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Azacitidine and Venetoclax Treatment in Acute Myeloid Leukemia: Real-Life Experience

Azasitidin ve Venetoklaks Tedavisi ile Akut Myeloid Lösemi: Gerçek Yaşam Deneyimi

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ÖZET

Amaç: Bu çalışma, yoğun kemoterapiye uygun olmayan yeni tanı almış akut myeloid lösemi (AML) hastalarında azasitidin-venetoklaks (AZA-VEN) tedavisinin gerçek yaşam koşullarındaki etkinliğini, güvenilirliğini ve sağkalım sonuçlarını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: İki merkezde 2022–2025 yılları arasında tedavi edilen 36 AML hastası retrospektif olarak analiz edildi. Veriler arasında demografik özellikler, tedavi döngüleri, doz ayarlamaları, yanıt oranları (tam remisyon, parsiyel remisyon, refrakter hastalık), hematolojik iyileşme, yan etkiler ve genel sağkalım yer aldı.

Bulgular: Ortanca yaş 66 (dağılım: 27–98) idi ve hastaların %61,1'i tam remisyon (CR) sağladı. Ortanca genel sağkalım (OS) 22 ay idi (95% GA: 13,1–30,9); ≥3 kür alan hastalarda sağkalım anlamlı olarak daha uzundu (23,7 aya karşılık 6,4 ay; p=0,031) ve erken nötrofil iyileşmesi gösterenlerde (>1000/µL, 7. gün itibariyle: 29,4 aya karşılık 13,7 ay; p=0,009) de benzer şekilde anlamlı fark mevcuttu. Grade 3 toksisite görülen hastalarda (%33,3) sağkalım daha kötüydü (6,4 aya karşılık Grade 2 için 22 ay; p=0,006). İnvaziv fungal enfeksiyona rastlanmadı.

Sonuç: AZA–VEN tedavisi, yoğun kemoterapiye uygun olmayan AML hastalarında etkili ve güvenli bir seçenek olup, sağkalım sonuçları büyük klinik çalışmalarla karşılaştırılabilir düzeydedir ve bazı yönlerden onlarla uyum göstermektedir. Bulgularımız, özellikle üç veya daha fazla kür tedavi alabilen hastalarda sağkalımın anlamlı şekilde uzadığını göstermiştir; bu durum, yan etkiler uygun biçimde yönetildiğinde tedavi sürekliliğinin önemini vurgulamaktadır. Çalışmamızda invaziv fungal enfeksiyonların hiç görülmemesi, literatürde bildirilen değişken oranlarla karşılaştırıldığında dikkat çekicidir ve uyguladığımız profilaksi stratejisinin olumlu katkı sağlamış olabileceğini düşündürmektedir. Ayrıca, kadın hastalarda gözlenen sağkalım avantajı kayda değer olmakla birlikte, dikkatle yorumlanmalı, hipotez oluşturucu bir bulgu olarak kabul edilmeli ve daha büyük, iyi tasarlanmış çalışmalarda doğrulanmalıdır.

Anahtar Kelimeler: Akut Miyeloid Lösemi, Azasitidin, Venetoklaks, Gerçek Yaşam Verileri, Sağkalım

ABSTRACT

Objective: This study evaluated the real-world efficacy, safety, and survival outcomes of azacitidine-venetoclax (AZA-VEN) therapy in newly diagnosed acute myeloid leukemia (AML) patients ineligible for intensive chemotherapy.

Materials and Methods: A retrospective analysis was conducted on 36 AML patients treated at two centers between 2022–2025. Data included demographics, treatment cycles, dose adjustments, response rates (complete remission, partial remission, refractory disease), hematologic recovery, side effects, and overall survival.

Results: The median age was 66 years (range: 27–98), with 61.1% achieving CR. Median OS (Overall Survival) was 22 months (95% CI: 13.1–30.9), significantly longer in patients receiving ≥3 cycles (23.7 vs. 6.4 months; p=0.031) and those with early neutrophil recovery (>1000/µL by day 7: 29.4 vs. 13.7 months; p=0.009). Grade 3 toxicity (33.3% of patients) correlated with poorer survival (6.4 vs. 22 months for Grade 2; p=0.006). No invasive fungal infections occurred.

