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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Next Generation Sequencing and Cytogenetics in Acute Myeloid Leukemia - Therapeutic and Prognostic Impact: A Retrospective Cohort from a Private Centre of Reference in Latin America

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Introduction: Acute Myeloid Leukemia (AML) is a prevalent and severe hematological disorder. The emergence of Next-Generation Sequencing (NGS) and karyotiping, has demonstrated associations between chromosomal abnormalities and mutations with worse treatment response and mortality in AML. Current classification of AML is based on its cytogenetic and molecular profile, as defined by World Health Organization (WHO) 2022 and European Leukemia Net (ELN) 2022. Despite its evident importance in AML, application of these diagnostic methods poses new challenges. In Latin America, particularly, there is a clear limitation of data and studies regarding molecular and cytogenetic analysis in AML patients, due to the relatively short time these techniques have been employed and the few accredited centers able to perform them. Therefore, this study primarily aims to provide an in-depth evaluation of the application of NGS and cytogenetic analysis in AML, identifying the impact of somatic mutations on AML mortality and progression free-survival based on the experience of a reference center in Latin America. Secondarily, we aim to determine the molecular and cytogenetic profile of these population and analyze the impact of age, sex and comorbidities in AML prognosis.
Methods: This is an unicentric, retrospective and non-interventional cohort performed in Brazilian Hospital Albert Einstein. Inclusion criteria were adult patients (aged ≥18 years) diagnosed with AML between May 2017 and August 2022, who underwent myeloid panel testing through NGS and cytogenetic evaluation at diagnosis. Independent variables analyzed were age, gender, prognostic risk according to ELN 2022, indication of bone marrow transplantation and molecular and cytogenetic risk at diagnosis. High cytogenetic risk was defined by the presence of at least one of the high-risk karyotype abnormalities described in ELN 2022 and high-risk NGS was defined by mutation in the genes ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, U2AF1, ZRSR2, TP53 or FLT3. The primary outcomes evaluated were overall survival (OS) and progression-free-survival (PFS), estimated by the Kaplan-Meier method. Secondary outcomes were disease relapse and non-relapse-related mortality (NRM).
Results: From a total of 168 selected patients, 64 filled out elegibility criteria and were included in the study. Mean age at diagnosis was 62,7 years old with a equal proportion of both sexes. 7 patients (10,9%) were classified as favourable risk according to ELN 2022, 13 (20,3%) as intermediate risk and 44 (68,8%) as high risk. 42 (65,6%) had a standard-risk karyotype, whereas high-risk karyotype was found in 22 (34,4%) patients. 47 (73,4%) individuals presented high-risk NGS mutations, with a higher prevalence of gene rearrangements in RUNX1 (20,1%), FLT3 (18,7%), TP53 (15,6%) and SRSF2 (15,6%). Only 17 (26,6%) patients reported exclusively standard-risk or no mutations. After a median follow-up was 26 months, estimated OS was 73% in 1 year and 54% in 2 years. 1 and 2 years PFS was 63% and 45%, respectively. 11% relapsed after 1 year and 27% after 2 years. The incidence of NRM was 25% and 28% after 1 and 2 years, respectively. High-risk karyotype was associated with a signficant reduction in overall survival (hazard ratio [HR] 2,27, 95% CI 1,09-4,70; p=0·028) and progression-free-survival (HR 2,15, 95% CI 1,23-4,11; p=0·02). On the other hand, there was no statistically significant association between high molecular

risk by NGS and OS (HR 1.45, 95% CI 0.59-3.58; p=0.41) or PFS (HR 1.43, 95% CI 0.65-3.13; p=0.37). Progressive age has discreetly impacted in OS (HR 1,05, 95% CI 1,02-1,08; p=00005), PFS (HR 1,03, 95% CI 1-1,05; p=0,025) and NRM (HR 1,06, 95% CI 1,02-1,11; p=0,002). No differences in outcomes were found between sex, ELN 2022 risk groups, and treatment with bone marrow transplantation.

Conclusions: Next-Generation Sequencing, combined with cytogenetic analysis, has improved precision in prognosis prediction of AML patients of each patient, allowing safe implementation of appropriate individualized therapy. This study showed and association between high-risk cytogenetics and worse prognosis in AML, but no association was observed between molecular risk and AML morbimortality. Further studies with a bigger population and longer follow-up should be conducted in Latin America in order to better clarify and delve deeper into the results reported in this cohort.

Disclosures No relevant conflicts of interest to declare.

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