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Real-World Efficacy And Safety Of Azacitidine-Venetoclax In Acute Myeloid Leukemia: A Retrospective Single-Center Study

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Abstract
Background: *Acute myeloid leukemia (AML) is an aggressive hematological malignancy with dismal outcome especially in older or comorbid patients not candidate for intensive chemotherapy. The gold standard first line therapy in this population has become the Azacitidine-Venetoclax combination in the wake of the practice changing VIALE-A trial.*
Methods: *We conducted a retrospective cohort study to evaluate 10 AML patients treated with Azacitidine-Venetoclax at the Clinical Hematology Department of Moulay Ismail Military Hospital, Meknes, between January 2021 to May 2025. Efficacy was based on modified IWG response criteria. The Kaplan-Meier method was used for survival analyses. Events were grade according to the CTCAE.*
Results: *The median age was 68.7 years (range, 60–76). Eight patients (80 %) were treated with the regimen as the first-line therapy. After three cycles, the composite CR rate was 70 %. The median OS and PFS were 21.93 months and 10.3 months, respectively. Grade 3–4 neutropenia was universal (100%), then thrombocytopenia (90%) and bacterial infections (90%).*
Conclusion: *Our results align with VIALE-A and real-world experiences, and In conclusion, the Azacitidine-Venetoclax combination showed encouraging activity and a fair toxicity profile in our cohort. Greater availability of this regimen is still a challenge in our setting.*

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I. Introduction:

Acute myeloid leukemia (AML) is a cancer originating from the bone marrow myeloid stem cells that undergoes a differentiation arrest and excessive proliferation [1], resulting in a blast or immature cells accumulation in the blood. According to the World Health Organization (WHO), the diagnosis is set when 20% or more blasts are detected in the peripheral blood (PB) or bone marrow (BM) [2]. It is the most common type of acute leukemia found in adults with an estimated 21,450 new cases diagnosed in 2019 [3]. The disease has a slightly male predominance and a median age of diagnosis of around 68 years. AML is a highly fatal disease, responsible for 1.8% of all cancer deaths in the United States [4].

For patients who can tolerate intense treatment, the standard therapy is a combination of cytarabine and daunorubicin, the "3+7" regimen. Standard regimen: The 3+7 strategy has been firmly in place since the 1970s for achieving long-term remission in 30–40% of younger patients [5]. Still, the prognosis for elderly patients or patients with significant co-morbidities who also have an adverse cytogenetic risk remains grim largely due to increased treatment-related toxicity and 5-year survival rate of less than 10–15% [6,7]. Typically, these individuals would be treated with less aggressive methods such as low-dose cytarabine or be referred for supportive care — treatments that mitigate about treatment toxicity, but provide little in the way of efficacy.

The landmark phase III VIALE-A trial, comparing the combination of Azacitidine and Venetoclax versus Azacitidine and placebo, published its first results in 2020 and dramatically shifted the therapeutic paradigm for elderly AML patients. Its unprecedented outcomes led to definitive FDA approval, establishing this combination as the gold standard for AML treatment in this population [8].

The aim of this study is to evaluate the clinical outcomes in terms of efficacy and tolerability of the Azacitidine-Venetoclax combination in patients with acute myeloid leukemia.

II. Materials And Methods:

1. Study Design and Setting

We conducted a retrospective cohort study in the Clinical Hematology Department of Moulay Ismail Military Hospital in Meknes, Morocco.

2. Study Population and Inclusion Criteria:

The study included patients aged 18 years or older diagnosed with AML according to WHO criteria, who received Azacitidine-Venetoclax combination therapy either as first-line treatment in patients ineligible for intensive chemotherapy, or as second-line treatment following failure of intensive therapy. All patients were diagnosed and treated in the Clinical Hematology Department of Moulay Ismail Military Hospital between January 2021 and May 2025.

3. Data Collection:

Patient data were retrospectively collected from both paper-based and electronic medical records.

