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613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Correlation between Number of Molecular Mutations and Outcomes in De Novo Acute Myeloid Leukemia

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Introduction

Genomic sequencing of cancer has led to a deeper genetic understanding of the pathogenesis of acute myeloid leukemia (AML). Studies in myelodysplastic syndrome have shown that as the number of oncogenic mutations increases, patient outcomes progressively worsen. We hypothesized that patients with AML may also have a worse prognosis if they have a higher number of somatic mutations. To test this hypothesis, we examined the somatic mutational profile of 225 patients with previously untreated AML.

Methods

A single-center retrospective analysis was done utilizing the Kentucky Cancer Registry (KCR) and evaluated patients with de novo AML diagnosed between January 2015 to January 2021. Patient characteristics, cytogenetics, and molecular data were collected by chart review. Patients with available cytogenetic and somatic mutations profile from next-generation sequencing (NGS) were included. Clinically significant (CS) mutations for AML were detected by NGS performed on the diagnostic bone marrow specimen. The list of clinically significant mutations was obtained from My Cancer Genome and was compared to the mutations present in our patients. Statistical analysis was done using the Mann-Whitney U test for continuous variables and proportions were compared using Chi-square test. Overall survival (OS) was calculated by the Kaplan-Meier method and compared using a log-rank test. P value was considered significant if < 0.05.

Results

A total of 225 De Novo AML patients met inclusion criteria. The median age at diagnosis was 61 (range, 21-86). The population was fairly distributed among males (52%) and females (48%). Approximately 51% (n=115) of patients had 0-2 CS mutations, 43% (n=97) had 3-5 mutations, and 6 % (n=13) had > 5 CS mutations. The median number of CS mutations for the entire cohort was 2 (range: 0-9). Survival was worse in the group with >5 mutations when compared to those with 5 or less mutations (23 vs 7 months, p= 0.012, Figure 1). When analyzing the number of CS mutations per cytogenetic group, those with intermediate risk cytogenetics had a higher median number of CS mutations compared to the favorable and adverse risk group combined (3 versus 1, p < 0.001). In patients with > 5 CS mutations, 11/13 had a mutation associated with an adverse prognosis. To determine whether overall survival was impacted by the presence of an adverse mutation, a subgroup analysis was done using 43 patients with a normal karyotype and at least 1 adverse mutation. The cohort with > 5 CS mutations had a significantly shorter OS compared to patients with $\leq$ 5 CS mutations (43 vs 9 months, p= 0.001, Figure 2).

Conclusion

In summary, we found that patients with intermediate-risk cytogenetics have a high number of CS mutations. When patients were stratified by number of mutations, we found that a higher number of mutations (>5) led to statistically significant difference in survival compared to those with $\leq$5 mutations. To determine whether this difference in survival was a result of the presence of adverse risk mutations vs. number of mutations alone, we analyzed our patients who had normal karyotype with at least one adverse genetic mutation and stratified them based on number of mutations. The presence of more than 5 CS mutations was associated with a worse OS compared to $\leq$ 5 mutations. It appears that the number of clinically significant mutations may be an independent predictor of overall survival in AML. This can serve as another tool in stratifying AML risk with normal karyotype. This finding will need to be validated in a large prospective clinical trial.

Disclosures Monohan: *Johnson and Johnson:* Current equity holder in publicly-traded company; *Novartis:* Current equity holder in publicly-traded company; *Quest Diagnostics:* Current equity holder in publicly-traded company; *Dupont:* Current equity holder in publicly-traded company; *Pfizer:* Current equity holder in publicly-traded company. **Yalniz:** *Legend biotech:* Ended employment in the past 24 months.
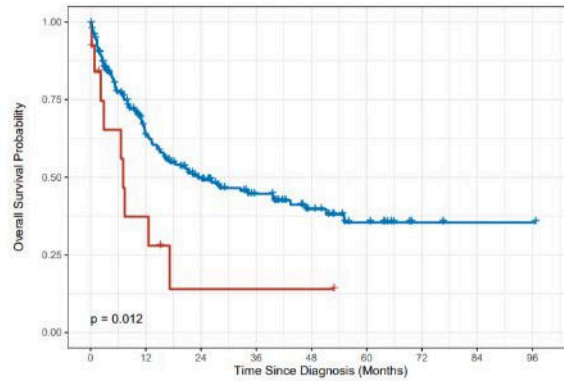

Figure 1: OS for patients divided amongst low (0-5) versus high (>5) CS mutations detected
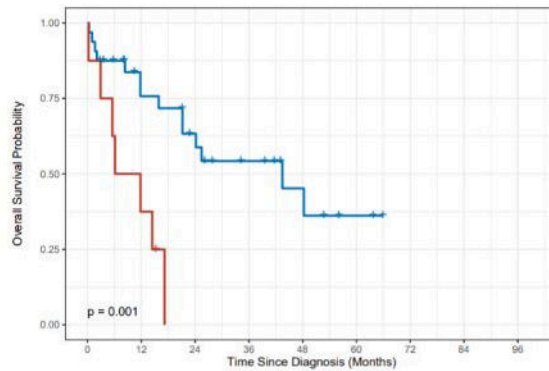

Figure 2. OS for patients in subset of patients with normal karyotype divided amongst low (0-5) vs high CS (>5) mutations detected.

Figure 1

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