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ORAL ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Pre-Transplant Somatic Co-Occurring Mutations (by next generation sequencing) in Acute Myeloid Leukemia: Frequency and Impact on Clinical Outcomes after Allogeneic Hematopoietic Cell Transplantation - a Large Study on Behalf of the EBMT Acute Leukemia Working Party

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Background: Acute myeloid leukemia (AML) is a very heterogeneous hematological malignancy, which includes numerous genetically defined subsets. The genomic classification of AML with the identification of mutations in transcription factors, epigenetic modifiers, spliceosome, cohesin complex, and signaling pathways has led to a more accurate risk stratification

model. The main genetic aberrations included in the European LeukemiaNet (ELN) 2022 classification are *NPM1* (risk group according to karyotype and *FLT3*-ITD status), *FLT3*-ITD (intermediate risk), bZIP in-frame mutated *CEBPA* (favorable risk), and *RUNX1, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2* and *TP53* mutations (all belonging to the adverse risk group). In the context of allogeneic hematopoietic stem cell transplantation (allo-HSCT), the frequency and prognostic value of different gene-gene interactions has not been studied and may differ from that of patients treated with chemotherapy alone. We aimed at evaluating, through the European Society for Blood and Marrow Transplantation (EBMT) database, the frequency and impact of different recurrent somatic mutations, either alone or in association, on prediction of relapse and survival in patients receiving allo-HSCT.

Methods: This is a retrospective, registry-based, multicenter analysis from the EBMT with the approval of the EBMT Acute Leukemia Working Party. Adult patients aged more than 18 years with a diagnosis ofAML who received an allo-HSCT between 2013-2022, with an available genetic profile determined at diagnosis by next generation sequencing (NGS) were included.

Results: We identified 836 allografted AML patients who had NGS performed at diagnosis. Most of these patients had *de novo* AML (88%), with a median age of 53 years (range: 18-78 years). Karyotype was favorable in 7%, intermediate in 69% and adverse in 24% of patients. At transplant, 74% of patients were in first remission (CR1) and 13% in CR2. The most frequent detectable mutations by frequency were *DNMT3A (33%), FLT3 (29%), NPM1 (29%), TET2 (28%), NRAS (23%), RUNX1 (22%), WT1 (22%), BCOR (19%), ASXL1 (17%), IDH2 (17%), IDH1 (15%), SRSF2 (13%), STAG2 (12%), CEBPA (11%), TP53 (10%), KRAS (10%), and PTPN11* (10%) . By multiple correspondence analysis, two independent groups of co-occurring mutations were identified, the first group included *DNMT3A*, *NPM1* and *FLT3*, the second group included *ASXL1*, *SRSF2* and *RUNX1*. Outcome analysis was performed on the subset of 298 patients allografted in CR1 with available data for the aforementioned six genes (*DNMT3A, NPM1, FLT3, ASXL1, SRSF2 and RUNX1)*. Most of these patients had *de novo* AML (90%), with a median age of 53 years (range: 19-75 years). Patients received primarily reduced intensity conditioning (58%) and peripheral blood stem cells (93%) from matched sibling donors (35%), matched unrelated (28%), and haploidentical donors (21%). Seventy percent of these patients had intermediate-risk cytogenetics, while 27% were classified as adverse-risk. Median follow up calculated by the reverse Kaplan-Meier method was 2.5 years. Overall, the 2-year relapse incidence (RI), leukemia-free survival (LFS) and overall survival (OS) were 24%, 62% and 69%, respectively. When outcome analysis was performed according to the presence or absence of single mutations, none of the six mutations significantly affected RI or LFS. The 2-year OS was positively affected by the presence of *NPM1* mutation (78% vs 66%; p=0.02) and *FLT3* (79% vs 65%, p=0.01) but not significantly affected by the other 4 mutations. When mutations were investigated in groups, the 2-year RI, LFS and OS were 24%, 70% and 78%, respectively, for patients with *NPM1* mutation regardless of other co-mutations, 35%, 56% and 69% for patients with *FLT3*-ITDand/or *DNMT3A* mutation, wild type *NPM1*, regardless of other co-mutations, 17%, 70% and 74% for patients with *RUNX1* and/or *ASXL1* and/or *SRSF2* mutation without *FLT3*-ITD and with wild type *NPM1* and wild type *DNMT3A* and 20%, 56% and 61% for patients with all six genes unmutated.

Conclusion: NGS at diagnosis can be extremely useful in risk stratification of AML patients undergoing allo-HSCT, potentially allowing adequate post-transplant interventions. Notably, the 2-year LFS of 70% for patients harboring *RUNX1* and/or *ASXL1* and/or *SRSF2* mutation indicates that allo-HSCT can overcome the adverse risk associated with these somatic mutations at diagnosis.

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