Venetoclax and Azacitidine Treatment in Relapsed Acute Myeloid Leukemia after Hematopoietic Stem Cell Transplantation: A Cohort Study in the Real-World Setting of a Tertiary Center

Hematopoetik Kök Hücre Nakli Sonrası Nüks Eden Akut Myeloid Lösemide Venetoklaks ve Azasitidin Tedavisi: Üçüncü Basamak Kohortunda Gerçek Yaşam Deneyimi

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To the Editor,

Approximately half of all acute myeloid leukemia (AML) patients eventually relapse after allogeneic stem cell transplantation (aHSCT) [1], and the best treatment after aHSCT is unclear. The present study sought to demonstrate the outcomes of the combination of venetoclax and azacitidine (VEN-AZA) in patients with relapsed AML after aHSCT who were unsuitable for intensive regimens.

This study had a single-center, retrospective cohort design. The study sample consisted of patients treated at Hacettepe University in Türkiye. Ethical approval was obtained from the local ethics committee with document number GO22/307. Adult patients aged >18 years admitted between January 2018 and December 2021 were screened.

The inclusion criteria were receiving aHSCT for the treatment of AML, experiencing AML relapse after aHSCT, and being treated with the VEN-AZA combination. Patients with acute promyelocytic leukemia were excluded. The basic demographic data of the patients, test results, treatments received, disease status, final status, and causes of death were recorded.

VEN was started at 100 mg with a 3-day ramp-up to a target dose of 400 mg for the first cycle and was continued unless severe cytopenia or drug interaction ensued. AZA was given at 75 mg/m^2/day on days 1-7 in combination with VEN in 28-day cycles. Response assessments were performed according to the modified response criteria of the International Working Group [2].

Statistical analyses were performed using IBM SPSS Statistics 25 for Windows. The distribution of variables was investigated using the Shapiro-Wilk test. Z tests were used to compare values between two independent groups. Survival analyses were performed using the Kaplan-Meier test and differences were evaluated by log-rank test. Values of $p<0.05$ were considered to indicate statistical significance.

A total of 14 patients were included. Their basic characteristics and descriptive data are shown in Table 1.

Eleven patients received myeloablative conditioning (78.5%) for aHSCT. The median relapse-free survival time after aHSCT was 10.1 (5.3-22.9) months. Three (21.4%) patients received treatment for molecular relapse (preemptive setting) and the rest for morphological relapse. For two patients, the VEN-AZA courses were followed by donor lymphocyte infusions (DLIs).

Table 1. Basic descriptive findings of the patients.

Parameters	Median (IQR)
Age (years)	50.5 (28.2-60.5)
	n (%)
Sex	
Female Male	6 (42.9) 8 (57.1)
AML type	
De novo Secondary or therapy-related	11 (78.6) 3 (21.4)
ELN 2022 risk category at initial diagnosis	
Adverse Intermediate Low	4 (28.6) 9 (64.3) 1 (7.1)
Molecular genetics at relapse *FLT3-ITD* mutation	 1 (7.1)
aHSCT type	
Fully matched related donor MAC RIC	11 (78.6) 9 2
Haploidentical donor MAC RIC	3 (21.4) 2 1
Relapse type	
Morphological relapse Molecular relapse	11 (78.6) 3 (21.4)

AML: Acute myeloid leukemia, ELN: European LeukemiaNet, aHSCT: allogeneic hematopoietic stem cell transplantation, MAC: myeloablative conditioning, RIC: reduced intensity conditioning.

The median follow-up time was 6.8 (range: 0.8-14.8) months. A median of 2 courses (range: 1-6) of VEN-AZA were applied until the best response was achieved. Composite complete remission (CR) + CR with incomplete count recovery (CRi) was achieved in 6 (54%) patients with morphological relapse, while molecular CR (CRm) was achieved and sustained in 2 (67%) patients with molecular relapse.

During follow-up, 6 patients (42.9%) died, all of whom were in the morphological relapse group. The causes of death were infection in 4 cases (67%), sudden cardiac death in 1 case, and gastrointestinal bleeding in 1 case. The Kaplan-Meier curves are shown in Figure 1.

