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Abstract Title : Inferior survival in black AML patients treated with intensive chemotherapy in ECOG-ACRIN clinical trials is independent of cytogenetic profiles

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Abstract Body

Background: Population registries and the Alliance co-operative group database have highlighted racial disparities in AML survival attributed to differential prevalence and impact of oncogenic drivers on disease biology. However, the small number of Black patients with well-annotated genomic profiles limits the validity of these findings. The current study leverages ECOG-ACRIN cytogenetic and outcomes data from newly diagnosed adult AML patients treated on intensive chemotherapy-based clinical trials over three decades.

Methods: Self-reported race was categorized as White, Black or Other. Descriptive statistics were used to summarize baseline characteristics using the Wilcoxon rank-sum and Fisher's exact tests. Multivariable Cox proportional hazards regression models evaluated the association between race and survival outcomes adjusting for age, hemoglobin, platelet count, white blood cell count, blast percentage, performance status and ELN cytogenetic risk score (RS). All Cox models were stratified by protocol. Subgroup analyses of overall survival (OS) and disease-free survival (DFS) were performed using Kaplan-Meier curves stratified by race using log-rank tests. All statistical tests were two-sided. Analyses included only patients with complete data for the variables of interest.

Results: Data was collected across 10 phase II and III interventional trials for newly diagnosed adult AML that accrued patients between 1984 and 2019. The study population included 3469 White, 184 Black, and 156 Other patients with a Black representation of 1.1-11% across trials. Blacks were significantly younger at diagnosis with a median age of 47.9 years compared to 53.5 years in Whites ($p<0.001$). Racial groups were well matched for gender and performance status.

Black race was an independent prognostic factor for inferior OS (HR 1.212, CI 1.01 – 1.453; $p = 0.0383$) and DFS (HR 1.313, CI 1.05-1.641; $p = 0.017$). Complete cytogenetic results were available for 117 Black and 2162 White patients and revealed no significant racial differences in the distribution of ELN 2017 cytogenetic RS, although core binding factor AML was non-significantly enriched in Black patients (12.8% vs 8.3%). No difference was observed between Blacks and Whites in the prevalence of complex karyotype (CK), CK with -5/del(5q), -7/del(7q), or -17/del(17p), and AML-MRC including +8 and del(20q).

Notably, the ELN 2017 cytogenetic RS effectively predicted OS in Black (57.8 vs 14.2 vs 5.8 months in

favorable, intermediate and adverse RS, p = 0.018), and White patients (60.1 vs 15.2 vs 7.1 months, p < 0.0004 for Whites) but only predicted DFS for White AML patients (p < 0.0001 for Whites, p=0.48 for Blacks). In patients with molecular data for *FLT3*-ITD (n=1218), *CEBPA* (n=576), *TP53* (n=572), or *NPM1*(n=683), no racial difference in the prevalence of these mutations was observed. However, *NPM1* mutations were associated with inferior OS in Blacks compared to Whites (19.1 vs 8.9 months; p = 0.0095).

Black and White AML patients had similar responses with complete remission rates of 58.2% vs 57.5%, p=0.55, and treatment tolerability with 30-day mortality of 7.1% vs 8.9%, p=0.50. However, consolidation approaches differed significantly. Among patients that underwent stem cell transplant (SCT), a significantly higher percentage of White patients received allogenic SCT compared to Blacks (48.5% versus 37.1%, p <0.01).

Conclusions: This study represents one of the largest race-based comparisons of cytogenetic abnormalities and clinical outcomes in prospective trials of intensive chemotherapy in AML . Our data confirms the independent prognostic relevance of race in AML survival and validates the predictive ability of the ELN 2017 cytogenetic RS for OS across racial groups. There is ancestry-based attenuation of the survival benefit of *NPM1* mutations as previously reported, underscoring the need to tailor the current treatment approach to *NPM1* mutated AML based on race. The availability of NGS data limited the genomic analysis to a subset of patients. Future studies should examine the depth of treatment response incorporating MRD biomarkers and explore the effect of race on co-occurring mutations and the leukemic stem cell transcriptome to better explain the observed disparities. Finally, persistent disparities in access to allo-SCT even within the context of clinical trials reinforces the need to address diversity in the stem cell donor pool and social barriers to transplant.

Keywords: Clinical Research, Study Population, Myeloid Malignancies, Diseases, Research

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