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POSTER ABSTRACTS

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

A Pro-Inflammatory Gene Signature Characterizes a Better Risk Aged AML Patient Group in ECOG-ACRIN Cancer Research Group's Clinical Trial E3999

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Background: Acute myeloid leukemia in patients over the age of 60 (aAML) is associated with poor prognosis. aAML patients are the majority diagnosed but are underrepresented in large molecular studies. We have identified two clinical subgroups of aAML patients with distinct survival outcomes (low-risk and high-risk) in ECOG-ACRIN Cancer Research Group's clinical trial E3999 (NCT00046930). We hypothesize that these two groups are characterized by distinct biological mechanisms that contribute to leukemogenesis. We also hypothesize that the low-risk group harbor molecular and phenotypic signatures characteristic of known better-risk AMLs.
Methods: Diagnostic specimens were obtained from patients enrolled in NCT00046930. Disease enriched cells were isolated by negative selection of lymphocytes (magnetic beads). Flow cytometry was used to characterize the blast population. Bulk RNA-sequencing was performed on 220 blast enriched samples and 10 age matched normal controls (CD34+ bone marrow cells). Transcriptional differences were determined using DESeq2. Differentially expressed genes (DEGs) were identified as those with an absolute log2 fold change greater than 1 and q less than 0.05. Gene set enrichment analysis (GSEA) was performed against the MSigDB databases. Upstream regulators associated with gene expression changes were identified using Ingenuity Pathway Analysis (IPA). DESeq2 was used to identify genes that were differentially associated with overall survival times between the risk groups. Enrichment for transcription factor gene targets was calculated using EnrichR based on the CHEA Transcription Factor Target Dataset. Cytokines were quantified in a subset of patient serum samples using a Luminex assay.

Results: We identified 2314 DEGs between the low-risk and high-risk aAMLs with high-risk as the baseline. The upregulated genes in the low-risk aAMLs were positively enriched for gene signatures derived from: 1. Favorable risk AML (*NPM1* mutated), 2. M4 and M5 AML patients, 3. Differentiated hematopoietic cells and 4. Inflammatory response pathways. On the contrary, upregulated genes in the high-risk aAMLs were enriched for gene signatures identified in hematopoietic and leukemic stem cells and known poor-risk AMLs (for example: *EVI1* fusion). Accordingly, immunophenotypic data from flow cytometry results gated on the blast populations validated differences in the surface expression of hematopoietic cell markers between the two groups. Next, we sought to determine upstream regulators associated with the DEGs using IPA. We identified 107 potential upstream regulators that associated with the changes in gene expression observed between the low- and high-risk groups (87 activated and 20 inhibited). The results suggested that several pro-inflammatory cytokines (ex. tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ)) were predicted activators in the low-risk aAML group. Accordingly, we detected significantly higher levels of TNFα and IFNγ in the serum levels of a subset of low-risk aAML patients. Finally, we assessed for genes whose expression significantly associated with overall survival. Interestingly, in agreement with a previously proposed inflammation score (iScore), we identified higher iScore associated with the high-risk group. Of note, the upstream regulators identified do not overlap with those contributing to the calculation of iScore. Additionally, longer overall survival times were associated with higher levels of expression of genes associated with heme metabolism and erythroblast differentiation in the low-risk aAML patient group.
Conclusions: Our results suggest that the low-risk aAML patients were characterized by a more mature hematopoietic cell gene expression signature and cell surface markers as well as a pro-inflammatory state. Our study supports the possibility that pro-inflammatory cytokines and/or signaling could mediate AML cell survival in the low-risk aAML patient group. The high-risk aAML patients were characterized by a more primitive hematopoietic and leukemic stem cell gene expression signature. Collectively, we propose that differences in the underlying molecular and/or immune-based mechanisms could contribute to leukemogenesis in the two risk groups. These findings suggest that distinct therapeutic approaches may need to be considered to improve clinical outcomes in the two aAML risk groups.

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