Azacitidine plus venetoclax for maintenance treatment in intermediate-to-low-risk acute myeloid leukemia: A comparative analysis of clinical outcomes in an observational cohort

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Received December 6, 2024; Accepted April 2, 2025

DOI: 10.3892/ol.2025.15064

Abstract. The combination of azacitidine (AZA) and venetoclax (VEN) for maintenance treatment in patients with intermediate-to-low-risk acute myeloid leukemia (AML) is a contentious issue. The aim of the present study was to investigate the relationship between the use of VEN plus AZA (VEN-AZA) and the relapse rate of intermediate-to-low-risk AML among adult Chinese participants. The primary endpoint was AML relapse, analyzed using time-to-event methods. A multivariate Cox proportional hazards model was used to compare outcomes between patients who continued VEN-AZA for maintenance treatment and those who discontinued such therapy. Among the 43 patients, 22 (51.1%) received VEN-AZA with treatment cycles every 2-3 months, while the remaining 21 patients discontinued maintenance therapy. The median ages for the two groups were 59 and 49 years, respectively, with an age range of 21-81 years. With a median follow-up of 29.6 months (range 7-74), the median progression-free survival (PFS) was not reached in the maintenance therapy group and was 47.3 months in the group that discontinued treatment. The number of grade 3-4 adverse events was low in the maintenance group, with neutropenia and thrombocytopenia as the primary hematological adverse events, and respiratory infection as the main non-hematological adverse event. Univariate analysis indicated that age, white blood cell count and maintenance therapy were associated with AML relapse. After adjusting for confounding factors, multivariate Cox proportional hazards model showed that maintenance treatment was associated with a reduced risk of relapse and a longer PFS time, compared with discontinued treatment (hazard ratio, 0.06; 95% confidence interval, 0-0.77). Therefore, patients treated with VEN-AZA exhibited a longer PFS time, suggesting that further clinical trials are warranted.

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Key words: acute myeloid leukemia, azacitidine, venetoclax, maintenance treatment, progression-free survival

Introduction

Acute myeloid leukemia (AML) is a highly heterogeneous hematological malignancy that poses significant treatment challenges. Despite considerable advancements in induction and consolidation therapies for AML in recent years, the risk of relapse after achieving complete remission (CR) remains high (1). Specifically, among patients aged <60 years, >50% experienced relapse, whereas relapse rates reached 90% in those aged ≥60 years. This high disease recurrence rate contributes to an aggregated 5-year overall survival (OS) of 30.5% across all cases (2). This underscores the urgent need for effective and safe post-remission treatment strategies to enhance disease-free survival and ultimately OS survival. While consolidation therapy has been established to improve survival outcomes in low-risk patients with AML, maintenance therapy, a standard treatment component for certain hematological malignancies, such as acute lymphoblastic leukemia and acute promyelocytic leukemia (3,4), remains a contentious issue in AML. For patients with AML harboring high-risk factors for recurrence and who have undergone allogeneic hematopoietic stem cell transplantation, maintenance therapy is deemed necessary to mitigate the risk of recurrence (5,6). However, for those with intermediate-to-low-risk disease, maintenance therapy is not yet part of the standard treatment regimen due to insufficient evidence of its benefits. Thus, the exploration of maintenance therapy for patients with intermediate and low-risk AML is of importance.

The combination of azacitidine (AZA) and venetoclax (VEN) has demonstrated synergistic effects, enhancing the anti-leukemic efficacy while potentially reducing drug dosages and associated toxicities (7,8). This VEN and hypomethylating agent regimen has emerged as the standard treatment for elderly or unfit patients with AML who are not suitable for intensive chemotherapy, where unfitness is defined as meeting ≥1 of the following: Eastern Cooperative Oncology Group

Table I. PCR primer sequence information.

Gene name	Forward primer sequence (5'-3')	Reverse primer sequence (5'-3')
AML1-ETO	CACCTACCACAGAGCCATCAAA	ATCCACAGGTGAGTCTGGCATT
CBFβ-MYH11	CATTAGCACAACAGGCCTTTGA	AGGGCCCGCTTGGACTT
HOX11	TGGATGGAGAGTAACCGCAGAT	GGGCGTCCGGTTCTGATA

performance status ≥2; Hematopoietic Cell Transplantation Comorbidity Index ≥3; organ dysfunction; or active infection requiring intravenous antimicrobial therapy (9-11). Although studies have explored the use of AZA or VEN individually for maintenance therapy in AML (12), there is a paucity of research on the application of the combined VEN plus AZA (VEN-AZA) regimen for maintenance therapy in patients with low-to-intermediate-risk AML.

In the present study, a retrospective analysis of 43 patients newly diagnosed with intermediate-to-low-risk AML who underwent maintenance therapy at Beijing Luhe Hospital Affiliated to Capital Medical University (Beijing, China) was conducted to evaluate the efficacy and safety of the combination regimen of VEN-AZA in maintenance therapy for patients with this disease.

Materials and methods

Patient selection and data collection. A retrospective analysis of patients with primary intermediate-to-low-risk AML admitted to Beijing Luhe Hospital Affiliated to Capital Medical University between March 2018 and June 2024 was conducted. Prognostic risk stratification was conducted according to the 2022 European Leukemia Net AML criteria (13). The inclusion criteria were as follows: i) Patients who remained in CR following induction and consolidation therapy, with blasts of <5% and no evidence of extramedullary tumor infiltration and received either VEN-AZA treatment regimen or no treatment; ii) patients who were not eligible for or unwilling to undergo allogeneic or autologous hematopoietic stem cell transplantation; iii) patients who had not received other targeted drugs; and iv) patients with complete clinical data. The study variables including the patient's age, sex, prognosis stratification, white blood cell (WBC) count, platelet count, lactate dehydrogenase levels, bone marrow blast percentage, chromosomal analysis, fusion genes, gene mutations and minimal residual disease (MRD) monitoring prior to maintenance therapy were retrospectively extracted from electronic medical records.

