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The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Genomic Characterization of Newly Diagnosed Acute Myeloid Leukemia in Patients Age 60 Years and Older; A Report from the Beat AML Master Trial

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Background. Acute myeloid leukemia (AML) is a heterogenous disease that occurs primarily in older adults with a median age of 69 years at diagnosis. Most studies that characterize the genomic landscape of AML include younger adults with the majority of patients being younger than 60 years of age. We aimed to study the mutational landscape of newly diagnosed AML patients aged 60 years or older.
Methods.Samples were collected from the multi-center Beat AML Master Trial (Burd, Nat Med 2020). Patients were enrolled between 2016 and 2023. Informed consent was obtained according to the *Declaration of Helsinki*. Patients diagnosed with non-APL AML and who were aged ≥ 60 years old were included. Patients underwent bone marrow aspiration and biopsy, cytogenetic analysis, *FLT3-ITD* ratio assessment (LeukoStrat CDx *FLT3* Mutation Assay, Invivoscribe) and next generation sequencing (NGS) using FoundationOne®Heme(Foundation Medicine) to interrogate the entire coding region of 406 genes and select introns of 31 genes involved in rearrangements, as well as RNA sequencing to interrogate 265 genes known to be somatically altered in human hematological malignancies. The presence of multiple hotspot mutations within one gene in an individual patient was counted as one gene mutation. Patterns of co-occurrence between gene mutations were calculated using the Phi correlation coefficient. Statistical analyses were performed using R statistical software. $P<0.01$ was considered statistically significant.
Results. A total of 1088 newly diagnosed AML patients were identified, of whom 1032 were 60 years or older. Patients had a median age of 72 years at time of diagnosis (range 60-92 years). Forty-two percent of the patients were female, most patients were non-Hispanic and 79% were Caucasian. NGS data were available for 1024 patients and mutations were identified in 461 different genes. Patients had a median number of 11.0 mutations (range 3.0 to 28.0). The most frequently mutated genes were *DNMT3A* (n=257; 25.1%), *TP53*(n=255; 24.9%), *TET2* (n=243; 23.7%), *RUNX1* (n=225; 22.0%), *SRSF2* (n=221; 21.6%), *ASXL1* (n=216; 21.1%), *NPM1* (n=206; 20.1%), *FLT3* (n=205; 20.0%), *IDH2* (n=190; 18.6%), *NRAS* (n=208; 16.9%), *PTPN11*(n=104; 10.2%), *STAG2* (n=101, 9.9% and *IDH1* (n=99; 9.7%) (Figure 1A). *FLT3-ITD* was present in 98 (12.1%) of the 810 patients who were tested. Strongest significant co-occurrence was found between *FLT3*and *NPM1* (n=103), *STAG2* and *ASXL1* (n=63), *ASXL1* and *RUNX1* (n=92), *ASXL1* and *SRSF2* (n=88), *RUNX1* and *SRSF2* (n=94), *STAG2* and *SRSF2* (n=51) and *DNMT3A* and *NPM1* (n=92) ($p<0.01$). Pairwise negative correlations were observed between *TP53* and *NPM1* (n=6), *TP53* and *SRSF2* (n=17), and between *NPM1* and *RUNX1* (n=6) ($p<0.01$) (Figure 1B). The cytogenetic profiles and the full genomic landscape will be presented during the ASH meeting.
Discussion. This is the largest study investigating the mutational profile in older adults with AML aged 60 years and older. Due to the 7-day screening period of the Beat AML study, patient selection was biased towards less-rapidly proliferative AML. We showed that the pattern of gene mutations was markedly different from other studies in AML that mainly included younger AML patients (Papaemmanuil, NEJM 2016; TCGA, NEJM 2013). The frequency of mutated *TP53* was substantially higher in older AML patients, as was the occurrence of myelodysplasia-related gene mutations (e.g., *SRSF2*, *RUNX1*, ASXL1, *STAG2*, *U2AF1*, and *SF3B1)* and gene mutations in *IDH1*, *IDH2* and *TET2*. In contrast, *NPM1* mutation was less frequently mutated in older AML patients. Furthermore, we demonstrated that a large proportion (46%) of the AML patients older than 60 years of age do have a mutation that is potentially targetable for treatment (*FLT3 IDH1 IDH2* and *NPM1*). The high incidence of mutated *TP53* and MDS-related gene mutations underscores the increased incidence of high-risk AML and the need for innovative personalized therapies in this older age group.
Figure 1. A. Co-occurrence of the 15 most frequently mutated genes, and B. co-correlation between the 15 most frequently mutated genes. Blue indicates positive correlation, red indicated negative correlation. Only significant correlations ($p<0.01$) are shown.

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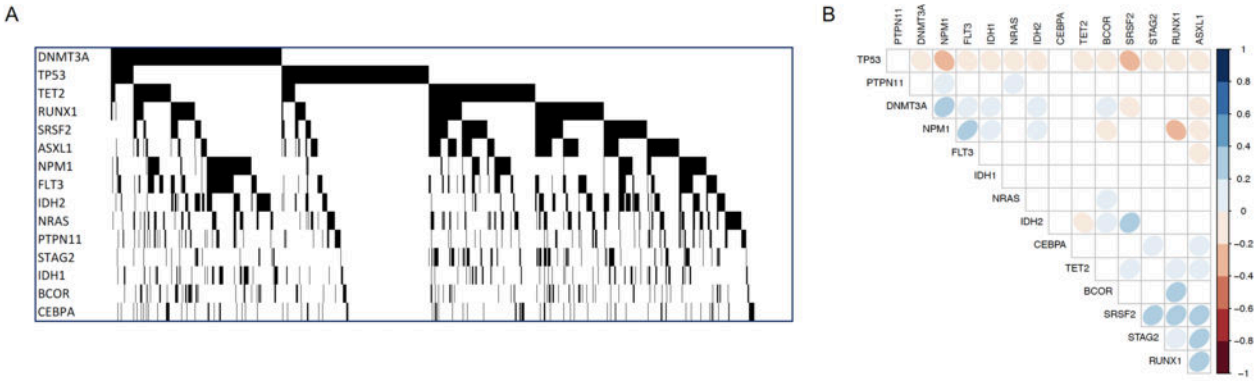

Figure 1

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