Salvage Treatment with Venetoclax (Ven) and Hypomethylating Agents (HMA) for Relapsed/Refractory FLT3-mutated Acute Myeloid Leukemia (AML) Patients: Clinical Characteristics and Outcomes

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ABSTRACT

Introduction:

FLT3 mutation (m) significantly impacts the prognosis of acute myeloid leukemia (AML), necessitating effective therapeutic strategies. Management of relapsed/refractory (R/R) FLT3m AML is challenging due to lower complete remission (CR) rates and shorter CR duration. This study assesses clinical outcome of R/R FLT3m AML patients undergoing salvage therapy with venetoclax (Ven) + hypomethylating agent (HMA) combination in a real-world setting.

Methods:

Thirty FLT3m AML patients with R/R disease, treated at Mayo Clinic with HMA+Ven (with/without gilteritinib [Gilt]) between 2019 and 2022, were analyzed. Responses were evaluated per 2022 ELN criteria, and overall survival (OS) was calculated from the salvage treatment starting date to the last follow-up or death.

Results:

The median age of the patients was 62 years [21-80], 53% were male, and 93% were White. De novo AML was the most common (91%) AML sub-type. Fifty-seven percent of patients had diploid cytogenetics (CG), and 43% had additional CG abnormalities. Patients with concurrent NPM1 mutation were 27%. Majority of the patients (n=26 [87%]) had the FLT3 ITD sub-type. Frequently reported mutations (≥ 5%) at diagnosis were NPM1 (37%), DNMT3A (27%), WT1 (20%), RUNX1 (17%), and TET2 (13%). Decitabine-Ven was used in (n=19) 63% and Azacitidine-Ven in (n=11) 37% of patients. HMA-Ven-Gilt triplet was used in (n= 6, [20%]) of patients. The CR with or without count recovery (i) (CR/CRi) was 50%. The median number of HMA+Ven cycles to achieve CR/CRi was 2 (range, 1-5). The median duration of response was 8 months (range, 1-23), and median OS for our cohort was also 8 months (range, 1-24 months). Univariate analysis for OS showed a significantly better OS with FLT3m ITD subtype ($p<0.0001$), FLT3 allelic ratio <0.5 ($p=0.03$), and TET2 mutation ($p=0.007$). No impact on OS with cytogenetics at diagnosis ($p=0.38$), NPM1 mutation ($p=0.24$), or HMA+Ven with/without Gilt ($p=0.73$). At the last follow-up, 37% of the patients were alive.

Conclusion:

Hypomethylating agent plus Ven based combination seem to be effective as salvage therapy in patients with FLT3m AML. Effective therapies are warranted to improve long-term outcome of these adverse-risk patient population.

BACKGROUND

- FMS-like tyrosine kinase 3 (FLT3) mutation (m) is a common and clinically significant genetic alteration in acute myeloid leukemia (AML).
- FLT3 mutation (m) significantly impacts the prognosis of acute myeloid leukemia (AML), necessitating effective therapeutic strategies.
- While treatment strategies are well-defined for treatment-naive patients, management of relapsed/refractory (R/R) FLT3-mutated AML remains a major therapeutic challenge due to lower complete remission (CR) rates and shorter CR duration.
- The combination of Venetoclax (Ven) with hypomethylating agents (HMA) has emerged as a promising therapeutic option for managing R/R FLT3-mutated AML.

OBJECTIVES

- This study assesses clinical outcome of R/R FLT3m AML patients undergoing salvage therapy with venetoclax (Ven) + hypomethylating agents (HMA) combination in a real-world setting.

METHODS

- We identified a cohort of thirty FLT3m AML patients with R/R disease who received salvage HMA+Ven therapy (with or without Gilteritinib) at the Mayo Clinic between June 2019 and May 2022.
- Treatment-naive patients were excluded from this analysis.
- We retrospectively analyzed the patients for clinical characteristics and treatment outcomes.
- Each patient completed at least one cycle of HMA, consisting of either azacitidine (75 mg/m2 from day 1 to 7) or decitabine (20 mg/m2 from day 1 to 5).
- The assessment of therapeutic responses followed the 2022 European Leukemia Net (ELN) criteria.
- Overall survival (OS) was calculated from the day of initiating salvage HMA+Ven therapy until the date of the last follow-up or death, whichever occurred first.

RESULTS

- Patients Characteristics (n=30):

Patient Characteristics at diagnosis	No. (%), or Median [range]
Age, Years	62 [21-80]
Age ≥ 65 years	14 (47)
Male	16 (53)
Caucasian	28 (93)
WBC, x 10(9)/L	8 [6-14]
Hemoglobin, g/dL	43 [2-341]
Platelet, x 10(9)/L	49 [6-175]
BM Blasts, %	45 [2-97]
Peripheral Blood Blasts, %	74 [23-95]
Type of AML	
Denovo AML	27 (91)
Secondary AML	1 (3)
AML with MDS-related changes	1 (3)
Therapy-related AML	1 (3)
Cytogenetics at Diagnosis	
Diploid	17 (57)
With concurrent NPM1 mutation	8 (27)
Without concurrent NPM1 mutation	9 (30)
Additional Cytogenetics Abnormality	13 (43)
Complex	3 (10)
17p deletion	1 (3)
t(8;21)	2 (7)
Others*	1 (3)

WBC, white blood cells; BM, bone marrow.

