Characterization of Immunophenotypic Changes Following Menin Inhibition in Acute Myeloid Leukemia

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Abstract

INTRODUCTION: Menin inhibitors (menin-i) reverse aberrant gene expression in acute leukemia with *KMT2A-rearranged* or *NPM1-mutant* genotypes, leading to hematopoietic differentiation and antileukemic effects. However, the immunophenotypic determinants of response remain unknown.

AIM: To assess phenotypic determinants of response to menin-i and identify immunophenotypic changes in AML blasts following treatment.

METHODS: We identified 55 patients with R/R AML treated with revumenib monotherapy at our center under a phase 1/2 clinical trial or via compassionate use. Pre-menin-i blast immunophenotype was determined by flow cytometry and categorized as myeloid/stem-like (SL), myelomonocytic, monocytic/monoblastic, or megakaryocytic based on expression patterns of CD4, CD14, CD34, CD36, CD45, CD54, CD61, CD64, CD117, CD133, HLA-DR, and myeloperoxidase. Response was assessed by ELN, and measurable residual disease (MRD) by 12-color multiparameter flow cytometry (MFC).

RESULTS: The median age was 25 years (range 0.8–79), with 42 patients (76%) previously treated with venetoclax and 31 patients (56%) relapsed post-transplant. Genetic alterations included *KMT2A-r* (n=39; 71%), *NPM1m* (n=6; 11%), and other genotypes (n=10; 18%). AML blasts at baseline had a myeloid/stem-like phenotype in 22 patients (40%), myelomonocytic in 16 (29%), monocytic in 14 (25%), and megakaryocytic in 2 (3.5%); one case lacked phenotyping. The overall response rate among *KMT2A-r* or *NPM1m* pts was 24/45 (53%), with CR or CR with partial hematologic recovery in 11/45 (24%). No difference in morphologic remission rates was observed by baseline immunophenotype in *KMT2A-r* or *NPM1m* patients. Among 12 patients achieving morphologic remission with MRD positivity by MFC, 8 (67%) showed aberrant blasts with immunophenotypic shift from pre-menin-i, either in differentiation state (n=4) or antigen expression pattern/intensity (n=4). Baseline vs relapse phenotype comparison was available in 9 relapsed patients, with 8 (88%) showing immunophenotypic shift, including 3 with altered differentiation. MRD-neg remission was associated with improved survival (median OS 23.6 months). Immunophenotypic shift without leukemia clearance correlated with better survival than no shift, suggesting differentiation and potential benefit for subsequent therapies.

CONCLUSION: Acute myeloid leukemia following menin inhibitor treatment frequently exhibits phenotypic shifts, either in differentiation state or antigen expression patterns/intensity.

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Methods

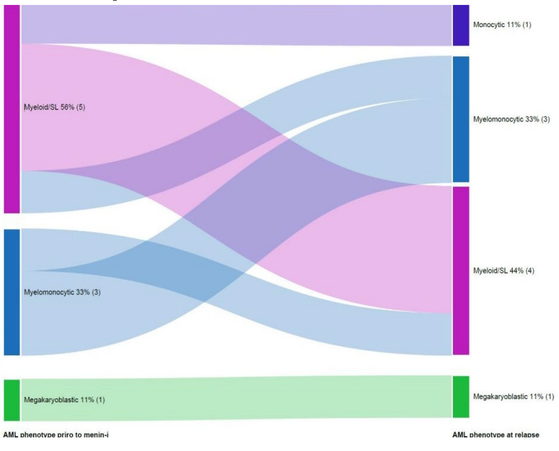
- We identified 55 patients with R/R AML treated with revumenib monotherapy at our center under a phase 1/2 clinical trial or via compassionate use.
- Pre-menin-i blast immunophenotype was determined by flow cytometry and categorized as myeloid/stem-like (SL), myelomonocytic, monocytic/monoblastic, or megakaryocytic based on expression patterns of CD4, CD14, CD34, CD36, CD45, CD54, CD61, CD64, CD117, CD133, HLA-DR, and myeloperoxidase.
- Response was annonated by European Leukemia Net criteria.
- Measurable residual disease (MRD) was assessed using 12-color multiparameter flow cytometry (MFC).
- We compared the blast immunophenotype pre-menin-I to MRD and relapse (when applicable)

Results

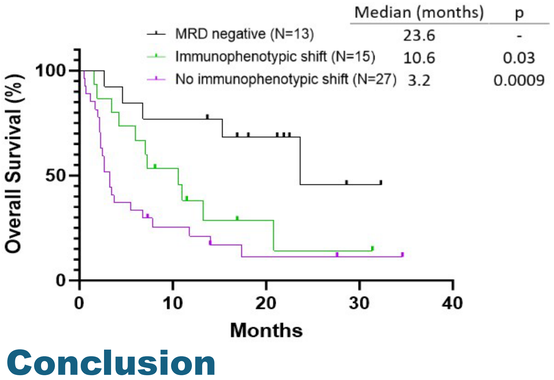
Baseline characteristics

Relapsed/refractory AML	N=55
Median age, years [range]	25 [0.8-79]
Sex, n%	
Male	48
Female	52
Genotype, n%	
KMT2Ar	71
NPM1m	11
NUP98r	5
Other	13
Extramedullary disease, n%	20
Best Response, ELN n%	
CR, CRh, CRp	38
MLFS	9
No response	44
Not assessed	9
MRD at Best Response, n%	
Positive	46
Negative	50
Not Evaluable	4
Previous therapies, n%	
Venetoclax	78
allo-HSCT	56
Pretreatment phenotype, n%	
Myeloid/stem	40
Myelomonocytic	30
Monoblastic	26
Megakaryoblastic	4

Comparison of AML phenotype at baseline with relapse



Survival



Conclusion

Acute myeloid leukemia following menin inhibitor treatment frequently exhibits phenotypic shifts, either in differentiation state or antigen expression patterns/intensity.