4. Treatment Protocol:

All patients received the Azacitidine-Venetoclax combination regimen. Given the significant financial constraints and taking into consideration the pharmacokinetic interaction between Voriconazole and Venetoclax — which requires a 75% dose reduction of Venetoclax — Voriconazole was systematically administered throughout each cycle, simultaneously serving as antifungal prophylaxis. The treatment protocol was as follows:

- Azacitidine 75 mg/m² per day for 7 days
- Venetoclax at a dose of 25 mg on day 1, 50 mg on day 2, and 100 mg from day 3 onwards

Each cycle lasted 28 days, with the possibility of extending the cycle duration or reducing the Venetoclax dose in cases of grade 3 or 4 toxicity.

5. Statistical Analysis:

Categorical variables were described using frequencies and percentages, while continuous variables were expressed as means and standard deviations. Statistical analyses were performed using SPSS software. Survival and follow-up analyses were conducted using the Kaplan-Meier method.

6. Study Endpoints:

Overall Survival (OS):

Overall survival was defined as the number of days from the date of AML diagnosis to the date of death from any cause.

Progression-Free Survival (PFS):

Progression-free survival was defined as the number of days from the date of diagnosis to the date of disease progression, treatment failure, relapse, or death. Data for patients who did not experience any of these events were censored at the date of the last follow-up visit or the last date the patient was known to be alive.

Treatment Response:

Therapeutic response was assessed using the modified International Working Group (IWG) response criteria for AML. Complete remission (CR) was defined as an absolute neutrophil count greater than 1,000 cells/mm³, a platelet count above 100,000/mm³, red blood cell transfusion independence, and bone marrow containing less than 5% blasts. Complete remission with incomplete hematologic recovery (CRi) was defined as meeting all CR criteria except for persistent neutropenia (ANC ≤ 1,000/mm³) or thrombocytopenia (platelet count ≤ 100,000/mm³). Complete remission with partial hematologic recovery (CRh) was defined as meeting all CR criteria except for neutrophil and platelet counts remaining below complete recovery thresholds (ANC > 500/mm³ and platelet count > 50,000/mm³). Disease progression was defined according to the European LeukemiaNet recommendations. Refractory disease was defined as the absence of response after four treatment cycles [8].

Treatment Tolerability:

Tolerability was assessed through clinical observation and biological monitoring for adverse events, which were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [9].

III. Results:

Table 3: Efficacy and Tolerability Outcomes of the Azacitidine–Venetoclax Combination

Efficacy and Tolerability	N = 10 (%)
Response Assessment after Cycle 1	
Complete Remission (CR)	2 (20%)
Complete Remission with incomplete hematologic recovery (CRi)	3 (30%)
Treatment Failure	5 (50%)
Disease Progression	0
Not Evaluated	0
Toxicity	

Grade 3–4 Anemia	6 (60%)
Grade 3–4 Thrombocytopenia	9 (90%)
Grade 3–4 Neutropenia	10 (100%)
Grade 3–4 Infectious Complications	7 (70%)
Diarrhea	2 (20%)
Nausea / Vomiting	0 (0%)
Grade 3 Hypokalemia	2 (20%)
Tumor Lysis Syndrome	1 (10%)
Treatment Modifications	
Cycle Delay	10 (100%)
Venetoclax Duration Reduction	10 (100%)
Survival Outcomes	
Median Follow-up	30.23 months (1.43–32.4)
Median Overall Survival (OS)	21.93 months (1.43–34.8)
Median Progression-Free Survival (PFS)	10.3 months (1.4–32.4)

CR: Complete Remission; CRi: Complete Remission with incomplete hematologic recovery; OS: Overall Survival; PFS: Progression-Free Survival.

A total of 10 patients were included in this retrospective analysis. The mean age was 68.7 ± 4.94 years (range: 60–76), with 80% of patients aged 65 years or older. Male patients predominated, accounting for 80% of the cohort (sex ratio M/F = 4:1). Comorbidities were present in 40% of patients, including hypertension and type 2 diabetes mellitus.

