# Real-Life Experience of Dose-Adjusted Venetoclax in Acute Myeloid Leukemia Patients Concomitantly Using Posaconazole for Antifungal Prophylaxis: A Single-Center Experience

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**ABSTRACT**

The treatment process in acute myeloid leukemia (AML) often results in prolonged neutropenia, especially in the early period, and this requires antifungal prophylaxis. In the era of venetoclax (VEN), concomitant antifungal prophylaxis has been abandoned because azole antifungals inhibit cytochrome P450 3A4, the primary enzyme responsible for VEN metabolism. If azole antifungal prophylaxis is used with VEN, the dose of VEN needs to be reduced, but the clinical consequences in this situation are unknown. Limited clinical data exist on outcomes for patients treated with VEN, a hypomethylating agent (HMA), and posaconazole. We retrospectively evaluated our single-center experience on 46 patients, 20 treatment-naive and 26 relapsed/refractory (RR) AML patients. VEN was used after dose adjustment due to concomitant posaconazole use for antifungal prophylaxis. The median age was 65.5 years (range, 18-78). The median follow-up was 5.5 months (range, 1-25). The overall response rate (ORR) was 60.8%. The incidence of invasive fungal infection was 15.2%. The median OS from venetoclax initiation of all the patients and those with CR/CRi was 6 and 10 months, respectively. After VEN dose reduction due to concomitant posaconazole use, the observed ORR was comparable to the ORR previously reported in the literature without VEN dose reduction and antifungal prophylaxis. However, the OS obtained in our patients was shorter than previously reported in the literature. In addition, the incidence of invasive fungal infections in our patients was not less than that reported in the VEN and HMA studies without antifungal prophylaxis.

**Keywords:** Acute myeloid leukemia, Hypomethylating agent, Venetoclax, Posaconazole, Dose adjustment

## INTRODUCTION

Expression of B-cell leukemia/lymphoma-2 (BCL-2) in acute myeloid leukemia (AML) has been associated with decreased sensitivity to cytotoxic chemotherapy and a higher recurrence rate.[1] BCL-2 inhibition with the targeted oral agent venetoclax (VEN) has reshaped the treatment landscape for AML. Excellent outcomes have been reported with the combination of hypomethylating agents (HMAs) and VEN.[2,3] VEN in combination with azacitidine or decitabine received approval by the US Food and Drug Administration (FDA) for the treatment of newly diagnosed adult AML patients 75 or older, or younger patients unsuitable for standard induction chemotherapy because of comorbidities. VEN in combination with HMAs has become the new standard of care for frontline AML treatment in older patients or those unfit for intensive chemotherapy. The exciting results with VEN in unfit treatment-naive AML also led to its off-label use in relapsed/refractory (RR) AML.

Patients with AML are at high risk for febrile neutropenia and life-threatening fungal infections.[4] To reduce the risk of fungal infections, antifungal prophylaxis with posaconazole is the standard of care.[5] However, due to drug-drug interactions, antifungal prophylaxis has been abandoned in AML patients receiving VEN-based therapy, regardless of whether it can be used together after VEN dose adjustment.

Azole antifungals were excluded in the clinical trials evaluating VEN and HMA therapy. To our knowledge, there is only one real-life data in the literature demonstrating the activity of VEN in combination with posaconazole in the setting of VEN and HMA therapy; in this study, the dose of VEN was 100 mg for concomitant posaconazole use.[6] Here, we present "real life" evidence from our institution regarding the use of dose-adjusted VEN in combination with azacitidine or decitabine in patients with AML who also received posaconazole for antifungal prophylaxis.

## PATIENTS AND METHODS

### *Patients*

We retrospectively reviewed all consecutive patients with AML per the World Health Organization classification[7] admitted to our department between May 2019 and August 2022. Newly diagnosed or relapsed/refractory AML patients treated with dose-adjusted VEN in combination with decitabine or azacitidine and concomitantly received antifungal prophylaxis were included in the study. Following institutional ethics review approval, baseline characteristics for the 46 patients were collected by reviewing electronic medical records.

