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Molecular profiling at diagnosis for risk stratification of patients with AML undergoing allogeneic transplant in first remission

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Allogeneic hematopoietic stem cell transplantation (HSCT) is still considered the only curative treatment option for most patients with intermediate and high-risk acute myeloid leukemia (AML). However, elderly patients often have worse outcomes after HSCT when compared with younger patients. Older age coincides with increased probability of genetic abnormalities that are associated with high-risk AML. Therefore, Moses Murdock from the Dana Farber Cancer Institute, Philadelphia, US, and colleagues undertook a retrospective multi-center study evaluating the impact of genetic alterations present at the time of diagnosis on the outcome of HSCT in patients with AML aged 60 or older, undergoing HSCT in first complete remission (CR1). Below is a summary of his presentation given during the 61st ASH Annual Meeting in Orlando, US.

Methods

- In total, 300 patients with AML aged ≥ 60 years old who received allogeneic HSCT in CR1 (patients characteristics in Table 1)
- Targeted sequencing of 112 genes commonly mutated in AML was performed on samples from patients

Results

- Median follow-up of survivors was 3.75 years
- Median 3-year overall survival and leukemia-free survival (LFS) were reported in 48% and 44% of patients, respectively

Table 1. Patient and transplant characteristics

Age	66 (60 – 76)
Recipient sex	
Male	178 (59.3%)
Female	122 (40.7%)

HCT-CI score	
0	83 (27.7%)
1 –2	81 (27%)
3+	124 (41.3%)
Missing	12 (4%)
Type of AML	
Secondary	91 (30.3%)
Therapy-related	32 (10.7%)
De novo	177 (59%)
Cytogenetics	
Core binding factor mutations	8 (2.7%)
Normal karyotype	139 (46.3%)
Complex karyotype	41 (13.7%)
2017 ELN Risk	
Favorable	57 (19%)
Intermediate	86 (28.7%)
Adverse	152 (50.6%)

Donor type	
Unrelated	179 (59.7%)
Matched	148 (49.3%)
Unmatched	31 (10.3%)
Related	60 (20%)
Matched	54 (18%)
Unmatched	6 (2%)
Alternative	59 (19.7%)
Haploidentical	51 (17%)
Cord	8 (2.7%)
Missing	2 (0.6%)
Graft Source	
PBSC	221 (73.7%)
Bone marrow	71 (23.7%)
Cord	8 (2.7%)

Conditioning intensity	
Reduced intensity	197 (65.7%)
Non-myeloablative	75 (25%)
Myeloablative	28 (9.3%)

ELN, European Leukemia Net; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; PBSC, peripheral blood stem cell

- All patients had recurrent genetic alterations at the time of diagnosis, including 288 (96%) with gene mutations and six with cytogenetic abnormalities
- The most frequent gene mutations were *DNMT3A* (25%), *NPM1* (22%), *FLT3-ITD* (22%), *ASXL1* (21%), *TET2* (21%), *RUNX1* (20%), and *SRSF2* (18%)
- Secondary-type mutations occurred in 43% of patients
- *TP53* mutations were detected in 11% of samples
- High-risk was associated with mutations in *TP53* or *JAK2* or *FLT3*-ITD/*NPM1-WT*
- Patients with *DNMT3A*, *GATA2* or *DDX41* mutations and had an absence of high-risk mutations where classified as low-risk, while patients without high- or low-risk mutations had an intermediate-risk CR *vs* CRi and adverse karyotype alongside the genetic mutations were integrated into clinical and molecular risk model which allowed stratification of patients into
    - Very high-risk group (16.4% of patients) with a 3-year LFS of 5%
    - High-risk group (31.5% of patients) with a 3-year LFS of 29%
    - Intermediate-risk group (26.8% of patients) with a 3-year LFS of 51%
    - Low-risk group (25.2% of patients) with a 3-year LFS of 70%
- Relapse mortality was the most common treatment failure after transplantation in high-risk patients, while a combination of relapse and non-relapse mortality was contributing to treatment failure in other patient groups

Conclusion

The presented data demonstrated that the integrated model based on molecular and clinical features present at diagnosis can predict outcomes of HSCT in first remission in elderly patients with AML. The model can stratify patients based on prognosis and therefore identify patients with very high-risk genetics who might benefit from adapted treatment approaches, such as increasing conditioning intensity or different maintenance strategies. Moreover, patients assigned to intermediate or high-risk groups may require additional disease monitoring such as measurable residual disease (MRD) or post-transplant genetic assessment. However further prospective clinical trials are needed to assess consolidation strategies in these risk groups.

References

1. Murdock M. *et al*., Genetic alterations at diagnosis predict outcome of AML patients age 60 or older undergoing allogeneic transplant in first remission. Blood. 2019 Nov 13;134(Supplement_1):48. DOI: 10.1182/blood-2019-125967