Quality Assurance Evaluation of Venetoclax and Hypomethylating Agents in Acute Myeloid Leukemia

Cameron Hallisey, PharmD Candidate - Project 729
Advisors: Ali Rejali, PharmD, BCPS, Brittany McGalliard, PharmD, BCOP, Michelle She, PharmD
Cedars Sinai Medical Center, Los Angeles

Background

- Acute Myeloid Leukemia (AML) is an aggressive form of leukemia that disrupts hematopoiesis and results in bone marrow failure. It largely affects the elderly population in which treatment options are limited due to the high incidence of comorbidities and reduced tolerance to intensive chemotherapy.[1-3]
- Venetoclax is an oral antineoplastic that was recently approved for use in combination with a hypomethylating agent (azacitidine or decitabine) in the setting of AML. Its direct inhibition of B-cell lymphoma-2 (BCL-2), an antiapoptotic protein, allows for restoration of the apoptosis pathway and the elimination of dormant leukemic stem cells (LSC).[4] This, in combination with the increased tumor suppressor gene expression associated with HMAs, has shown to significantly increase patients' complete remission (CR), complete remission with incomplete count recovery (CRi), and overall survival (OS) rates in recent studies.[5-7]
- While VEN-HMA does have favorable outcomes, there are notable hematological adverse effects, including neutropenia, leukopenia, thrombocytopenia, anemia, and associated infections.[5-6] In clinical practice, many oncologists attempt to mitigate these adverse effects by truncating the duration of VEN therapy (usual range 5 to 21 days) as opposed to that of the FDA approved continuous dosing regimen.

Objective

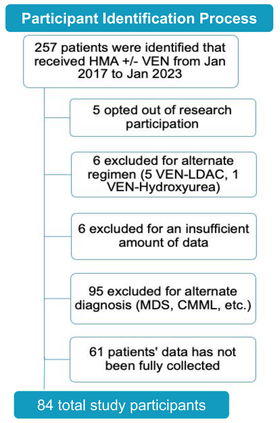
The primary objective of this study is to assess the associated risks and benefits of the truncated dosing regimens of VEN-HMA combination therapy often seen in practice, in comparison to that of the FDA approved continuous dosing regimen.

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
18 years of age or older	Alternate diagnosis or regimen
Received VEN-HMA or HMA-monotherapy for AML	Opted out of research participation

Results

Participant Identification Process



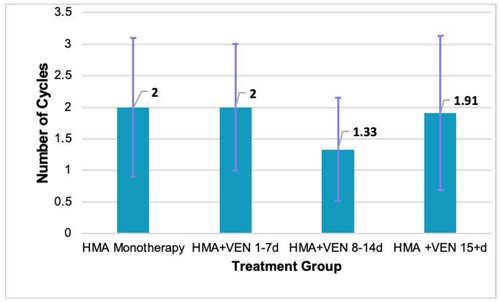
Baseline Characteristics of Patients by Treatment Group

Characteristic	HMA Alone (n= 53)	HMA+VEN 1-7 Days (n= 10)	HMA+VEN 8-14 Days (n= 14)	HMA+VEN 15+ Days (n= 25)
Age at C1 - yr.	67.1 ± 16.5	64.8 ± 20.3	65.9 ± 17.8	66.9 ± 10.7
Male Sex - no. (%)	28 (52.8%)	9 (90%)	8 (57.1%)	13 (52%)

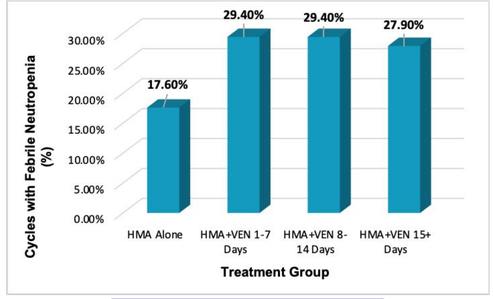
Disease Status of Patients by Treatment Group

	HMA Alone (n= 53)	HMA+VEN 1-7 Days (n= 10)	HMA+VEN 8-14 Days (n= 14)	HMA+VEN 15+ Days (n= 25)
Complete remission (CR, CRi, CR MRD+, CR MRD-)	7 (13.2%)	3 (30%)	6 (42.9%)	11 (44%)
Partial remission or lack of response	21 (39.6%)	2 (20%)	2 (14.3%)	9 (36%)
Relapse	1 (1.9%)	0 (0%)	1 (7.1%)	1 (4%)
Unknown (no bone marrow biopsy)	25 (47.2%)	5 (50%)	6 (42.9%)	5 (20%)

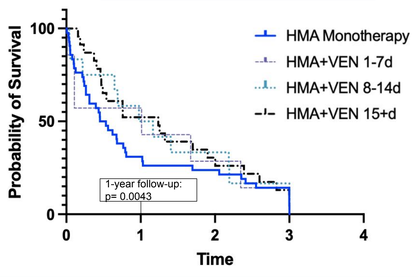
Mean Number of Cycles to Response



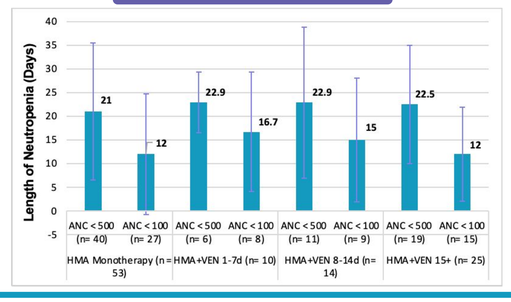
Incidence of Febrile Neutropenia



Length of Survival



Duration of Neutropenia



Methods

This retrospective, single site study at Cedars-Sinai Medical Center (CSMC) analyzes patients via medical record review (CS-Link) over a period of approximately 6 years. The original data extracted from CS-Link contained 257 patients. 112 were excluded and 61 have yet to be collected (n=84). Participants were divided into groups for analysis by treatment regimen. The groups include an HMA-monotherapy treatment group and 3 VEN-HMA treatment groups based on VEN duration of therapy (1-7, 8-14, 15+ days) in each 28 day cycle. Statistical analysis was performed using one-way ANOVA tests and Kaplan Meier survival tests.

Outcome Measures

- Number of cycles to response (CR, CRi, CR MRD+, CR MRD-)
- Number of patients with complete remission, partial remission, lack of response, or relapse
- Incidence of febrile neutropenia
- Duration of neutropenia
- Length of survival

Conclusions

01 VEN-HMA treatment groups showed statistically significant increased 1-year median survival rates in comparison to the HMA monotherapy group. This aligns with published data demonstrating improved survival with HMA in combination with continuously dosed VEN.

02 Shortened exposure to VEN did not appear to negatively impact cycles to response in this study, supporting the use of truncated dosing regimens in practice. Additionally, higher powered studies are needed to confirm if VEN-HMA regimens with 8-14 days of VEN per cycle may be optimal.

03 While there was no statistically significant difference in incidence or duration of neutropenia between the groups, there was a trend towards increased incidence of febrile neutropenia in the VEN treatment groups. This study requires more statistical power for this analysis.

Limitations

- Limited to the Cedars-Sinai Medical Center patient population
- Myelosuppression can result from both the underlying malignancy and treatment with HMA/VEN
- Bone marrow biopsies were not routinely performed after each cycle for all patients
- Some patients may have follow-up at other institutions that is not reported in CS-Link
- Patients did not receive all cycles inpatient, so our ability to assess duration of venetoclax and exposure to prophylactic antimicrobials is limited by physician documentation and outpatient prescriptions

References

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