Incidence and Screening Patterns of CNS Involvement in AML Patients Treated With Hypomethylating Agents and Venetoclax in the Frontline Setting

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Introduction

- In newly diagnosed AML patients, white blood cell (WBC) count >40 x10^3/mcL, *FLT3-ITD/TKD*mut, monocytic differentiation (MoD), and extramedullary disease (EMD) predispose patients to central nervous system (CNS) involvement.[1]
- For such patients screening lumbar puncture (sLP) is recommended in first remission (CR1).
- Data on the optimal timing of sLP, incidence, and outcomes of CNS positive AML patients treated with hypomethylating agent and venetoclax (HMA/Ven) are lacking.

Aims

- Determine proportion of newly diagnosed AML patients treated with frontline HMA/Ven meeting criteria for CNS screening
- Evaluate frequency and timing of screening lumbar puncture (sLP)
- Determine the incidence of CNS involvement in screened patients and rate of late CNS involvement detection in non-screened patients
- Compare survival outcomes between high-risk (HR) and low-risk (LR), and between those who did and did not undergo sLP

Methods

- *Study design*: Retrospective chart review
- *Study population*: Adults (≥18 years) with AML treated with HMA/Ven in frontline setting at Vanderbilt University Medical Center and University of Kansas Cancer Center from 10/2017 to 2/2025
- *Primary outcomes*: Incidence of CNS involvement in CR1 following HMA/Ven frontline therapy.
- *Secondary outcomes*: Overall survival (OS) in HR vs. LR patients, screened vs. unscreened patients
- *Statistical analysis*: Kaplan-Meier (GraphPad) for survival analysis. Multivariate analysis (R-studio) for predictors of sLP.

Results

295 newly diagnosed AML

173 treated with HMA/Ven

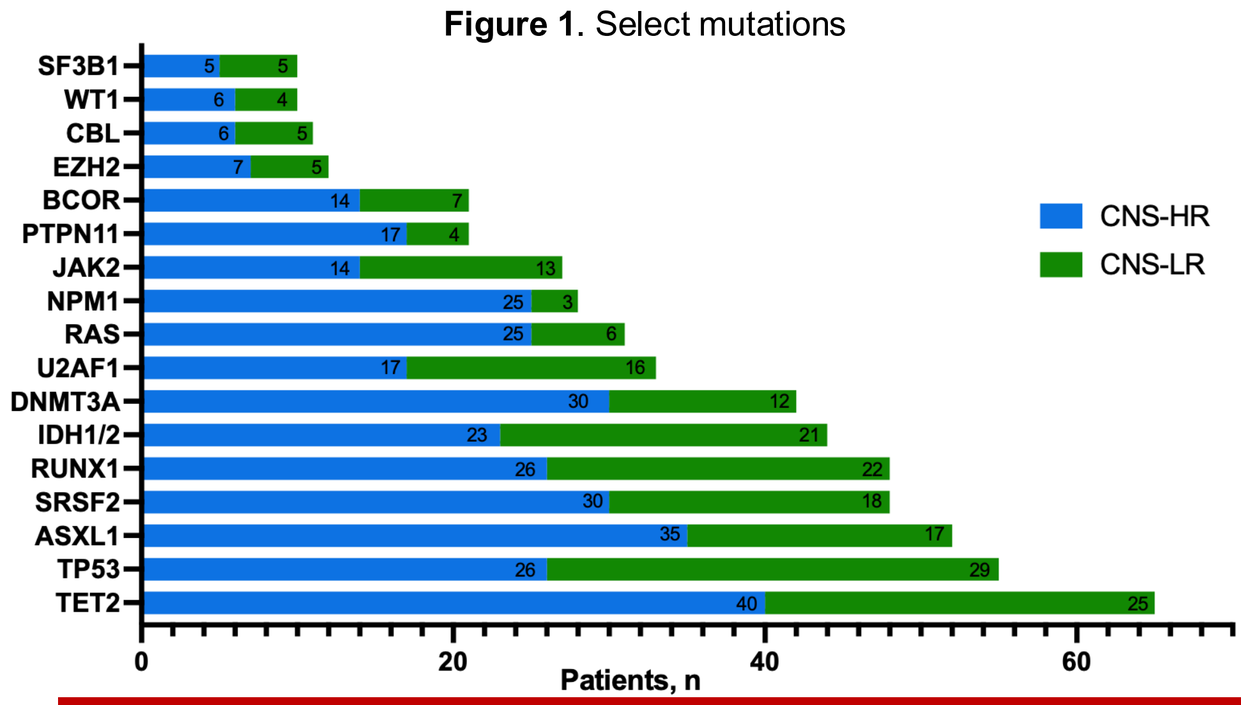
78 Low-risk for CNS disease (CNS-LR)
- 3 CNS+ late in therapy

