S131 CLINICAL IMPLICATIONS OF SECONDARY-AML TYPE MUTATIONS IN PATIENTS WITH DE NOVO ACUTE MYELOID LEUKEMIA

Topic: 04. Acute myeloid leukemia - Clinical

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Background:

More and more gene mutations have been identified in patients with de novo acute myeloid leukemia (AML). Among them, a set of gene mutations, including SRSF2, ZRSR2, SF3B1, U2AF1, ASXL1, EZH2, STAG2, and BCOR mutation, are categorized as secondary AML (sAML)-type mutations, for their distinct distribution in secondary AML, compared to primary AML (Lindsley et al, Blood 2015), but the reports regarding the prognostic impact have been scanty, especially in younger patients.

Aims:

In this study, we aimed to explore the clinical significance and prognostic implication of sAML-type mutations in non-M3 AML patients.

Methods:

We consecutively enrolled 921 de novo non-M3 AML patients; 368 were 60 years or older (older patients) and 553 were younger. Patients with an antecedent history of hematologic diseases, or therapy-related AML were excluded. sAML-type mutations were identified by targeted next-generation sequencing of 54 myeloid malignancies related gene mutations.

Results:

A total of 243 (26.4%) patients harbored sAML-type mutations (ST group), 40.2% in older patients and 17.2% in younger ones. Patients in the ST group were significantly older, had a lower WBC count, peripheral blast count and lactate dehydrogenase level at diagnosis. sAML-type mutations were negatively correlated with inv(16), monosomy 17, and complex karyotype, but positively associated with 2017 European LeukemiaNet (ELN)-defined unfavorable-risk genetic category.

Among the patients receiving standard chemotherapy (n=686, 74.5%), the ST group had a significantly lower CR rate (62.9% vs. 81.5%, P<0.01), especially among younger patients (70.8% vs. 86.7%, P<0.01), but only a trend in older patients (49.0% vs. 59.6, P=0.17). With a median follow-up of 4.7 years, patients in the ST group had a shorter overall survival (OS, median, 2.1 years vs. not reached, P<0.01) and disease-free survival (DFS, median, 0.4 years vs. 0.9 years, P<0.01) than the non-ST group. Subgroup analyses showed that sAML-type mutations conferred a significantly poorer DFS (median, 0 years vs. 0.5, P=0.03) and a trend of shorter OS (0.8 years vs. 1.1 years, P=0.08) in older patients, and a significantly worse OS (not reached vs. not reached, P=0.03) and a trend of shorter DFS (0.7 years vs. 1.0 years, P=0.16) in younger patients. The numbers of sAML-type mutations had prognostic impacts on both OS (median, 5.8 years vs. 1.5 vs. 1.3 for patients with 0, 1, and ≥2 mutations, respectively, P<0.01) and DFS (median, 0.9 years vs. 0.6 vs 0 for those with 0, 1, and ≥2 mutations, respectively, P<0.01). Intriguingly, these
findings were valid among both the younger and older patients. Furthermore, the ELN-defined intermediate-risk patients with sAML-type mutations had similar poor OS and DFS to the ELN unfavorable-risk patients in total cohort (Figure 1), as well as in the older and younger patients. Among the patients with sAML-type mutations, allogeneic hematopoietic stem cell transplantation did improve their outcome (median OS 3.0 vs. 0.8 years, P< 0.01).

Image:
A. Overall survival

B. Disease-free survival

Summary/Conclusion:

AML patients with sAML-type mutations had distinct clinical features and poorer outcomes. Incorporating sAML-type mutations can further refine the 2017 ELN risk stratification. It is suggested that AML patients with sAML-type mutations receive more intensive treatment, such as allo-HSCT, and/or novel therapies.