Relapsed AML after aHSCT is a particularly challenging therapeutic problem as transplant-related issues further increase the arising risks. The prognosis for relapsed AML after aHSCT is dismal, with most patients failing to achieve another durable remission and a 1-year overall survival rate of only 20-25% [3]. This rate is expected to be lowest in patients who have not received intensive treatment. In our cohort, the median overall survival rate was 12.8 months. In a similar study from China, the response rate was reported as 61.5% and half of those responses were CR [4]. In another study conducted by the German Cooperative Transplant Study Group consisting of 30 patients (5 with molecular relapse), the overall response rate was 47% (14 of 30 patients; 3 CR MRDneg, 5 CR, 2 CRi, 4 other) and the estimated median overall survival time was 3.7 months [5]. Consistent with our cohort, these studies showed that the efficacy and outcomes were good among patients with molecular relapse, while responses and results were not good among patients with high tumor burden and multiple relapses, indicating the importance of disease monitoring and early treatment.

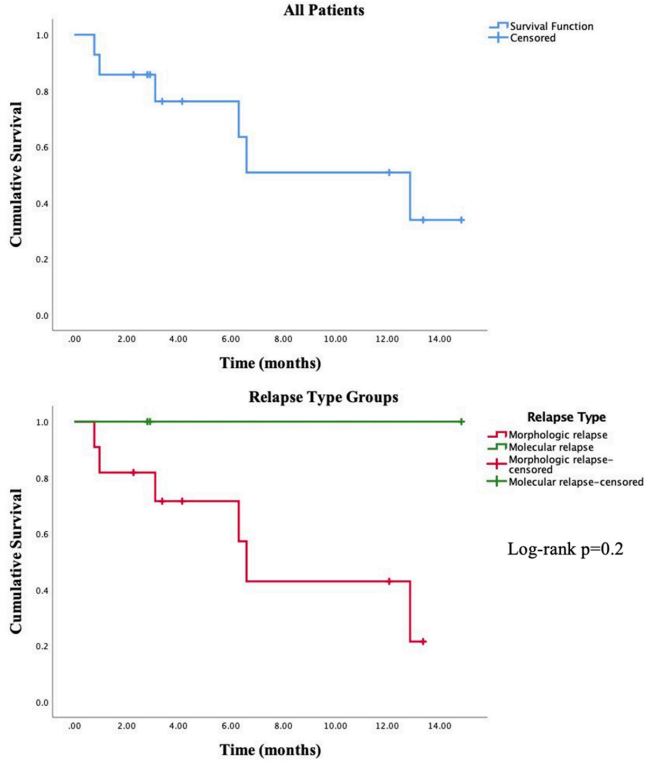

Figure 1. Kaplan-Meier overall survival curves of all patients and relapse groups.

The VEN-AZA combination is thought to have some advantages regarding the pathobiology of relapse after aHSCT. For example, AZA potentiates the effect of graft-versus-leukemia (GvL) by increasing tumor immunogenicity [6] without increasing the effects of graft-versus-host disease (GvHD). Since bcl-2 is an essential pathway for healthy T-cell functions [7], the question of how the use of VEN after aHSCT will affect GvL and GvHD is of significant importance. Similarly to AZA, it has been shown with in vitro assays that VEN can enhance the GvL effects [8]. In parallel, the findings of our cohort suggest that outcomes are promising with VEN-AZA, especially among patients with low tumor burden. Subsequent DLI, which will further increase the GvL effects, is also a valuable option in this setting.

The major limitations of our study are its retrospective, uncontrolled design and small sample size. The study's strengths are that it shares a real-world experience of a difficult-to-treat patient group with a paucity of data in the literature and it provides a basis for future studies.

In conclusion, the VEN-AZA combination may be a promising option for patients with relapsed AML after aHSCT who are unsuitable for intensive therapy, and the use of VEN-AZA treatment might be more beneficial in settings of molecular relapse with or without DLI. Well-designed prospective studies may further elucidate the role of this treatment approach in cases of relapse after aHSCT.

Keywords: Venetoclax, Azacitidine, Relapsed acute myeloid leukemia, Hematopoietic stem cell transplantation

Anahtar Sözcükler: Venetoklaks, Azasitidin, Nüks akut myeloid lösemi, Hematopoetik kök hücre nakli

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Hacettepe University Ethics Committee with document code GO22/307.

Informed Consent: All procedures were performed in line with the ethical standards of the Declaration of Helsinki.

Authorship Contributions

Surgical and Medical Practices: H.G., O.E.Ç., H.D., Ü.Y.M., E.A.K., Y.B.; Concept: H.G., H.D., Y.B.; Design: H.G. H.D., Y.B.; Data Collection or Processing: O.E.Ç., Ü.Y.M., Y.B.; Analysis or

Interpretation: H.G., H.D., Y.B.; Literature Search: O.E.Ç., E.A.K., Ü.Y.M., Y.B.; Writing: H.G., O.E.Ç.

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