At diagnosis, WHO performance status was 3 or 4 in 70% of patients, reflecting the overall frailty of this population. The most common presenting symptom was anemic syndrome, observed in 80% of patients, followed by infectious syndrome (40%), hemorrhagic syndrome (20%), and tumoral syndrome with peripheral lymphadenopathy (20%). No patient presented with leukostasis. Biologically, anemia was documented in 80% of patients, thrombocytopenia in 90%, and hyperleukocytosis in 50%. The median bone marrow blast count was 49.3% (range: 20–82%). Cytogenetic analysis, performed in all patients, revealed a normal karyotype in 90% of cases; one patient harbored a combined trisomy 13 and trisomy 22 abnormality. Molecular profiling, conducted in 6 patients, identified NPM1 mutations in 3 patients — one of whom had a concomitant IDH1 mutation — and a combined ASXL1/IDH2/SRSF2 mutation in one patient. No TP53 mutation was detected. Risk stratification according to the ELN 2017 classification categorized 70% of patients as intermediate risk, 10% as favorable, and 10% as adverse risk.

Eight patients (80%) received azacitidine-venetoclax as first-line therapy due to ineligibility for intensive chemotherapy, while 2 patients (20%) received it as salvage therapy following failure of a standard "3+7" induction regimen. The median number of treatment cycles administered was 5 (range: 1–24).

With a median follow-up of 30.23 months (range: 1.43–32.4), the composite complete remission rate (CR + CRi) reached 50% after the first cycle, increasing to 60% and 70% after the second and third cycles, respectively. Primary refractory disease was observed in 30% of patients. Among responders, 40% subsequently experienced disease relapse. The median time to first response was 1.57 months (range: 1–4 months). Median overall survival was 21.93 months (range: 1.43–34.8 months) (Figure 1). All deaths occurred in the refractory or relapsed setting, with septic shock accounting for 60% of fatal events and hemorrhagic complications for the remaining 40%. Median progression-free survival was estimated at 10.3 months; however, as more than 50% of patients remained censored at the time of analysis due to ongoing follow-up, this estimate should be interpreted with caution. (Figure 2)

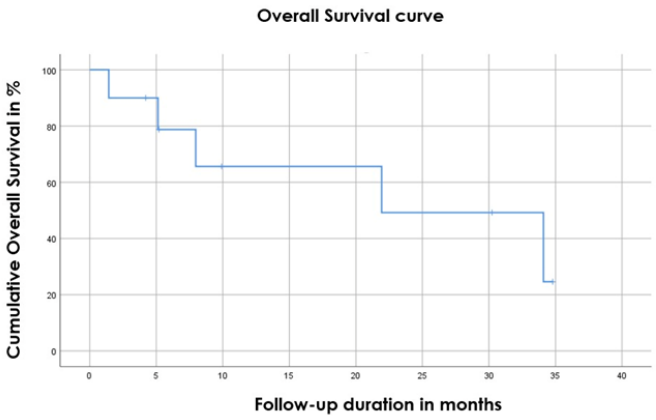

Figure 1: Overall Survival Curve

Figure 2: Progression Free Survival Curve

Regarding tolerability, hematologic toxicity was the predominant adverse effect. Grade 3–4 neutropenia occurred in all patients (100%), followed by grade 3–4 thrombocytopenia in 90% and grade 3–4 anemia in 60% of patients, needing red blood cell and platelet transfusions as well as G-CSF administration. In response to prolonged cytopenias, venetoclax duration was progressively reduced to 14 and subsequently to 7 days per cycle, and inter-cycle intervals were extended to 35 days in all patients. Grade 3–4 bacterial infections were observed in 90% of patients. One patient developed invasive pulmonary aspergillosis following voriconazole discontinuation, which resolved upon its reintroduction. Additional toxicities included grade 2 diarrhea in 20% of patients, grade 3 hypokalemia in 20%, and a single case of tumor lysis syndrome occurring during the Venetoclax ramp-up phase, which was successfully managed with standard supportive measures.

IV. Discussion:

Treatment options for older or intensive chemotherapy-ineligible adults with AML have substantially evolved over the past five decades, shifting toward more effective and individualized strategies with an acceptable safety profile. The Azacitidine-Venetoclax combination has emerged as the preferred first-line standard of care in this population, supported by robust efficacy and safety data, though its use is frequently complicated by cytopenias requiring transfusion support, cycle delays, or Venetoclax dose modifications.