### *Treatment*

Patients were treated by adjusting the dose of VEN for concomitant medications based on prescribing information.[8] All patients received two doses of a 300 mg posaconazole delayed-release tablet twice daily followed by 300 mg once daily for antifungal prophylaxis. During cycle 1, patients were hospitalized for intrapatient dose escalation of oral VEN (10 mg, 20 mg, 50 mg, and 70 mg on days 1, 2, 3, and 4, respectively). Patients were then administered 70 mg VEN daily. In patients who achieved remission, posaconazole prophylaxis was terminated, and the oral VEN dose was increased to 400 mg. The VEN doses of the patients were adjusted if antifungal prophylaxis with posaconazole was discontinued or changed to another antifungal due to invasive fungal infections (IFIs). Among them, VEN was administered at a median dose of 100 mg in combination with voriconazole and 400 mg in combination with liposomal amphotericin B. Patients received azacitidine at 75 mg per square meter of body-surface area subcutaneously on days 1 through 7 every 28-day cycle. Decitabine was administered at a dose of 20 mg per square meter of body-surface area per day intravenously on days 1 through 5 every 28-day cycle. No G-CSF was administered. Intravenous hydration and oral allopurinol were administered for prophylaxis for tumor lysis syndrome (TLS).

### *Efficacy Assessments*

Bone marrow aspirations, as an institutional approach, were performed at baseline and after cycles 1, 2, and 4 and after that when clinically indicated. Multiparametric flow cytometry was performed on bone marrow aspirates. Response assessments were retrospectively assessed using the 2017 European Leukemia Network (ELN) criteria.[9] The overall response rate (ORR) was defined as the combination of CR, CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR). Early death was defined as death occurring within the first 60 days of VEN-based treatment.

### Statistical Analysis

IBM SPSS Statistics (version 24) was used for statistical analysis. Descriptive statistics were used to present the data. Categorical data were presented as numbers and ratios, and numerical data were presented as median, minimum, and maximum. OS was defined as the duration from the first day of the treatment to the date of death or the time to the survivors' last follow-up date. Kaplan–Meier survival analysis was applied for OS, and log-rank tests were used to examine the factors affecting

**Table 1.** Baseline characteristics of the patients

| Characteristic | All patients n= 46 | Treatment naive, n= 20 | Relapsed/ Refractory n= 26 |
|---|---|---|---|
| Age | | | |
| Median (range) years | 65.5 (18-78) | 66.5 (57-78) | 61 (18-77) |
| ≥ 75 years, n (%) | 7 (15.2) | 4 (20) | 3 (11.5) |
| Male, n (%) | 33 (71.7) | 15 (75) | 18 (69.2) |
| Comorbid disease n (%) | | | |
| 0 | 10 (21.7) | 2 (10) | 8 (30.8) |
| 1 | 9 (19.6) | 6 (30) | 3 (11.5) |
| ≥ 2 | 27 (58.7) | 12 (60) | 15 (57.7) |
| AML type*, n (%) | | | |
| De novo | 31 (67.4) | 14 (70) | 17 (65.4) |
| Secondary | 15 (32.6) | 6 (30) | 9 (34.6) |
| Previous MDS | 7 (15.2) | 3 (15) | 4 (15.4) |
| Previous MPN | 2 (4.3) | 1 (5) | 1 (3.8) |
| Previous CMML | 3 (6.5) | 1 (5) | 2 (7.7) |
| Therapy related | 3 (6.5) | 1 (5) | 2 (7.7) |
| Bone marrow blast count, n (%) | | | |
| 5-19% | 11 (23.9) | – | 11 (42.3) |
| 20-30% | 13 (28.2) | 8 (40) | 5 (19.2) |
| ≥ 30 - < 50% | 8 (17.3) | 4 (20) | 4 (15.3) |
| ≥ 50% | 14 (30.4) | 8 (40) | 6 (23) |
| ELN risk category, n (%) | | | |
| Favorable | 7 (15.2) | 4 (20) | 3 (11.5) |
| Intermediate | 26 (56.5) | 12 (60) | 14 (53.8) |
| Adverse | 13 (28.3) | 4 (20) | 9 (34.6) |
| Somatic mutations, n (%) | | | |
| NPM1 | 9 (19.5) | 5 (25) | 4 (15.3) |
| FLT3 | 7 (15.2) | 4 (20) | 3 (11.5) |
| Treatment n (%) | | | |
| Venetoclax+Decitabine | 12 (26) | 4 (20) | 8 (30.8) |
| Venetoclax+Azacitidine | 34 (74) | 16 (80) | 18 (69.2) |
| Median number of venetoclax-based cycles (range) | 3 (1-30) | 4 (1-30) | 2 (1-16) |
| Invasive fungal infections, n (%) | 7 (15.2) | 3 (15) | 4 (15.3) |

survival. Cox regression analysis was applied to evaluate factors affecting survival. p values of ≤ 0.05 were considered statistically significant.