95 High-risk for CNS disease (CNS-HR)
- 24 screened, 3 CNS+

Table1. Patient characteristics

Demographics (n=173)	CNS-LR (n=78)	CNS-HR (n=95)
Male, n(%)	63 (80.8)	53 (55.8)
Median age, years [IQR]	72.7 [69.0-76.5]	72.0 [68.0-77.3]
ECOG 0-1, n(%)	25 (32.1)	24 (25.3)
ECOG 2, n(%)	39 (50.0)	49 (51.6)
ECOG 3, n(%)	8 (10.3)	17 (17.9)
ELN'22 risk[2]		
Favorable risk, n(%)	2 (2.6)	5 (5.3)
Intermediate risk, n(%)	12 (15.4)	16 (16.8)
Adverse risk, n(%)	64 (82.1)	74 (77.9)
mPRS/ELN'24 risk[3]		
Higher benefit, n(%)	51 (65.4)	44 (46.3)
Intermediate benefit, n(%)	4 (5.1)	33 (34.7)
Low benefit, n(%)	22 (28.2)	18 (18.9)
Select cytogenetics		
-5q, n(%)	21 (26.9)	14 (14.7)
-7, n(%)	18 (23.1)	15 (15.8)
-17p, n(%)	10 (12.8)	6 (6.3)
Complex, n(%)	23 (29.5)	17 (17.9)
Monosomal, n(%)	9 (11.5)	9 (9.5)

Figure 1. Select mutations



Results

Table 2. Demographics, disease characteristics and outcomes of CNS-HR patients

CNS-HR patients, (n=95)	sLP done (n=24)	sLP not done (n=71)	*p*
Age at diagnosis, median [IQR]	73.4 [71.3-76.6]	71.4 [65.7-77.5]	ns
ECOG >3, n(%)	0	17 (23.9%)	***0.005***
Monocytic differentiation, n(%)	18 (75.0)	51 (71.8)	ns
FLT3 ITD/TKD, n(%)	3 (12.5)	23 (32.4)	ns
WBC >40, n(%)	3 (12.5)	21 (29.6)	ns
EMD, n(%)	7 (29.2)	3 (4.2)	***0.002***
CR/CRh/CRi, n(%)	16 (66.7)	33 (46.5)	ns
Days from C1D1 to sLP, [IQR]	20 [5.8-24.0]	n/a	-
CNS involvement at sLP, n(%)	3 (12.5%)	n/a	-
Late CNS involvement, n(%)	0	3 (4.2)	ns
mOS, months [IQR]	7.3 [2.6-8.8]	6.0 [1.9-13.0]	ns

