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POSTER ABSTRACTS

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

Prognostic Value of Copy Number Aberrations and Copy Neutral Loss of Heterozygosity in Acute Myeloid Leukemia

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Background:
Chromosomal abnormalities are key to the diagnosis and prognosis of patients with acute myeloid leukemia (AML). Chromosomal genomic array testing (CGAT) can identify copy neutral loss of heterozygosity (cnLOH) and genomic copy number alterations (CNAs) that are undetected by conventional karyotype or fluorescence in situ hybridization (FISH). Previous studies have shown that cnLOH is correlated with a shorter duration of complete remission (CR) and worse overall survival (OS) in AML (Grosneth et. al, Cancer, 2015). The primary objective of this exploratory study is to examine the predictive power of CGAT in a cohort of AML patients with majority normal karyotype.
Methods:
CGAT analyses were collected from 187 subjects with AML or other high grade myeloid neoplasm (myeloid blasts >10% in peripheral blood or bone marrow) between 2012 and 2022 at Fred Hutchinson Cancer Center. CGAT utilized CytoScan™ HD Array (ThermoFisher, MA), targeting genome-wide region with 2.4 million markers for copy number and approximately 750,000 genotype-able SNPs. The data were analyzed using the Nexus Copy Number software with manual curation. Based on the assay validation in our CLIA-certified diagnostic lab, the cutoff is 100 Kb for copy number aberrations and 10 Mb for cnLOH.
Survival predictive power analysis (SPP), a log-rank based test using Nexus, was applied to identify aberrations significant for event free survival (EFS) and overall survival (OS). SPP analysis tabulated genomic segments based on p-values with the alpha value cutoff at 0.05. Using frequency as the filtering criteria (present in >5 patients), 132 SPP for EFS, and 73 SPP for OS were identified. SPP were then manually curated to (1) remove those representing constitutional absence of heterozygosity (AOH) and those overlapping with benign copy number variance and (2) connect adjacent SPP into contiguous regions. The presence and absence of the identified SPP were then tabulated, cleaned up, and used to generate Kaplan-Meier curves for EFS and OS. This process identified 5 SPP that are significant for EFS and 2 SPP for OS. A multivariate analysis was performed to determine the hazard ratio (HR) of these 5 genetic aberrations for EFS and OS, adjusted for patient age, secondary/treatment related AML, ELN 2022 risk, and receipt of allogeneic hematopoietic cell transplantation (HCT) as a time-varying covariate.
Results:
In our 187 subject cohort, the median age was 63 (range 20-87). 76 (41%) had secondary or treatment related disease. 97 (52%) went on to receive a hematopoietic stem cell transplant. 3 had favorable risk disease, 14 had adverse risk, and 170 had intermediate risk by karyotype and FISH using ELN 2022 criteria. 120 (64%) had normal karyotype. 5 subjects had 4q cnLOH, 6 had 5q (*EGR1*) loss, 7 had 9p cnLOH, 10 had mixed-lineage leukemia gene partial tandem duplication (*MLL-PTD*), and 4 had 7q deletion.
Univariate analysis identified five SPP that are significant for EFS: 4q cnLOH (p=0.002), 5q (*EGR1*) loss (p<0.001), 9p cnLOH (p<0.001), *MLL-PTD* (p<0.001), and 7q deletion (p<0.001). 2 SPP were significant for OS: 9p cnLOH (p=0.001) and *MLL-PTD* (p=0.036).
Multivariate analysis for EFS adjusted for age, secondary/treatment related disease, ELN 2022 risk, and receipt of HCT as a time-varying covariate demonstrated a hazard ratio (HR) of 3.5 for 4q cnLOH (p=0.008), 2.3 for 5q (*EGR1*) loss (p=0.16), 4.5 for 7q deletion (p=0.007), 5.7 for 9p cnLOH (p<0.001), and 2.9 for *MLL-PTD* (p=0.002). Multivariate analysis for OS adjusted for age, secondary/treatment related disease, ELN 2022 risk, and receipt of HCT as a time-varying covariate demonstrated a

hazard ratio (HR) of 2.0 for 4q cnLOH (p=0.23), 0.5 for 5q (*EGR1*) loss (p=0.36), 1.3 for 7q deletion (p=0.66), 4.9 for 9p cnLOH (p=0.001), and 2.3 for *MLL-PTD* (p=0.04).

Discussion:

This study has found 5 key genetic changes identifiable via CGAT that are significant for shorter EFS and/or OS in AML patients. Our next step is to validate these findings in a large independent cohort of AML patients. CGAT is a powerful adjunct to conventional karyotype and FISH for the detection of cnLOH and can be used to identify CNAs below the level of detection of karyotype. For these reasons, CGAT may be most useful in intermediate risk patients. Further research is warranted to fully understand the prognostic power of CGAT in AML.

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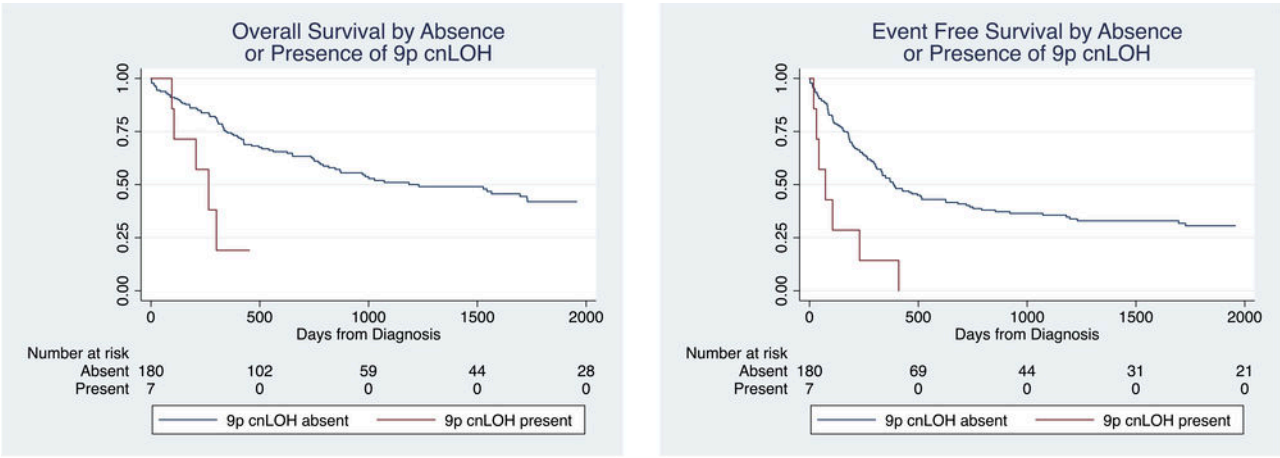

Figure 1

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