## RESULTS

### *Patient*

A total of 46 patients with AML who underwent therapy with a VEN-based regimen were consecutively included in this retrospective observational study. At the time of analysis, patients received a median of 3 cycles of VEN-based treatment (range, 1-30). The median age was 65.5 years (range 18–78 years), and 15.2% were more than 75 years old. Patient demographics and disease characteristics are shown in Table 1.

All patients received VEN and posaconazole concurrently, in whom VEN dose adjustment is strongly recommended due to CYP3A4 inhibition caused by azole antifungals. VEN was administered at a dose of 70 mg in combination with posaconazole. Among seven patients who developed probable or proven IFIs, 4 received liposomal amphotericin B and three voriconazole. The dose of VEN was adjusted to 400 mg in patients receiving liposomal amphotericin B and 100 mg in patients receiving voriconazole.

**Table 2.** Treatment response

| Characteristic | All patients n= 46 | Treatment naive n= 20 | Relapsed/ refractory n= 26 |
|---|---|---|---|
| Response, no (%) | | | |
| ORR (CR+CRi+PR) | 28 (60.8) | 15 (75) | 13 (50) |
| CR 11 (23.9) | 5 (25) | 6 (23.1) | |
| CRi 13 (28.3) | 8 (40) | 5 (19.2) | |
| PR 4 (8.7) | 2 (10) | 2 (7.7) | |
| NR 18 (39.1) | 5 (25) | 13 (50) | |
| Early death (≤ 60 days) | 11 (23.9) | 2 (10) | 9 (34.6) |

***Abbreviations***: CR, complete response; CRi, complete response with incomplete blood count recovery of ANC or PLTS; NR, no response; ORR, objective response rate.

Of the 46 patients, 20 were treatment-naive and were treated with VEN in combination with HMAs as initial therapy for AML. The remaining 26 patients were patients with RR AML and were treated with off-label use of VEN in combination with HMAs. All patients received a combination of VEN and HMA. Of the treatment-naive AML patients (n= 20), 16 received azacitidine, and 4 received decitabine. Of the RR AML patients (n= 26), 18 received azacitidine, and 8 received decitabine. At the time of analysis, the median number of VEN-based cycles for treatment-naive and RR AML patients was 4 (range, 1-30) and 2 (1-16), respectively.

### *Safety*

None of the patients experienced tumor lysis syndrome (TLS). Consistent with prior studies in AML, the most frequently reported grade 3 or 4 adverse events were hematologic, which included neutropenia (32.6%) and thrombocytopenia (28.2%). The most common nonhematologic adverse events of any grade were nausea (39.1%), skin rash (32.6%), and abdominal pain (28.2%), most of which were grade one or two. The most common serious adverse events included febrile neutropenia (30.4%) and sepsis (28.2%).

The number of patients who developed any IFIs (possible, probable or proven) during VEN-based treatment in entire cohort was 7 (15.2%), 3 (15%) of whom were in the treatment-naive group and, 4 (15.3%) of whom were in the RR patient group. IFIs were more common among nonresponders than responders to VEN-based treatment. The best response states in these patients were 1 CRi, 1 PR, and 5 NR.

### *Efficacy*

For treatment-naive AML patients, with a median follow-up duration of 6 months (range, 1-25 months), the ORR was achieved in 15 (75%) patients, including 5 (25%) CR, 8 (40%) CRi, no MLFS and 2 (10%) PR (Table 2). For RR AML patients, with a median follow-up duration of 4 months (range, 1-18 months), the ORR was achieved in 13 (50%) patients, including 6 (23%) CR, 5 (19%) CRi, no MLFS and 2 (8%) PR. Six responding patients, 2 with treatment-naive and 4 with RR AML, were bridged to allogeneic hematopoietic stem cell transplantation. The median time to best response was 1.5 months (range, 1-4) and two months (range, 1-4) for treatment-naive and RR AML patients, respectively.

Minimal residual disease (MRD) analysis by quantitative PCR was performed on six patients who responded to therapy as CR/CRi and were initially positive for NPM1. Among them, the best MRD response was MRD negativity for three patients. The other three patients had persistent MRD positivity; however, they remained in remission.