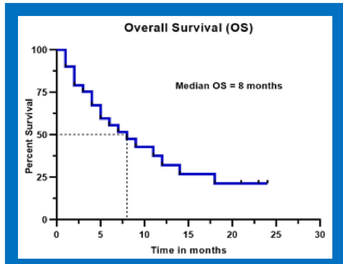
* Including t(5;11), t(6;11), t(1;11), t(10;12), Del 9q, Trisomy 4, and Trisomy 14 - 1 patient (3%) for each

Patient Characteristics at diagnosis	No. (%)
Most commonly occurring mutations (≥ 5%) at Diagnosis	
NPM1	11 (37)
DNMT3A	8 (27)
WT1	6 (20)
RUNX1	5 (17)
TET2	4 (13)
NRAS	4 (13)
IDH2	3 (10)
ASXL1	2 (7)
Spliceosomal; SF3B1, U2AF1, SRSF2	2 (7)
TP53	1 (3)
IDH1	1 (3)
CEBPA	1 (3)
KRAS	1 (3)
EZH2	1 (3)
STAG2	1 (3)

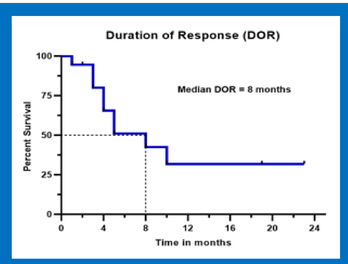
Patient Characteristics at diagnosis	No. (%)
FLT3 mutation subtype at diagnosis	
FLT3-ITD	26 (87)
FLT3-TKD	4 (13)
FLT3 Mutation Allelic Ratio at diagnosis (n=16)	
< 0.5	8 (50)
≥ 0.5	8 (50)
Chemotherapy regimen	
Decitabine – Venetoclax	16 (53)
Azacitidine – Venetoclax	8 (27)
HMA - Venetoclax - Gilteritinib	6 (20) #
Response to induction treatment	
CR	8 (27)
CRi	7 (23)
PR	3 (10)
Refractory Disease	12 (40)
The median duration of response	8 months (range, 0.5-23)
The median overall survival	8 months (range, 1-24)
Alive at last follow up date	11 (37)

The HMA used were Azacitidine and Decitabine – 3 patients (10%) for each

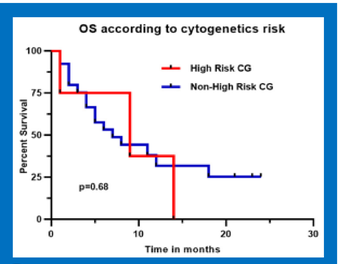
RESULTS



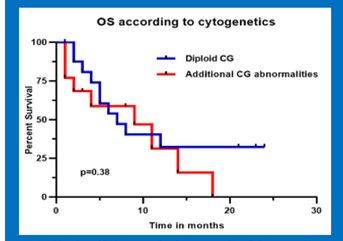
A Kaplan Meier survival curves for Overall Survival (OS)



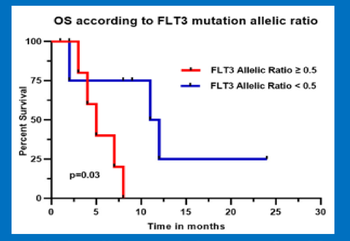
B Kaplan Meier survival curves for Duration of Response (DOR)



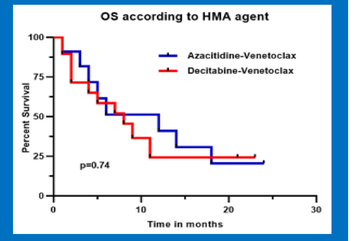
C Kaplan Meier survival curves for OS according to cytogenetics at diagnosis



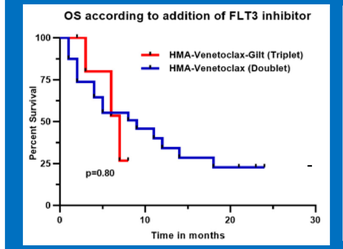
D Kaplan Meier survival curves for OS according to cytogenetics at diagnosis



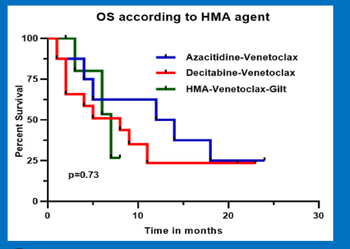
F Kaplan Meier survival curves for OS according to FLT3 mutation allelic ratio



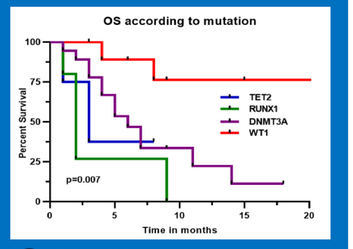
G Kaplan Meier survival curves for OS according to HMA type used



H Kaplan Meier survival curves for OS when adding Gilteritinib



L Kaplan Meier survival curves for OS according to HMA agent +/- Gilteritinib



M Kaplan Meier survival curves for OS according to mutation

CONCLUSIONS

- The use of the HMA+Venetoclax regimen, either alone or in combination with Gilteritinib, represents a viable salvage therapeutic approach for patients with relapsed/refractory FLT3-mutated AML.
- Our study underlines the potential of this regimen in this challenging patient population.
- Effective therapies are warranted to improve long-term outcome of these adverse-risk patient population.