Clinical Experience with HDAC Inhibitor-Based Protocols in MECOM-Rearranged Acute Myeloid Leukemia

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Introduction

•MECOM rearrangements (MECOMr) occur in ~1% of AML and define a high-risk subtype

•CR rates are 30–50% in newly diagnosed and 10–25% in relapsed/refractory cases. Three-year overall survival is <10%.

•MECOMr-AML is ERG dependent. ERG is a transcription factor and key regulator of hematopoietic stem cell (HSPC) self-renewal

•ERG is a direct transcriptional target of EVI1 and a key leukemogenic driver

•Previous studies showed that ERG restricts myeloid differentiation in HSPCs through interaction with the NCoR-HDAC3 repression complex and that ERG-dependent AML is sensitive to HDAC3 inhibition.

•MECOMr-AML shows enhanced sensitivity to HDAC inhibition in preclinical models

•Targeting the EVI1–ERG–HDAC axis may offer a therapeutic strategy in MECOMr-AML

Aim

To evaluate the efficacy of HDAC inhibitor-containing regimens in MECOMr-AML through a retrospective analysis of clinical trial data from a single institution.

Methods

- We analyzed 562 patients with MDS/AML treated with HDAC inhibitor–based protocols at MD Anderson Cancer Center (1999–2018).
- MECOMr cases were identified by cytogenetics and defined as inv(3)(q21q26.2) or t(3;3)(q21;q26.2), per WHO 2022/ICC criteria.
- These classifications now define MECOM rearrangement as AML regardless of blast count.
- Original MDS or AML classifications were retained to reflect diagnoses made prior to classification updates.
- Clinical characteristics, treatment details, and responses were assessed.
- NGS analysis not feasible as trials were completed before its adoption as a diagnostic tool.

Results

•Nine MECOMr patients (1% of cohort) were identified (median age 57, range 16–76).
•Two cases were therapy-related AML.
•Eight patients received HDAC inhibitor-based protocols as first-line therapy; one received it after HMA failure
•Cytogenetics:
- •Complex karyotype in 4 (44%)
- •-7/del(7q) in 2 (22%)
- •-5/del(5q) in 1 (11%)
- •Isolated MECOMr in 2 (22%)

•Overall, -7/del(7q) was present in 6 patients (67%)—4 with complex karyotype, 2 isolated.
•HDAC inhibitors used: valproic acid (n=3), vorinostat (n=3), mocetinostat (n=2), panobinostat (n=1).
•Overall response rate: 67% (CR in 5, CRi in 1).
•Median time to CR: 1 cycle (range 1–3).
•With a median follow-up time of 8.5 months (range, 1-31 months), the median relapse-free survival was 5 months (95% CI, 3-15) and the median overall survival was 11 months (95% CI, 4–NA).
•Among 6 responders, 4 relapsed (median duration of response: 3.1 months, range 0.5–14.5).
•One responder underwent allo-SCT in CR after 3 cycles.
•One patient died in CR due to pneumonia.
•Among 3 non-responders, 1 had complex karyotype and 1 had therapy-related AML.

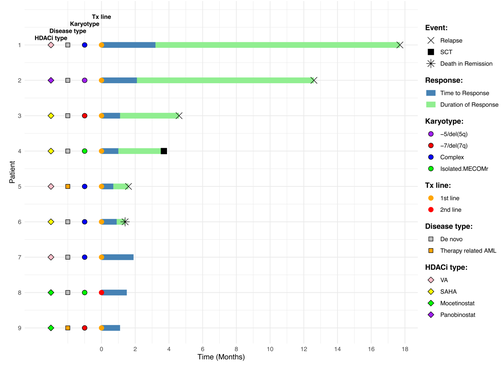
Patient Characteristics

Variable	N = 9 [1]
Age (years)	57 (16, 76)
Gender	
M	6 (67%)
F	3 (33%)
Diagnosis	
MDS	3 (33%)
AML	6 (67%)
Therapy-related disease	2 (22%)
BM Blasts (%)	25 (8, 48)
Karyotype	
Complex	4 (44%)
-7/del(7q)	2 (22%)
-5/del(5q)	1 (11%)
Isolated.MECOMr	2 (22%)
MECOMr type	
inv(3)(q21q26.2)	6 (67%)
t(3;3)(q21;q26.2)	3 (33%)
Treatment protocol	
HMA+VA+ATRA	2 (22%)
HMA+VA	1 (11%)
HMA+SAHA (Vorinostat)	2 (22%)
IA+SAHA (Vorinostat)	1 (11%)
Mocetinostat	2 (22%)
HMA+Panobinostat	1 (11%)
Response	
CR	5 (56%)
CRi	1 (11%)
NR	3 (33%)
Cycles to response	1 (1, 3)

[1] Median (Min, Max); n (%)

Abbreviations: BM - Bone Marrow; VA - Valproic acid; IA - idarubicine and Cytarabine; HMA - hypomethylation agent; CR - complete remission; CRi - complete remission without hematologic recovery; NR - no response

Clinical outcomes of MECOMr MDS/AML patients treated with HDAC inhibitors



Swimmer plot showing time to response (blue bars) and duration of response (green bars) in months for nine patients. Each row represents an individual patient with corresponding disease characteristics (karyotype, disease type) and treatment information (HDACi type, treatment line) shown on the left. Clinical events including relapse (X), stem cell transplantation (square), and death in remission (asterisk) are indicated. VA = valproic acid; SAHA = vorinostat; t-MDS/AML = therapy-related MDS/AML.

Discussion

- HDAC inhibitor–based therapy achieved an overall response rate of 67% (CR in 5 patients, CRi in 1) in MECOMr-AML.
- Findings suggest potential therapeutic benefit of HDAC inhibition in this high-risk subgroup.
- Interpretation is limited by small sample size and heterogeneous treatment regimens.
- Supports the need for dedicated clinical trials to define optimal HDAC-based strategies.

References

- Richard-Carpentier, G., et al., *Characteristics and clinical outcomes of patients with acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2).* Haematologica, 2023. **108**(9): p. 2331-2342.
- Knudsen, K.J., et al., *ERG promotes the maintenance of hematopoietic stem cells by restricting their differentiation.* Genes Dev, 2015. **29**(18): p. 1915-29.
- Schmoellerl, J., et al., *EVI1 drives leukemogenesis through aberrant ERG activation.* Blood, 2023. **141**(5): p. 453-466.
- Masamoto, Y., et al., *EVI1 exerts distinct roles in AML via ERG and cyclin D1 promoting a chemoresistant and immune-suppressive environment.* Blood Adv, 2023. **7**(8): p. 1577-1593.
- Kugler, E., et al., *The NCOR-HDAC3 co-repressive complex modulates the leukemogenic potential of the transcription factor ERG.* Nat Commun, 2023. **14**(1): p. 5871.
- Marchesini, M., et al., *Orthogonal proteogenomic analysis identifies the druggable PA2G4-MYC axis in 3q26 AML.* Nat Commun, 2024. **15**(1): p. 4739.

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