Conclusion: AZA–VEN is effective and safe in chemotherapy-ineligible AML, providing survival outcomes that are comparable to, and in some aspects even consistent with, those observed in pivotal clinical trials. Our findings indicate that extended therapy, especially in patients who were able to continue for three or more cycles, was associated with a meaningful improvement in overall survival, thereby emphasizing the importance of maintaining treatment continuity whenever possible. The complete absence of invasive fungal infections in our cohort, in contrast to the variable rates reported in previous studies, suggests that our prophylaxis strategy may have contributed positively and could be of clinical relevance. In addition, the female survival advantage observed in our study, while noteworthy, should be interpreted with caution, considered as hypothesis-generating, and further validated in larger, well-designed studies.

Keywords: Acute myeloid leukemia, azacitidine, venetoclax, real-world data, survival

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INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy resulting from the malignant transformation of hematopoietic stem cells and characterized by abnormal proliferation of immature myeloid cells. AML is particularly more common in the elderly population, with a significant proportion of patients being 65 years or older at the time of diagnosis. The clinical course and prognosis of the disease depend on many factors, including genetic and molecular characteristics, cytogenetic changes, and the patient's overall performance status (1). The traditional treatment approach for AML involves intensive induction chemotherapy with the cytarabine- and anthracycline-based "7+3" regimen. Although this regimen provides high complete response rates in young and healthy patients, intensive chemotherapy may not be suitable for patients aged 65 and older due to myelosuppression and treatment-related complications. For this group of patients, low-intensity chemotherapy regimens and targeted therapies have come to the forefront (2).

In recent years, the use of targeted agents in AML treatment has brought about a significant shift. Venetoclax, a B-cell leukemia/lymphoma 2 (BCL-2) inhibitor, has emerged as an effective anti-leukemic agent by inducing apoptosis in leukemic cells. Its combination with hypomethylating agents (HMAs) such as azacitidine or decitabine provides an effective treatment option for newly diagnosed AML patients who are ineligible for intensive chemotherapy (3,4). Although azacitidine and venetoclax have become standard treatment in many centers today, significant differences are observed between real-world data and clinical trial results due to variations in practice.

In our study, we aimed to share our experience regarding the differences between real-life data and clinical trials in terms of treatment duration, side effect profile, and survival outcomes with azacitidine-venetoclax therapy.

MATERIALS AND METHODS

In this retrospective study, we included adult AML patients who were ineligible for intensive chemotherapy at diagnosis and were initiated on AZA-VEN therapy between January 2022 and May 2025 at Gazi Yaşargil Training and Research Hospital and Van Yüzüncü Yıl University Faculty of Medicine Hospital. Demographic data (age, sex), disease subtype, laboratory findings at diagnosis (WBC, hemoglobin, platelets, blast percentage), genetic/molecular characteristics, ECOG performance status, and whether AML was de novo or secondary were recorded. The treatment start date, venetoclax dose and possible dose reductions, side effects and their severity, bone marrow response after the first cycle, response status, and the number of cycles received during treatment were evaluated. Venetoclax dose adjustments due to drug side effects were documented. A history of invasive fungal infections and antifungal prophylaxis was investigated. Patients were regularly monitored during treatment, and the last follow-up date and survival status were included in the data. Our study has ethics committee approval dated 23/05/2025, numbered 497.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)." Descriptive statistics were presented as n and % for categorical variables and as mean ± SD and median (min-max) for continuous variables. The Kaplan-Meier method was used to compare survival durations between clinical groups. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 36 AML patients were included in this study. The mean age was 66.05 ± 14.75 years, with an age range of 27 to 98 years, and the median age was calculated as 66.0 years. Of the patients, 55.6% were over 60 years old, while 44.4% were 60 years or younger. The gender distribution showed that 38.1% were female and 61.1% were male. When the distribution of AML subtypes was evaluated, the most common was M1 subtype at 58.3%; other subtypes were M0 (8.3%), M2 (16.7%), M4 (8.3%), and M5 (8.3%). ECOG performance status assessment revealed that 16.6% of patients were ECOG 0, 41.7% were ECOG 1, and 41.7% were ECOG 2. Two patients were diagnosed with chronic myelomonocytic leukemia, one with prostate cancer, and one with secondary AML following ovarian cancer treatment. None of the patients had poor genetic risk. For venetoclax treatment doses, 400 mg was administered to 55.6% of patients, 100 mg to 19.4%, 200 mg to 16.7%, and 300 mg to 8.3%. The mean number of venetoclax cycles received by patients was 5.77 ± 3.57, with a median of 6 (1–12). Of the patients, 30.6% received 1–2 cycles, while 69.4% received 3 or more cycles. The mean day for neutrophil count to reach >500 cells/μL after treatment was 11.69 ± 14.86, and the rate of patients reaching this value by day 7 was recorded as 57.7%. The mean day for neutrophil count to reach >1000 cells/μL was 13.47 ± 13.98, and the rate of patients reaching this value by day 7 was calculated as 47.6%. The mean day for platelet count to reach >50,000/μL was 25.42 ± 12.84, with a median day of 27. At diagnosis, the mean bone marrow blast percentage was 54.27 ± 25.30, while the mean blast percentage after the first cycle was 10.11 ± 12.68. In the bone marrow evaluation after the first cycle, the rate of patients with blast count <5% was 61.1%, while the rate with ≥5% was 38.9%. In terms of treatment response, 61.1% of patients achieved complete remission, 33.3% achieved partial remission, and 5.6% were refractory. Among the side effects requiring venetoclax dose reduction, the most frequently reported was neutropenia at 62.5%, followed by abdominal pain at 25.0% and diarrhea at 12.5%. When the severity of side effects was examined, Grade 1 side effects were observed in 20.0% of patients, Grade 2 in 46.7%, and Grade 3 in 33.3%. The mean follow-up duration was 18.60 ± 17.74 months, with a median of 15 months (min: 2.77 – max: 97.73). Kaplan-Meier survival analysis revealed a median overall survival of 22.00 months for the entire patient group (95% CI: 13.09–30.90); the two-year survival rate was 43.0%, and the five-year survival rate was 27.9%. During the follow-up period, 52.8% of patients died