A total of 11 (23.9%) patients did not survive more than two months, primarily due to sepsis with con-

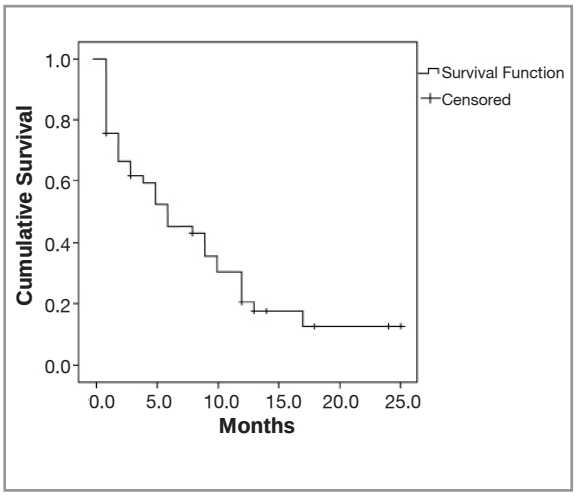


**Figure 1a.** Kaplan–Meier curve of the entire cohort of AML patients.

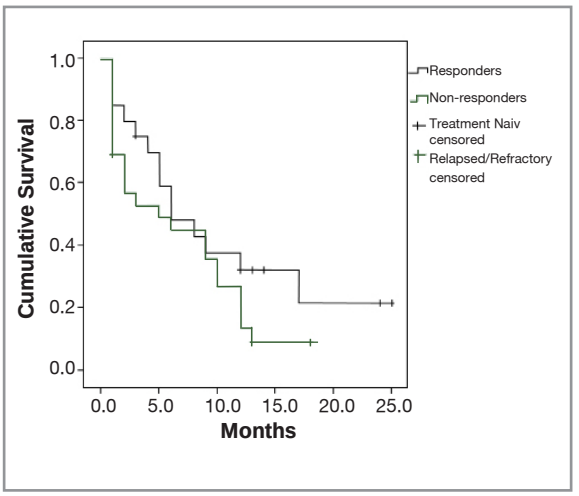


**Figure 1b.** Survival in treatment-naive and relapsed/refractory patients.

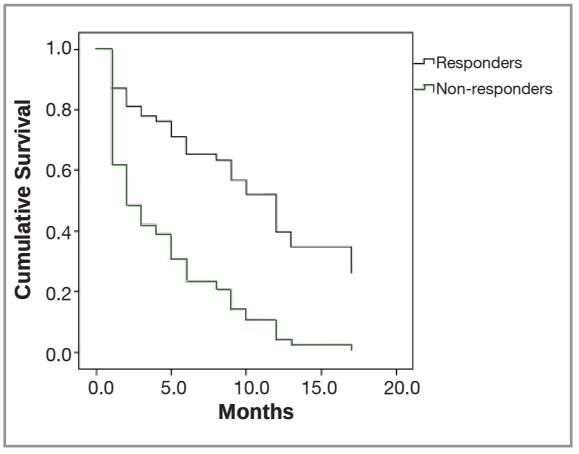


**Figure 1c.** Survival in responding and nonresponding patients.

comitant disease progression (n= 6), coronavirus disease (n= 3), or sudden cardiac death (n=2, related to cardiac comorbidities). There was no significant difference in CR/CRi between treatment-naive and RR AML patients (p> 0.127). We also did not find a significant difference in ORR or CR/CRi between patients according to the ELN risk category (p> 0.677).

Univariate analysis, considering sex, age, MDS/myeloproliferative neoplasm background, ELN risk category at diagnosis, and the number of lines of treatment before VEN, did not find a correlation between any of these parameters and survival (all p values > 0.05). Patients who did not respond to VEN had worse survival in the univariate Cox regression analysis (p< 0.001; HR: 3.43; 95% CI: 1.683-7.010).

At a median follow-up of 5.5 months (range, 1-25), 10 (21.7%) patients were alive, of whom six were still using VEN. Among the surviving patients, the causes of drug discontinuation were toxicity (n= 2) and patient decision (n= 2).

The median OS from starting VEN for entire cohorts was six months, shown in Figure 1a. The median survival for RR AML patients was slightly shorter (5 months vs. six months) compared to treatment-naive AML patients, shown in Figure 1b. Survival among patients did not differ according to the type of HMA combined with VEN. Patients with CR/CRi showed a survival advantage over those without (p= 0.001), shown in Figure 1c. The median OS for responding and nonresponding patients was ten months (95% CI: 7.848-12.152) and one month, respectively.

## DISCUSSION

We reported a real-life experience of VEN-based therapy in a cohort of patients with treatment-naive and RR AML. This is the first report of VEN activity at the 70 mg dose when concomitantly used with posaconazole, a commonly used oral antifungal agent with a survival benefit in the setting of antifungal prophylaxis in AML. Antifungal prophylaxis is widely used in patients with AML because

prolonged neutropenia is common, especially during induction therapy, and may lead to serious fungal infections.[4,10] Posaconazole compared to other antifungal therapies reduces rates of infections.[5] However, due to drug–drug interactions with posaconazole, a strong CYP3A4 inhibitor, and VEN, these therapies were not permitted in most patients who participated in the VEN plus HMA clinical trials.[11-14] Therefore, when used together, this drug-drug interaction requires a reduction in the VEN dose. It was reported in a study including a small number of patients that posaconazole can be used for antifungal prophylaxis in patients with AML receiving VEN after reducing the VEN dose by at least 75%.[15] However, the clinical efficacy of the reduced doses of VEN when given with azoles is uncertain. The thought that dose reductions may impair effectiveness has raised concerns.[16] Therefore, it is controversial whether antifungal prophylaxis with posaconazole should be performed in patients treated with VEN.

