

# Venetoclax-Azacitidine Salvage Chemotherapy in Relapsed/ Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrome: A Single-Center Experience

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## To the Editor

Acute myeloid leukemia (AML) is a malignant bone marrow disorder arising from early myeloid progenitors leading to clonal expansion and myeloid maturation arrest [1]. It is the commonest acute leukemia in adults with a rising incidence with age. The median age of diagnosis is 69 years, and the estimated age-adjusted annual incidence is 4.3/100,000 per year in the United States [1, 2]. The management of AML is rapidly evolving and the use of the BCL2 inhibitor, venetoclax in combination with azacitidine in previously untreated AML has revolutionized the management particularly in elderly comorbid patients ineligible for intensive chemotherapy. The VIALE-A trial showed an overall survival (OS) advantage of 14.7 months compared to azacitidine monotherapy in previously untreated AML patients [3].

We assessed the response to venetoclax-azacitidine in a small cohort of patients with relapsed/refractory (R/R) AML and high-risk myelodysplastic syndrome (MDS) and the results were overall promising as this regimen could potentially be consolidated with stem cell transplant (SCT) or to donor lymphocyte infusion (DLI) in patients who previously had an SCT. Venetoclax-azacitidine can be mostly delivered in an outpatient setting, thus significantly reducing inpatient bed days and transfusion requirements compared to intensive salvage chemotherapy in selected patient cohort.

R/R AML has been a challenging entity for decades with a 5-year OS of approximately 10-20%. In the absence of targeted molecular therapy, conventional cytotoxic, high-dose cytarabine-based chemotherapy has been the gold standard induction therapy with allogeneic SCT representing the preferred consolidation strategy [4]. The combination of venetoclax and azacitidine is increasingly being used as a salvage therapy in

R/R AML as a bridge to either SCT or DLI. However, the evidence available so far is obtained from small, single-arm studies and retrospective case series emphasizing the importance of running well-conducted randomized prospective clinical trials to obtain better-quality evidence [5].

A phase 2 study performed by Bazinet et al assessed the role of oral decitabine/cedazuridine with venetoclax in R/R AML and showed an overall response rate (ORR) of 50% after a median follow-up of 12.8 months [6]. The median OS was 7.6 months, with a median duration of response (DOR) of 4.6 months [6]. DiNardo et al performed a retrospective analysis of 39 R/R AML patients and two patients with MDS and blastic plasmacytoid dendritic cell neoplasm (BPDCN) treated with venetoclax and hypomethylating agent (HMA) or low-dose cytarabine (LDAC) [7]. The median OS was 3 months for the whole cohort and 4.8 months for responding patients, with better ORR seen in IDH1/2 and RUNX1-mutated patients with 27% and 50%, respectively [7].

In a propensity score matching analysis performed by Unglaub et al, 37 patients with R/R AML who received venetoclax-based combination chemotherapy were compared to 90 patients from the German Study Alliance Leukemia who were treated according to the physician's personal choice with non-venetoclax-based chemotherapy [8]. The ORR and the median event-free survival (EFS) were significantly higher in the venetoclax group (62% vs. 42%;  $P = 0.049$  and 8.0 months vs. 3.7 months;  $P = 0.006$ , respectively). The median OS was not superior in the venetoclax-treated group. In a cohort of 43 R/R AML patients treated with venetoclax-based combination therapy, the ORR was 76.2% and the OS was 9.3 months [9].

We retrospectively analyzed the response of 15 patients with R/R AML and four patients with high-risk MDS treated with venetoclax-azacitidine as salvage therapy from September 2021 to February 2023 at the Queen Elizabeth Hospital Birmingham. The baseline characteristics of the study population can be seen in Table 1. As per the four-gene expressor European LeukemiaNet (ELN) 2024 risk stratification [10], 10 patients (66.6%) had favorable risk disease, two (13.3%) had intermediate risk, and three (20%) had adverse risk disease. Prior to venetoclax-azacitidine chemotherapy, 12 AML patients (80%) received one line of chemotherapy, whereas three patients (20%) had two lines including FLAG-Ida salvage. Two MDS patients (50%) achieved remission with azaciti-

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**Table 1.** Baseline Characteristics of the Study Population