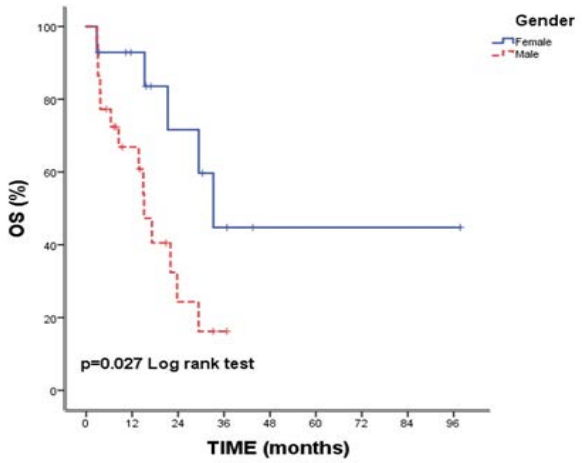

Figure 1. Overall survival (OS) according to gender. Median OS was 33.2 months for female patients and 15.1 months for male patients (p=0.027, Log-rank test).

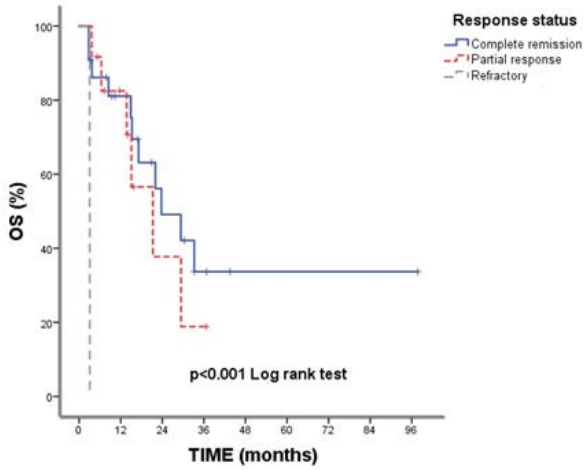

Figure 3. OS based on response status. Median OS was 23.73 months in complete remission, 21.26 months in partial response, and 3.06 months in refractory patients (p<0.001).

(exitus), while 47.2% survived. Significant survival differences were observed based on some variables. The median survival for female patients was 33.2 months, while for males it was 15.1 months, and the gender variable was found to be statistically significant (p=0.027) (Figure 1). The median survival of patients whose neutrophils reached >1000 cells/μL within 7 days after treatment was 29.43 months, while it was 13.73 months for those who reached this value on or after day 7, and the difference was statistically significant (p=0.009) (Figure 2). The median survival of patients who achieved complete remission was 23.73 months, while it was 21.26 months for those with partial response and only 3.06 months for refractory patients. The survival difference based on response status was statistically significant (p<0.001) (Figure 3). The median survival of patients who received ≥3 cycles of venetoclax treatment was 23.73 months, while it was 6.43 months for those who received only 1–2 cycles, and this difference was also significant (p=0.031) (Figure 4). When evaluated in terms of side effect severity, survival was 6.43 months in patients with Grade 3 side effects, 22.00 months in Grade 2, and 15.10

