic profile of pts with inv(16) AML: aberrations of genes involved in chromatin modification were rare events (in the *ASXL1* gene - 0%), as were mutations related to the cohesion complex, which were absent in all cases. A mutation in the transcriptional corepressor *BCORL1* was detected in one pnt.

Approximately half (45.7%) of pts with CBF-AML had mutations in genes that activate signaling pathways, and the prognostic significance of such mutations was examined (Fig.1). A significant increase in the risk of relapse was found in pts with these mutations compared to pts without them (p=0.046). Pts with mutations in *KIT* gene had a significantly worse recurrence-free survival rate than pts without the mutation (p=0.031).

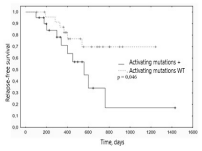

Fig. 1. RFS of CBF-AML pts with and without mutations in genes that activate signaling pathways

Summary/Conclusion:

Patients with CBF-AML have a highly heterogeneous molecular genetic profile. Two CBF-AML groups hold their own unique genetic features, what makes it appropriate to analyze them separately in the research. The most frequent molecular events in CBF-AML are mutations in *N/KRAS, KIT* and *FLT3* genes, which activate intracellular signaling pathways involving tyrosine kinases. Mutations in *KIT* gene and other mutations in genes involved in the activation of signaling pathways negatively affect the relapse-free survival of pts with CBF-AML. The use of the latest molecular genetic technologies, such as NGS, makes it possible to obtain a detailed characterization of the mutational profile for each pt, which is critical for CBF-AML pts, given the high frequency of mutations in them and the development of effective targeted therapy.

Keywords: Mutation analysis, Core binding factor leukemia, Prognosis