Abstract: S140

Title: LLS 2024 ELN-REFINED RISK STRATIFICATION IN OLDER ADULTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA TREATED WITH LOW-INTENSITY THERAPY

Abstract Type: Oral Presentation

Session Title: Acute myeloid leukemia - Clinical 3

Background:

Acute myeloid leukemia (AML) is a heterogeneous disease of older adults with a median age of 69 yrs. In 2022, European LeukemiaNet (ELN) provided updated recommendations to risk stratify patients with AML. While these have been proven to be effective in predicting outcome for patients treated with intensive chemotherapy (IC) and/or patients <60 yrs, it is unclear whether this risk assignment schema applies to adults ≥60 yrs treated with lower-intensity treatment (LIT).

Aims:

To validate the prognostic impact of the 2022 ELN risk stratification in patients ≥60 yrs with newly diagnosed (ND) AML treated with LIT and to refine this risk stratification system using a large cohort of those treated on a Leukemia and Lymphoma Society-sponsored (LLS) trial.

Methods:

Patients ≥60 yrs with ND AML who were enrolled in the Beat AML trial (NCT03013998) before May 10, 2023 were included. Cytogenetic analysis, *FLT3-ITD* ratio assessment (LeukoStrat CDx *FLT3* Mutation Assay, Invivoscribe) and next generation sequencing (FoundationOne®Heme) were obtained. Overall survival (OS) was estimated using the Kaplan-Meier method. Cox proportional hazard models were used to describe the relative risk of each variable on death over time. Statistical analyses were performed using R statistical software.

Results:

A total of 1028 patients with ND AML were included. 2022 ELN risk was available for 940 patients. 2022 ELN risk was favorable, intermediate, or adverse in 14.9% (N=140), 11.6% (N=109) and 73.5% (N=691) of the patients, respectively. Patients were treated with LIT (N=584), IC (N=132), supportive care (N=59) or unknown (N=165). For patients who received LIT, 2022 ELN risk stratification reliably assigned those with poor OS to adverse risk (P<0.001; N=460/584, 79%) but did not distinctly stratify favorable- from intermediate-risk (P=0.22) (Figure 1A).

We reconsidered the impact of molecular abnormalities to refine our ability to risk stratify ND AML patients >60 yrs receiving LIT, focusing first on those categorized as adverse risk by ELN 2022 (N=460). Multivariable analysis was performed on a training set (N=303) that incorporated mutation and cytogenetic data. Among patients currently assigned adverse-risk by ELN 2022, we identified *IDH2* mutation as an independent favorable prognostic variable, and *KRAS, MLL2* and *TP53* mutations as independent unfavorable prognostic variables (P<0.05). A negative point was assigned to *IDH2*, and +1 to each of *KRAS*, *MLL2*, or *TP53*. A "mutation score" was calculated for each combination of mutations assigning patients into two risk groups: ≤0 points ("LLS-intermediate") vs ≥1 points ("LLS-adverse"). A validation cohort analysis was performed (N=157) resulting in a significant prognostic separation (P=0.004). Considering the entire cohort of LIT patients, we further reclassified those who were assigned ELN 2022 "favorable-risk" (N=58) and "intermediate-risk" (N=66) now grouped together as "LLS-favorable risk" (N=124), resulting in a refined risk model (18-month OS 57% vs 40% vs 19%, respectively; P<0.001) (Figure 1B).

Summary/Conclusion:

Among patients ≥60 yrs with ND AML given LIT, the current 2022 ELN risk system classifies most (79%)

patients as adverse risk and does not reliably distinguish favorable from intermediate-risk, highlighting the limitations of the model in this patient population. We propose a refined LLS classification using a "mutation score" incorporating *IDH2*, *MLL2*, *KRAS* and *TP53* mutations for those previously assigned ELN 2022 adverse risk, as well as redefining the definition of LLS-favorable risk.

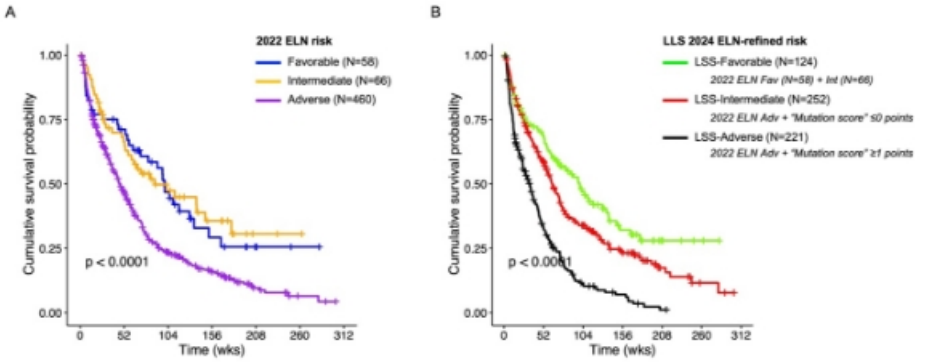

Figure 1. LLS 2024 ELN-refined risk model. A. 2022 ELN in ND AML patients age ≥60 years who are treated with lower-intensity treatment. B. LSS risk model refines 2022 ELN for older adults treated with lower-intensity chemotherapy.

Keywords: Risk-adapted, AML