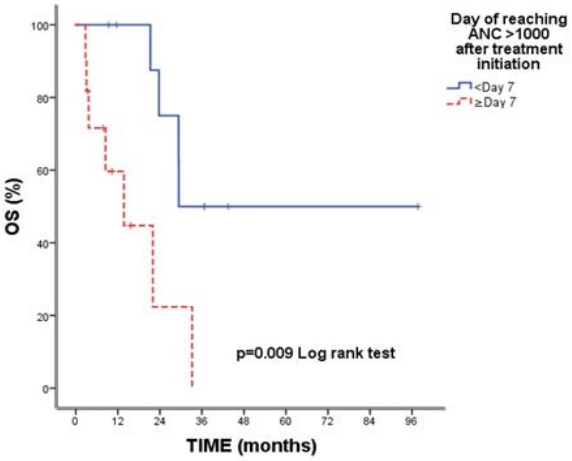

Figure 2. OS according to neutrophil recovery time. Patients who reached ANC >1000/μL before day 7 had significantly longer OS (29.43 vs. 13.73 months, p=0.009).

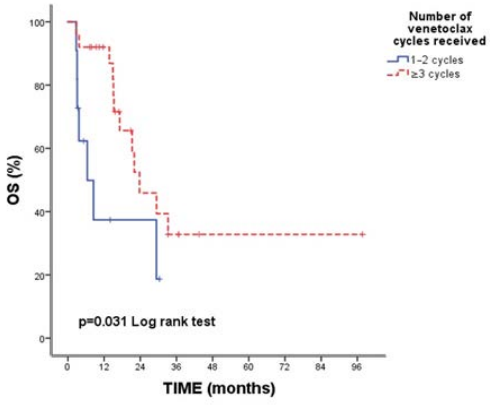

Figure 4. OS according to number of venetoclax cycles. Patients receiving ≥3 cycles had significantly better OS (23.73 vs. 6.43 months, p=0.031).

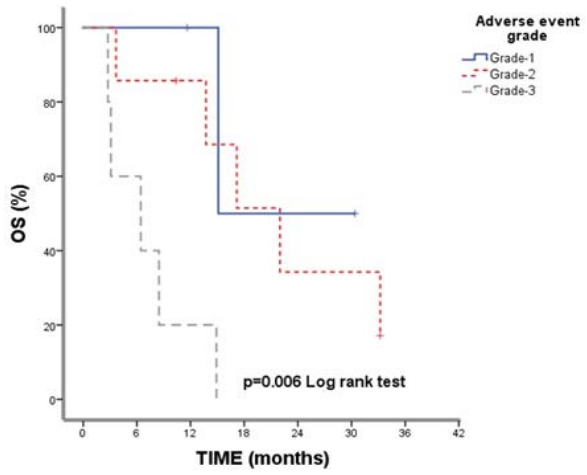

Figure 5. OS based on severity of adverse events. Median OS was 6.43 months for Grade 3, 22.00 months for Grade 2, and 15.10 months for Grade 1 (p=0.006).

months in Grade 1. The survival difference based on side effect severity was statistically significant (p=0.006) (Figure 5).

DISCUSSION

In this study, the efficacy and tolerability of AZA-VEN combination therapy in previously untreated AML patients under real-life conditions were evaluated. Due to the early achievement of response with AZA-VEN, response assessment was performed after the first cycle, in parallel with the literature (4). In the VIALE-A Phase III study, the complete response rates for azacitidine and venetoclax combination were 66.4%, and the median overall survival (OS) was reported as 14.7 months (4). In our patient group, the complete remission rate was 61.1%, and the median overall survival was calculated as 22.0 months. In addition to VIALE-A, the phase 3 VIALE-C trial evaluated venetoclax + low-dose cytarabine (LDAC) versus LDAC alone in chemotherapy-ineligible, newly diagnosed AML. VIALE-C improved response rates and showed a trend toward longer overall survival; in subsequent follow-up analyses, an OS benefit became more apparent with longer observation, although the primary OS endpoint was not met at the initial analysis due to limited follow-up time. These findings contextualize our results within the broader landscape of venetoclax-based, low-intensity regimens (5). These data support that the AZA-VEN combination is an effective alternative, especially for patients ineligible for intensive chemotherapy. Additionally, the finding that survival durations were consistent with or higher than the literature is important in demonstrating the feasibility and efficacy of this treatment in real-life conditions.