In our series, with a median follow-up of 30.23 months, the median overall survival and progression-free survival were 21.93 months and 10.3 months, respectively. These outcomes compare favorably with those reported in the landmark phase III VIALE-A trial, which established a median OS of 14.7 months in the Azacitidine-Venetoclax arm versus 9.6 months in the Azacitidine-placebo arm (HR 0.58 [95% CI 0.47–0.72]; $p < 0.001$) over a median follow-up of 43.2 months [8]. Our results are also consistent with real-world data (RWD) from a large multicenter study conducted across 53 NHS hospitals in England, which reported a median OS of 13.6 months (95% CI: 11.7–15.1) among 587 patients treated with Azacitidine-Venetoclax [10]. A single-center Canadian RWD study from the University of Alberta similarly reported a median OS of 9.6 months in the overall population, rising to 16.3 months among patients achieving composite complete remission [11]. The relatively favorable survival observed in our cohort may be partly explained by the molecular profile of our patients, particularly the absence of TP53 mutations and the presence of NPM1 and IDH1/2 mutations, which are associated with enhanced sensitivity to Venetoclax-based regimens as demonstrated in VIALE-A subgroup analyses.

Regarding treatment response, the composite CR rate in our cohort progressively increased from 50% after cycle 1 to 70% after cycle 3, with a median time to first response of 1.57 months. This kinetic is consistent with VIALE-A, where 75%, 87%, and 91% of clinical responses were achieved after 1, 2, and 3 cycles, respectively [8]. Among the two patients who received Azacitidine-Venetoclax as salvage therapy, outcomes were expectedly inferior, consistent with retrospective data reporting an overall response rate of 63.3% and a median OS of only 7 months in relapsed/refractory settings [12].

Concerning tolerability, the toxicity profile observed in our cohort was consistent with previously published data. Hematologic toxicity was universally present, with grade 3–4 neutropenia occurring in all patients, grade 3–4 thrombocytopenia in 90%, and grade 3–4 anemia in 60%. These rates are in keeping with those reported

across the literature, where grade 3–4 neutropenia ranges from 43% to 98%, severe thrombocytopenia from 42% to 88%, and significant anemia from 28% to 57% [8,10,11]. Grade 3–4 infectious complications were recorded in 90% of our patients, a rate higher than the 19–22% reported in VIALE-A [8], likely reflecting the greater baseline frailty of our population and the resource-limited context of management. Gastrointestinal toxicities remained mild and manageable. Notably, the single case of invasive pulmonary aspergillosis following voriconazole discontinuation underscores the critical importance of maintaining antifungal prophylaxis throughout treatment.

Our study has several limitations, including the small sample size, the retrospective single-center design, the inclusion of two patients treated beyond first line, and the limited availability of molecular analysis. The latter represents a significant prognostic tool, as mutational status — particularly IDH1/2, NPM1, FLT3, and TP53 — is included in AML risk stratification under the revised ELN 2022 classification and directly influences therapeutic decision-making. These limitations preclude robust subgroup analyses and highlight the need for larger, prospective, and ideally multicenter national studies, which remain challenging given the limited accessibility and high cost of Venetoclax in our setting.

V. Conclusion:

Acute myeloid leukemia remains a life-threatening hematological malignancy with a poor prognosis. Even though intensive chemotherapy is considered the standard of care, it is restricted to younger and fit patients, because it carries high toxicity risks making it unsuitable for elderly or comorbid patients. However, this latter population represents the most frequently affected group, given the age-related accumulation of somatic mutations. Historically, these patients lacked access to effective therapeutic options. The landmark phase III VIALE-A trial revolutionized the management of this population by demonstrating the superiority of Azacitidine-Venetoclax over Azacitidine alone in terms of overall and progression-free survival, making this combination the gold standard for AML treatment in elderly patients.

In our retrospective cohort, conducted at the Clinical Hematology Department of Moulay Ismail Military Hospital in Meknes, the Azacitidine-Venetoclax combination yielded a median overall survival of 21.93 months and a median progression-free survival of 10.3 months. Grade 3–4 hematologic toxicity was the most frequent and clinically significant adverse effect, followed by infectious and gastrointestinal complications. These outcomes are consistent with those reported in the VIALE-A trial and available real-world data.

While Azacitidine-Venetoclax has become the preferred first-line therapy for elderly AML patients, its accessibility remains severely limited in our context due to its prohibitive cost. Efforts to ensure equitable access to this treatment are urgently needed to improve survival outcomes in this vulnerable population.

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