S130 NPM1 MUTATED AML: IMPACT OF CO-MUTATIONAL PATTERNS - RESULTS OF THE EUROPEAN HARMONY ALLIANCE

Topic: Acute myeloid leukemia - Clinical


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Background:

Acute myeloid leukemia (AML) is a heterogeneous disease in terms of clinical features, outcomes and genetics. While mutations of NPM1 are usually considered as a favorable prognostic marker, the vast majority of the patients carry several co-mutations that might influence the prognosis. Therefore, a better understanding of the NPM1mut AML mutational landscape is warranted. The large cohort of AML patients collected within the European HARMONY Alliance provides an excellent basis for this purpose.

Aims:

To identify clinically significant co-mutational patterns in NPM1mut AML in order to establish a revised risk stratification model.

Methods:

From the HARMONY Alliance AML database, a total of 1001 NPM1mut intensively treated patients were selected. Clinically significant co-mutations were evaluated using graphical patterns created with the Gephi tool and confirmed by detailed survival analysis using Kaplan-Meier and Cox regression models. Finally, a novel multi-state risk stratification model for NPM1mut AML was established.

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Results:

The study population of 1001 NPM1mut AML patients included 57% females and median age was 53 years. Regarding ELN2017 classification, 68% of patients were classified into the favorable, 29% intermediate and 3% adverse risk groups. The most frequent co-mutations were DNMT3A (54%), followed by FLT3-ITD (38%). In total, 24% of patients presented with a high allelic mutant-to-wildtype ratio ≥0.5 (FLT3-ITDhigh) while 14% had low allelic ratio <0.5 (FLT3-ITDlow). Other frequent co-mutations were NRAS (21%), TET2 (20%) and PTPN11 (15%).

The triple mutation pattern of NPM1mut + FLT3-ITDhigh + DNMT3Amut identified a subgroup with adverse prognosis (2-year OS of 25%), similar to NPM1mut + TP53mut. The combination of FLT3-ITDlow + DNMT3Amut or FLT3-ITDhigh + DNMT3Awt was associated with intermediate prognosis (2-year OS of 45% and 53% respectively). Notably, mutations of NRAS, KRAS, PTPN11 or RAD21 were identified to be associated with better OS. However, in the context of NPM1mut + DNMT3Amut these mutations did not affect the prognosis when a FLT3-ITD was present. This information is summarized in a 3-category risk classification model (Figure 1).

The revised NPM1mut favorable group presented with a 2-year OS of 73%, while for intermediate and adverse groups the OS was 54% and 27% respectively (p<0.001). Regarding relapse free survival (RFS), the median was not reached in the favorable group, while it was 23 months for intermediate and 6 months for adverse group (p<0.001). It should be noted that 171 patients in the NPM1mut intermediate group would be considered as favorable according to the ELN2017 criteria, as well as 162 patients in the NPM1mut adverse group were previously classified as intermediate risk. Therefore, our model was able to reclassify 33% of NPM1mut AML patients in comparison to ELN2017 criteria.

Multivariate analysis of OS in NPM1mut AML identified the following independent prognostic factors: NPM1mut model (taking favorable group as reference, HR 1.6 for intermediate and HR 2.7 for adverse group, p<0.001); secondary or therapy-related AML (HR 1.8, p<0.001), WBC at diagnosis >100x10³/μL (HR 1.5, p<0.001) and age >60 years (HR 1.4, p<0.001).

Image:
Summary/Conclusion:

Analysis of large NPM1mut AML cohorts allows the discovery of co-mutation patterns associated with prognostic outcome. In accordance, we propose a new genetic stratification model for NPM1mut AML that identifies 3 groups with different OS and RFS. This model improves ELN2017 criteria as it is able to correctly reclassify 33% of NPM1mut AML patients.