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Acute Leukemias

PROGNOSTIC IMPACT OF EXTENDED MOLECULAR CHARACTERIZATION BY NEXT-GENERATION SEQUENCING IN INTERMEDIATE RISK ACUTE MYELOID LEUKEMIA TREATED WITH INTENSIVE INDUCTION CHEMIOTERAPY: A RETROSPECTIVE MONOCENTRIC STUDY

F. Campagna[1], T. Liani[2], C. Callegari[1], M. Moro[2], C. Cozzarolo[1], S. Di Giusto[1], C. Filì[1], D. Lazzarotto[1], M. Fanin[1], G. Battaglia[1], R. Fanin[1|2], E. Toffoletti[1|2], M. Tiribelli[1|2]

[1]Division of Hematology and Bone Marrow Transplantation, Azienda Sanitaria Universitaria Friuli Centrale; [2]Department of Medicine, DMED, University of Udine.

Introduction: Acute myeloid leukemia (AML) is a heterogeneous disease with marked genetic and molecular variability. The intermediate-risk (IR) group often shows myelopoiesis-related gene mutations now included in the ELN2022 classification. This study retrospectively evaluated the prognostic impact of the molecular profile, analyzed through next-generation sequencing (NGS) in AML patients initially classified as IR by clinical and cytogenetic criteria, without extended mutational analysis. We also assessed outcome differences according to intensive induction chemotherapy regimens.

Methods: We included all AML cases classified as IR according to the diagnostic criteria in use at the time of diagnosis, treated with intensive induction chemotherapy at the Division of Hematology of Udine between 2010 and 2024. For all patients with available biological samples at diagnosis, we performed NGS mutational analysis using a 30 gene panel, to allow a retrospective prognostic re-stratification. Out of 106 patients, 94 (89%) underwent extended molecular analysis. The majority, 67 (63%), received FLAI (fludarabine, idarubicin, and cytarabine), 20 (19%) CPX-351 (liposomal encapsulation of daunorubicin and cytarabine) and 19 (18%) 3+7 (cytarabine and daunorubicin) in combination with gemtuzumab ozogamicin (GO) or midostaurin (MIDO). Overall, 66 patients (62%) underwent allogeneic stem cell transplantation as consolidation.

Results We identified 330 mutations, with at least one detected in 97% of patients. The most frequently affected genes were TET2 (n=35, 37%), DNMT3A (n=31, 33%), RUNX1 (n=29, 31%), FLT3 (n=28, 30%) and ASXL1 (n=26, 28%). Incorporation of molecular data enabled the reclassification of more than half of the patients (59.6%): 3 (3%) favorable, 38 (40%) intermediate, and 53 (56%) adverse. Molecular stratification was predictive for complete remission (CR) (p=0.0125) and overall survival (OS) (p=0.0217) (fig.1a). CR rates were 100% (3/3), 63% (24/38), and 39% (21/53) for favorable, intermediate, and adverse groups, respectively; 3-year OS was 100%, 52%, and 38%. Regarding induction therapy, there was a trend toward improved survival for patients treated with 3+7 (+GO/MIDO) and CPX-351 compared with FLAI (p=0.09) (fig.1b), with 3-year OS of 64%, 61%, and 39%, respectively.

Conclusions: In our experience, extended NGS analysis enabled reclassification of more than half of IR AML cases into favorable or, more frequently, adverse prognostic group according to ELN2022 criteria. This study highlights that comprehensive molecular profiling at diagnosis is essential for accurate prognostic stratification and early identification of optimal therapy. Future investigations on larger patient cohorts will be essential to validate the clinical utility of this approach, particularly in the setting of novel induction regimens incorporating targeted agents.

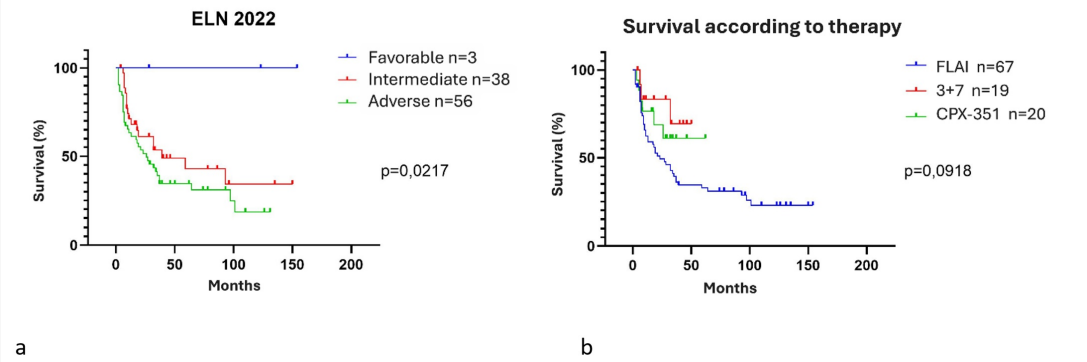

Fig.1 –(a) Overall Survival according ELN2022 prognostic stratification, favorable cases presented effectively good prognosis; (b) Overall Survival according to induction chemotherapy regimen, 3+7 and CPX regimens seem to show a better OS.