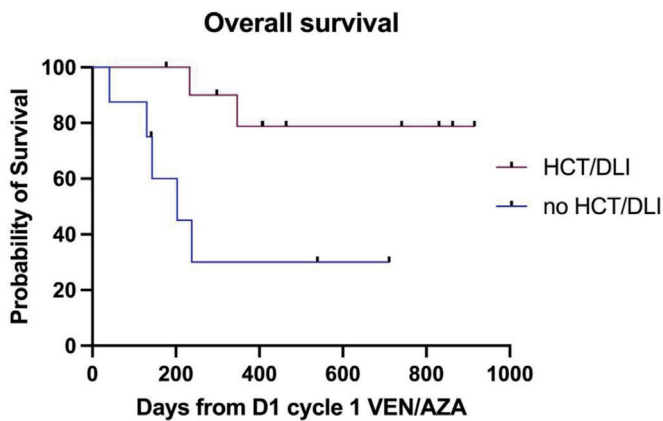
Variable	n (%)
Median age	65 (18 - 77 years)
Male/female ratio	1.1:1
Indication for venetoclax-azacitidine	
Primary refractory disease	6 (31.5%)
Relapse post consolidation chemotherapy	2 (10.5%)
Relapse post allogeneic stem cell transplant	11 (57.8%)
ELN risk	
Favorable risk (NPM1-mutated)	1 (6.6%)
Intermediate risk	4 (26.6%)
Adverse risk	10 (66.6%)
Number of previous lines of AML chemotherapy	
1 line	12 (80%)
2 lines (including FLAG-Ida)	3 (20%)
Chemotherapy regimen for the MDS patients	
Azacitidine	2 (50%)
FLAG-Ida	1 (25%)
Commonest adverse effects	
Neutropenia (grade 3-4)	19 (100%)
Admission with neutropenic sepsis	10 (52.6%)
Transfusion requirements	
Red cells	13 (68.4%)
Median number of red cell units	7 (1 - 16) units
Platelets	8 (42.1%)
Median number of platelets units	11 (2 - 23) units
Response	
CR/CRi	15 (78.9%)
Refractory disease	4 (20%)
Relapse	1 (5.2%)
Consolidation post venetoclax-azacitidine	
Allogeneic stem cell transplant	7 (36%)
DLI	6 (31.5%)

AML: acute myeloid leukemia; CR: complete remission; DLI: donor lymphocyte infusion; ELN: European LeukemiaNet; MDS: myelodysplastic syndrome.

dine, and one (25%) required FLAG-Ida salvage. No patients were previously exposed to venetoclax. The median number of delivered venetoclax-azacitidine cycles was 2. Four patients (21%) received 28 days of venetoclax, and the remaining patients had 14 - 21 days. Almost all patients developed at least grade 3 neutropenia, and 10 patients (52.6%) were admitted with neutropenic fevers during or after the first cycle. Red cell and platelet transfusion support were required in 13 (68.4%) and eight (42.1%) patients, respectively, with a median of seven red cell units (range 1 - 16) and 11 platelet units (range 2 - 23).

Fifteen patients (78.9%) achieved complete remission

(CR/CRi) post venetoclax-azacitidine chemotherapy, including the NPM1-mutated patients who achieved molecular remission. Seven patients (36.8%) underwent consolidation with allogeneic SCT and six patients (31.5%) received DLI. One patient (5.2%) had detectable molecular disease after two cycles and was refractory to gilteritinib. Four patients (20%) were refractory to venetoclax-azacitidine chemotherapy, two of whom had TP53 mutation, and the remaining two had t(3;3) and complex karyotype respectively. Twelve patients (63%) are alive and remain in remission. The median OS for the entire cohort was 11.3 months. Patients who underwent SCT or received DLI had an OS of 12.6 months



**Figure 1.** The difference in median OS between patients with and without an allograft or DLI post venetoclax-azacitidine. DLI: donor lymphocyte infusion; OS: overall survival.

compared to those who received neither therapy (OS 4.8 months,  $P = 0.01$ , hazard ratio (HR) 5.88 (95% confidence interval (CI) 1.164 - 29.7)), which is demonstrated in Figure 1. There was no statistically significant difference in the OS between ELN 2022 favorable/intermediate risk and adverse risk groups ( $P = 0.44$ , HR 0.53 (95% CI 0.12 - 2.4)), as shown in Figure 2.

Venetoclax-azacitidine is a low-intensity and largely outpatient-based chemotherapy that can be used as a salvage therapy in R/R AML and high-risk MDS. Its relatively low toxicity profile makes it a convenient approach that helps to maintain patient's fitness, an essential factor for those who receive this treatment combination as a bridge to either SCT or DLI. Furthermore, we were able to demonstrate a survival advantage in patients who had SCT or DLI following remission with venetoclax-azacitidine; however, those results should be cautiously interpreted due to the small cohort size.

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## Financial Disclosure

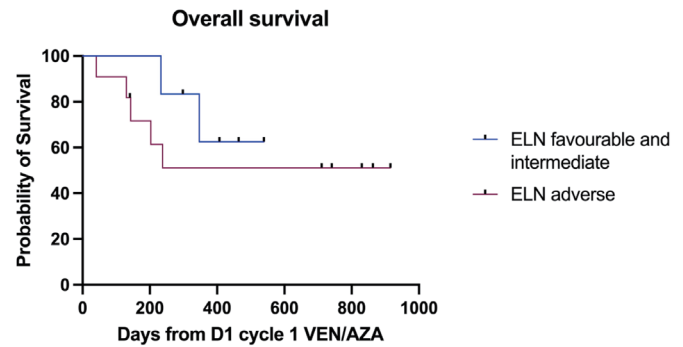
The authors declare no financial conflict of interest to disclose.

## Conflict of Interest

The authors declare no conflict of interest in this study.

## Informed Consent

Verbal consent has been obtained from patients and/or their families to obtain and share data for scientific purposes.



**Figure 2.** OS as per ELN 2022 risk stratification. ELN: European LeukemiaNet; OS: overall survival.

## Author Contributions

DO analyzed the data and wrote the manuscript. MLM and VM supervised and edited the manuscript. FL generated the survival curve.

## Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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