Studies investigating the combination of either decitabine or azacitidine with VEN in elderly treatment-naive AML patients demonstrated a composite complete response rate (CR + CRi) of 62% to 77%.[11-14,17-19] Unlike previous studies, our study, which included both treatment-naive and RR AML patients, used a reduced dose of VEN due to the concomitant use of posaconazole for antifungal prophylaxis, and response rates were comparable to response rates of previous studies. The combination of VEN with an HMA was also evaluated in RR AML. In contrast to the high response rates and durability of responses and OS in the front-line setting with VEN-based combinations, the efficacy of VEN combinations in the RR AML setting was reported with inconsistent response rates over a wide range. Previous studies have demonstrated variable responses, including a CR/CRi rate of 12% to 62% in the RR population.[20-28] The CR/CRi rate of our RR AML patients was 42.3%. Additionally, there was a correlation between response and survival. The fact that the dose of VEN was reduced due to the use of posaconazole in our patients and that the response rates of the dose adjusted VEN with posaconazole was not inferior to that in previous studies may shed some light on this controversial point.

IFIs were more common among nonresponders compared with responders to VEN-HMA therapy (28% vs 7%). The overall incidence of patients who developed any IFI was 15.2%. This was similar to the 17% incidence reported by another single-institution study in which antifungal prophylaxis was infrequent.[29]

Obtaining rapid responses with VEN-based therapies has become a feature of this therapy in AML. In a previous study, the median time to first response and the best response was reported as 1.2 months and 2.1 months, respectively, in patients treated with VEN plus HMA combinations.[12] Similarly, VEN-based therapies showed rapid responses in our evaluable patients. The median time to best response was 1.5 months and two months for treatment-naive AML patients and RR AML patients, respectively. While the early mortality rate was reported as 18% in studies using single-agent HMA[30] for AML, it was reported as 8% in studies using the combination of VEN and HMA.[14] In all these studies, a significant proportion of the cause of early death was associated with an infection in addition to disease progression. While effective treatments are required for AML, patients must survive long enough for these treatments to be effective. This increases the importance of prophylaxis in terms of infections even more. In our study, the rate of patients living less than two months among treatment-naive patients was 10%, which was better than the rates reported with single-agent HMA. This may be related to the fact that VEN-based treatments show better and more rapid efficacy. Additionally, improvement in the prophylaxis policy may further reduce early mortality in the future.

It is known that the presence of NPM1 mutation is associated with a good prognosis. The median survival of our treatment-responsive patients with NPM1 mutation at diagnosis, for whom MRD analysis was available, was over 12 months. However, we did not observe a difference in OS between MRD negative patients and MRD positive patients among patients with CR/CRi. This result suggested that VEN-based therapies, which are indefinite, can keep the disease under control even if MRD is positive. However, for this result our study data may not be sufficient to make a comment due to the limited number of patients and the need for a longer follow-up.

The median OS for our entire cohort (6 months) is less than that reported in the randomized study of VEN/HMA (14.7 months). The fact that, in contrast to the randomized trial, our cohort included patients with heavily pretreated RR AML (more than 50% of the entire cohort) probably contributed to the shorter survival. But it's hard to explain that alone with the RR AML ratio because we found no significant difference in subgroup analysis for OS between treatment-naive and RR AML patients. Also, the univariate analysis did not find a correlation between any parameter and survival. This raises the question of whether there is a difference in response to VEN, HMA, and posaconazole combinations according to race. Despite the study's retrospective nature with a relatively small sample size, all patients received an adjusted dose of VEN, which allows a higher confidence in the integrity of the reported response data.

## Conclusion

In conclusion, our study indicates that VEN-based therapy and antifungal prophylaxis with posaconazole are feasible after a dose reduction of VEN in both treatment-naive and RR AML patients. However, it is confusing that shorter survival was observed, and the expected decrease in the incidence of IFI was not observed in our patients receiving posaconazole compared to historical controls not receiving antifungal prophylaxis. Randomized controlled studies are needed in this regard.

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