The effect of treatment duration and the number of cycles on OS has been reported to a limited extent in the literature. In the long-term follow-up of the VIALE-A study, it was reported that 76% of patients who achieved complete remission received ≥6 cycles of treatment, and this group had a survival advantage (6). In our study, the median OS was 23.73 months in patients who received ≥3 cycles, while it was 6.43 months in those who received only 1–2 cycles, and the difference was significant (p=0.031). This finding suggests the potential impact of treatment duration on survival. This situation indicates that treatment adherence may directly affect survival when hematologic side effects are controlled.

The effect of gender on survival has not been clearly demonstrated in the literature. In the multivariate analysis of the VIALE-A study, it was reported that gender did not have a significant effect on OS (6). In our study, however, the median OS was 33.2 months in female patients and 15.1 months in male patients, and the difference was statistically significant (p=0.027). It is thought that this difference is hypothesis-generating, considering the sample size and patient characteristics, and needs to be confirmed in larger series. Subgroup analyses, particularly considering parameters such as advanced age, comorbidities, and performance status, may provide a more accurate assessment of the effect of gender on survival.

When evaluated in terms of side effects, hematologic toxicities were significantly increased in patients treated with AZA-VEN. Neutropenia and thrombocytopenia were among the most commonly observed complications during treatment (6,7). In the VIALE-A study, Grade ≥3 neutropenia was reported in 43%, thrombocytopenia in 46%, and febrile neutropenia in 43% of patients (6). In our study, neutropenia (62.5%) was the most frequent reason for venetoclax dose reduction, and Grade-3 side effects were observed in 33.3%, Grade-2 in 46.7%, and Grade-1 in 20% of patients. Although the literature emphasizes that hematologic toxicities are common, studies analyzing survival differences based on side effect severity are limited. In the long-term follow-up of VIALE-A, deaths due to infections secondary to Grade 3–4 neutropenia were reported, but no direct association with survival was made (6). In our study, survival was 6.43 months in patients with Grade-3 side effects, 22.00 months in Grade-2, and 15.10 months in Grade-1, and the difference was significant (p=0.006). This finding suggests that timely and effective use of supportive treatments may have significant effects on survival. Additionally, considering the impact of side effect severity on treatment continuity, it is understood that dose modifications and G-CSF support should be planned on an individualized basis. Our findings are consistent with emerging Turkish real-world data reporting manageable toxicity and encouraging responses with AZA–VEN combinations in chemotherapy-ineligible AML (8).

Finally, as a notable finding in our study, no invasive fungal infections (IFI) developed in any of our patients. Reports in the literature regarding IFI frequency are conflicting, with rates ranging from 1% to 20% (9–12). The main factors influencing this include the duration of neutropenia, mucosal barrier integrity, degree of immune suppression, and antifungal prophylaxis use. Some studies found no significant difference despite prophylaxis use, while others advocated a risk-based approach (10–13). In our series, although some patients

received posaconazole and others did not, the absence of IFI is noteworthy in terms of the effectiveness of our infection management. This finding suggests that infections are shaped not only by prophylaxis but also by patient-specific risk factors, supporting the need for individualized antifungal prophylaxis decisions.

Our study has some limitations. First, the study was designed retrospectively, and patient data were obtained from past records. This increases the risk of missing data and potential bias. The limited sample size reduces the generalizability of subgroup analyses (e.g., survival differences by gender). Molecular and cytogenetic risk classifications were not evaluated in our study; however, notably, none of the patients had poor prognostic genetic/cytogenetic features. Another limitation is the absence of adverse-risk molecular/cytogenetic cases in our cohort. This may partly explain the relatively favorable survival we observed and should be considered when interpreting external generalizability. This may have contributed to the better response and survival rates observed.

On the other hand, the study also has strengths. Being derived from real-life data, it directly reflects the challenges encountered in clinical practice and patient management. The statistically significant association between side effect severity and survival is an original finding contributing to the literature. Additionally, the significant correlation between the number of treatment cycles and survival provides clinically relevant guidance for treatment planning. A notable aspect of the study is that the azacitidine-venetoclax combination was administered not only to elderly and comorbid patients but also to those aged ≤60 years. Of our patient group, 44.4% were under 60 years old, and significant treatment responses were achieved in these patients as well. This suggests that the regimen is effective and tolerable in younger patients and that patient selection should be based on biological suitability rather than age alone.

In conclusion, AZA-VEN therapy, supported by real-life data, offers a valuable treatment option for AML patients ineligible for intensive chemotherapy, with its demonstrated efficacy, manageable side effect profile, and survival advantage. Our findings highlight the importance of treatment duration, side effect management, and individualized supportive therapies, providing data that will contribute to clinical practice in these aspects.

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