Figure 2. CNS-HR ECOG

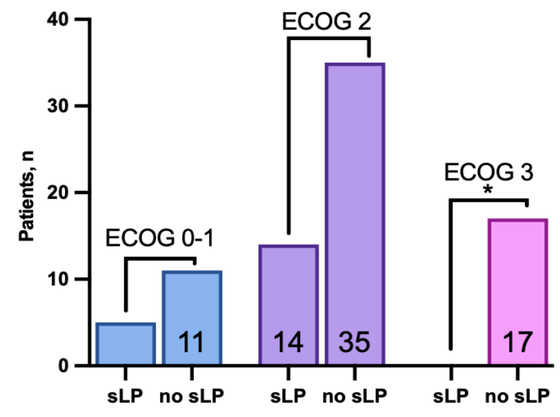


Figure 3. CNS risk factors in HR cohort

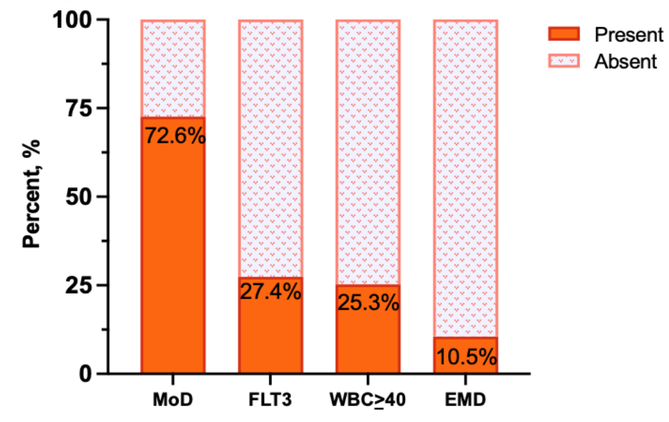


Figure 3. Cell counts at diagnosis in CNS-HR and CNS-LR cohorts

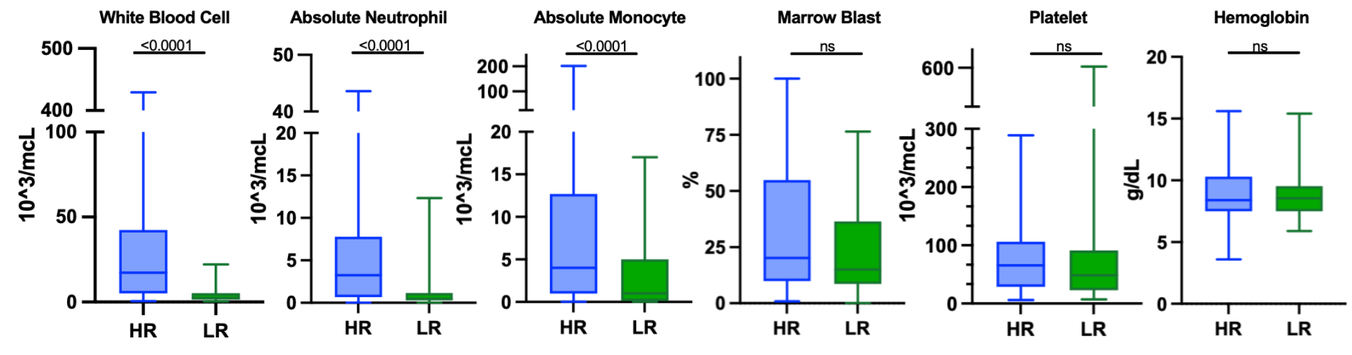


Figure 4. Overall Survival of CNS-HR vs. CNS-LR patients

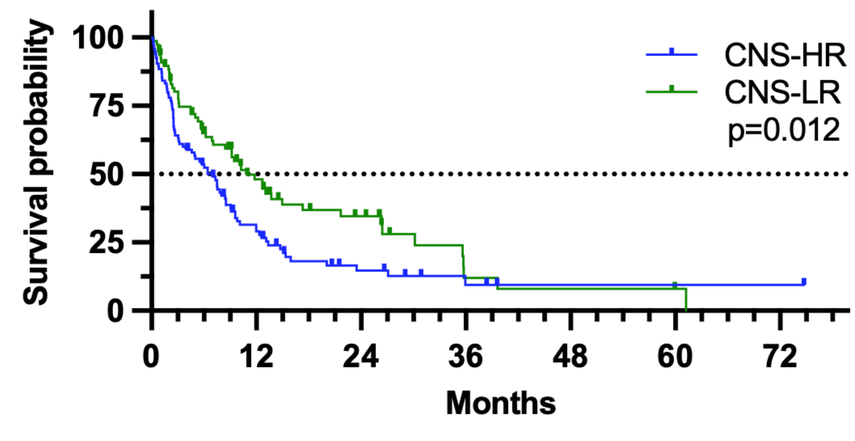


Figure 5. Overall Survival of CNS-HR patients with and without sLP

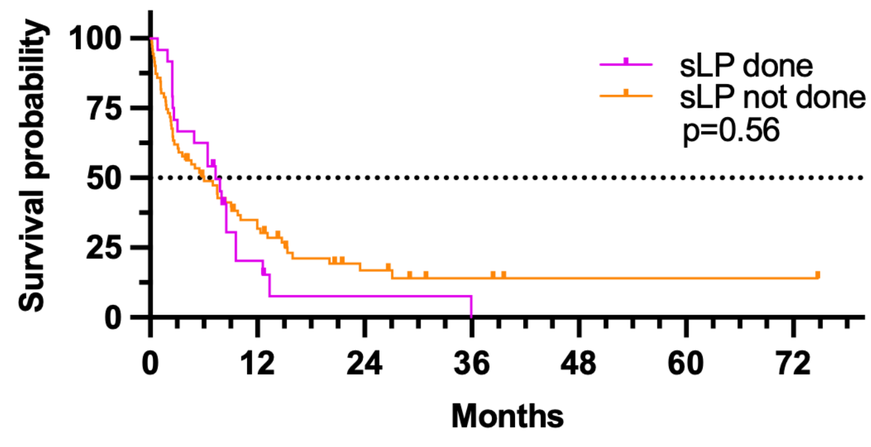
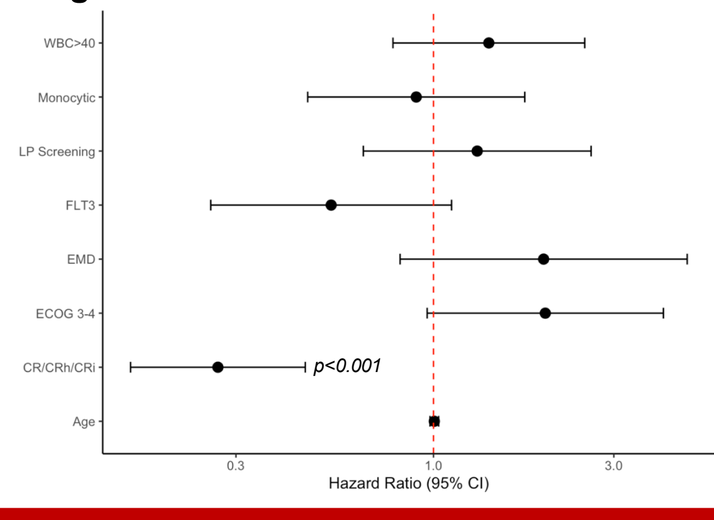


Figure 6. Hazard Ratios for Overall Survival



Discussion

- CNS-HR patients have worse OS despite low rate of initial CNS involvement at screening and low rates of CNS involvement detected later in disease course.
- No significant OS benefit achieved with or without sLP in CNS-HR patients.
- Patients with EMD were more likely to be screened for CNS involvement compared to patients with other CNS risk factors; while patients with ECOG ≥3 tended to not be screened.
- Abstract on CNS involvement outcomes in 122 intensively vs HMA/Ven treated patients was submitted to ASH2025.

References

1. NCCN AML V2.2025
2. Döhner doi:10.1182/blood.2024025409
3. Döhner doi:10.1182/blood.2024024944

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