Prognosis of Molecularly-Defined Secondary Acute Myeloid Leukemia Patients

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Background

- Eight mutations define AML with myelodysplasia-related gene mutations (AML-MRGM) independent of a history of MDS: *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1 and ZRSR2*[1].
- The 2022 ICC uses these genes and RUNX1 to define an AML subgroup with myelodysplasia-related gene mutations (AML-MRGM)[2].
- For older patients it is already known that the presence of these mutations define a subgroup within the ELN intermediate group with a worse outcome[3].
- Therefore, the latest ELN classification recommends to classify all patients bearing one of those mutations as adverse risk[4].
- Aim: to identify the impact of MRGM within different age and risk groups

Cohort

- 461 patients who were diagnosed with AML in different centers in Germany between 2000 and 2020
- Median age at diagnosis was 54 years.
- Blood or bone marrow samples were obtained at diagnosis and sequenced for mutations in a panel of 48 genes associated with AML.
- Patients were assigned to one of 3 groups: 1. AML-MRGM (n = 177, 38.4%), 2. patients with a history of MDS (prior MDS) bearing none of the 9 MRGM (AML-pMDS, n = 86, 18.7%) and 3. patients with genuine de novo AML (AML-other) (n = 198, 43%).

Table 1: Baseline characteristics of the 3 patient cohorts

Patients with AML-MRGM were older and more likely to be male. The WBC count at diagnosis was significantly higher than in patients with AML-pMDS. Patients with AML-MRGM were less likely to reach CR.

	AML-other (n = 198)	AML-MRGM (n = 177)	AML-pMDS (n = 86)	AML-other vs. AML-MRGM	AML-pMDS vs. AML-MRGM
sex					
male	90	101	46	*p* = .027	n.s.
female	103	71	37		
missing	5	5	3		
age (years)	47.3 (18-73.8)	55.6 (18-78)	52.6 (22.8-70)	*p* < .001	n.s.
ECOG					
≤1	135	124	71	n.s.	n.s.
>1	25	16	7		
missing	38	37	8		
WBC (k/µl)	46.6 (0.6-350)	46.6 (0.5-600)	23.4 (0.7-300)	n.s.	*p* = .005
Hb (g/dl)	9.3 (4.5-14.5)	9.3 (5.1-14.4)	9.3 (3.8-15)	n.s.	n.s.
Plt (k/µl)	81.8 (2-490)	91.8 (4-860)	81.8 (2-469)	n.s.	n.s.
CR	92%	80%	77%	*p* = .005	n.s.

Results

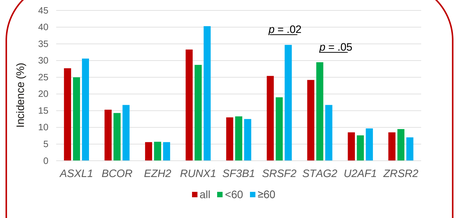


Figure 1: Incidence of myelodysplasia-related gene mutations

51.8% of patients ≥ 60 had MRGM, only 32.6% of patients < 60 (*p* <.001). *RUNX1* was the most common gene mutation, followed by *ASXL1*, *SRSF2* and *STAG2*. *SRSF2* was significantly more common in patients ≥ 60 years (*p* = .02). *STAG2* was more likely to be mutated in younger patients (*p* = .05).

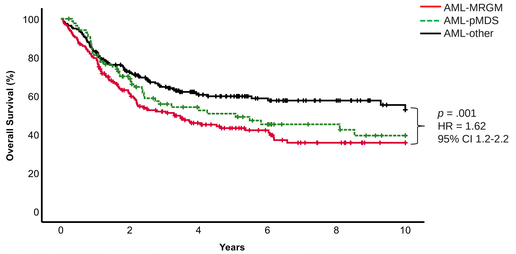


Figure 2: OS in AML-MRGM is significantly worse than in AML-other

The presence of myelodysplasia-related gene mutations was associated with a worse OS than patients with de novo AML. OS in AML-pMDS was similar to AML-MRGM.

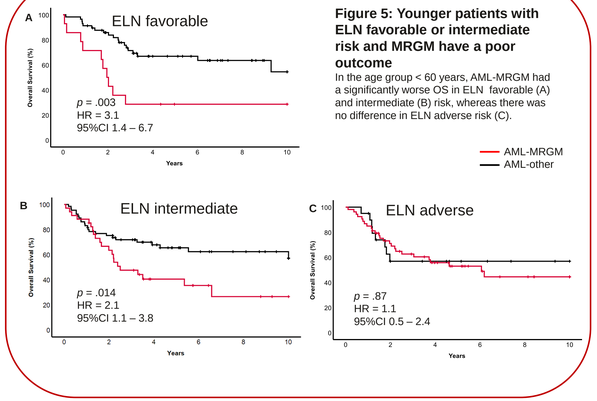


Figure 5: Younger patients with ELN favorable or intermediate risk and MRGM have a poor outcome

In the age group < 60 years, AML-MRGM had a significantly worse OS in ELN favorable (A) and intermediate (B) risk, whereas there was no difference in ELN adverse risk (C).

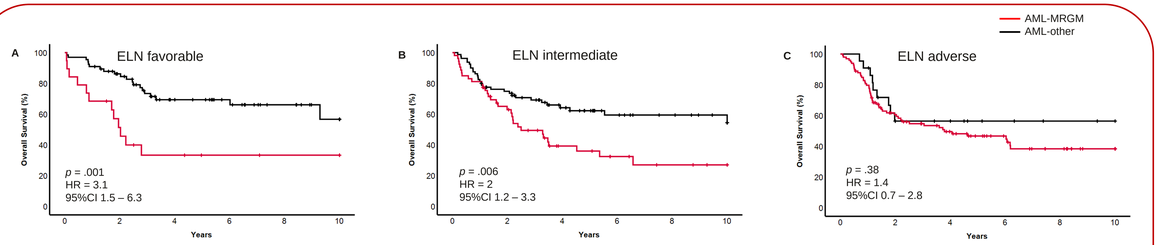


Figure 3: AML-MRGM classifies a group of patients with significantly worse outcome in ELN favorable and intermediate risk

The presence of at least one of the MRGM defined a cohort of patients within the ELN favorable (A) and intermediate risk group (B) with a significantly worse overall survival in comparison to patients without these mutations. Within the ELN adverse risk group there was no difference in OS (C).

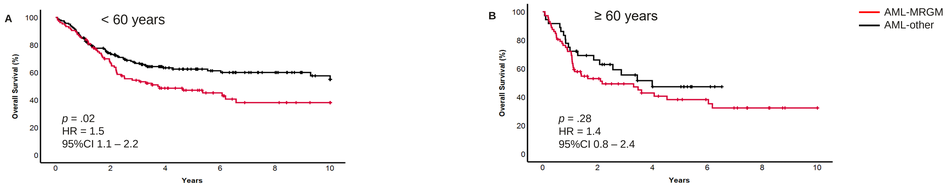


Figure 4: AML-MRGM has a worse outcome in younger patients < 60

In younger patients < 60 years AML-MRGM had a significantly worse OS (A). In patients ≥ 60 years the myelodysplasia-related gene mutations had no significant impact on overall survival (B).

Conclusion

- The nine myelodysplasia-related gene mutations are enriched in elderly, male AML patients.
- AML-MRGM is associated with shorter OS in younger patients.
- MRGMs reclassify 48 of 322 (14.9%) patients < 60 years from formerly ELN 2017 favorable and intermediate risk to ELN 2022 adverse risk.
- In patients ≥ 60 years the MRGM had no impact on OS in our cohort.
- These findings are in contrast with a patient cohort from Taiwan where presence of MRGM only impacted patients ≥ 60 years[5].
- Larger multicenter studies are needed to clarify the impact of MRGM in different age groups.

References

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