Diagnostic data collection Bone marrow morphological examination was performed using Wright's staining, with 200 nucleated cells counted under an oil-immersion lens. All molecular analyses, including reverse transcription-quantitative PCR (RT-qPCR) for AML1-ETO, CBFβ-MYH11 and HOX11 expression quantification, as well as next-generation sequencing (NGS)-based mutation profiling of 248 genes, were performed by Hightrust Diagnostics Medical Laboratory (Beijing, China). The RT-qPCR primer sequence information for various genes is shown in Table I. For NGS, libraries were constructed using the Hemaseq™ Myeloid 248 Gene Mutation Detection Kit (Healthy Biotechnology Co., Ltd; cat. no. S0918-S), a hybridization capture-based panel targeting exons and flanking ±20 bp intronic regions of 248 genes, including core driver genes [such as fms related receptor tyrosine kinase 3 (FLT3), nucleophosmin 1 (NPM1) and CCAAT enhancer binding protein α (CEBPA)], epigenetic regulators [(such as DNA methyltransferase 3α (DNMT3A), tet methylcytosine dioxygenase 2 (TET2), isocitrate dehydrogenase [NADP(+)] 1/2 (IDH1/2)], signaling pathway genes (such as Janus kinase 2 and calreticulin) and spliceosome complex genes (such as splicing factor 3b subunit 1 and serine and arginine rich splicing factor 2).

For bone marrow MRD detection, a Canto II flow cytometer (Becton, Dickinson and Company) with Diva software was used to acquire and analyze the data. Antibody reagents from Becton, Dickinson and Company and Beckman Coulter, Inc. were used to label CD34, CD117, CD38, HLA-DR, CD33, CD13, CD15, CD14, CD4, CD7, CD19 and CD56. After collecting 500,000 CD45+ cells, abnormal cell populations were identified by combining leukemia-associated immunophenotype and 'different from normal' approaches. The threshold was set at 0.1% as per the European LeukemiaNet recommendations to distinguish negative and positive results (14). Additionally, RT-qPCR targeting AML1-ETO and CBFβ-MYH11 fusion-gene transcripts was used for MRD detection.

Maintenance therapy and efficacy endpoint. Patients in the maintenance therapy group received VEN-AZA maintenance therapy 1 month after consolidation therapy. The specific VEN-AZA dosing regimen was as follows: Subcutaneous injection of 75 mg/m^2 AZA for 7 consecutive days and the dose of VEN was reduced from the standard 400 mg daily to 200 mg on days 1-21. If grade 4 myelosuppression (based on the Common Terminology Criteria for Adverse Events version 5.0) occurred during treatment (15), the VEN treatment was paused and supportive treatments such as leukocyte elevation, anti-infection measures or component blood transfusions were provided. One treatment cycle lasted 2-3 months. During the maintenance treatment period, an assessment was conducted per treatment cycle. The methods for detecting MRD included qPCR for detecting fusion genes and flow cytometry to identify leukemia-associated abnormal phenotypes in the bone marrow cells of patients. The primary efficacy endpoint was progression-free survival (PFS), defined as the time from the onset of the disease to recurrence, death or end of follow-up.

Statistical analysis. Continuous variables are presented as the median and range (minimum to maximum). Intergroup

Table II. Clinical and biological characteristics of patients with AML at diagnosis.

Characteristic	Off maintenance therapy, n=21	On maintenance therapy, n=22	P-value
Median age at diagnosis, years (range)	59.00 (24.00-81.00)	49.00 (21.00-75.00)	0.165
Median white blood cells, x109/l (range)	8.59 (0.84-362.06)	7.46 (0.88-76.20)	0.078
Median hemoglobin, g/l (range)	85.00 (51.00-150.00)	86.50 (34.00-127.00)	0.560
Median platelets, x109/l (range)	43.00 (8.00-265.00)	51.50 (2.00-333.00)	0.806
Median bone marrow blast count, % (range)	62.00 (1.00-91.00)	44.75 (13.00-78.00)	0.521
Sex, n (%)			0.432
Female	8 (38.10)	11 (50.00)	
Male	13 (61.90)	11 (50.00)	
Gene fusion, n (%)			0.956
Negative	9 (42.86)	11 (50.00)	
AML1-ETO	7 (33.33)	7 (31.82)	
HOX11	4 (19.05)	3 (13.64)	
CBFβ-MYH11	1 (4.76)	1 (4.55)	
NPM1 status n (%)			0.280
Wild type	13 (61.90)	10 (45.45)	
Mutant	8 (38.10)	12 (54.55)	
CEBPA status, n (%)			0.021
Wild type	14 (66.67)	21 (95.45)	
Mutant	7 (33.33)	1 (4.55)	
FLT3 status, n (%)			0.252
Wild type	15 (71.43)	12 (54.55)	
Mutant	6 (28.57)	10 (45.45)	
DNMT3A status, n (%)			0.069
Wild type	14 (66.67)	20 (90.91)	
Mutant	7 (33.33)	2 (9.09)	
KIT status, n (%)			0.475
Wild type	16 (76.19)	19 (86.36)	
Mutant	5 (23.81)	3 (13.64)	
ASXL1 status, n (%)			>0.999
Wild type	20 (95.24)	20 (90.91)	
Mutant	1 (4.76)	2 (9.09)	
ASXL2 status, n (%)			0.607
Wild type	19 (90.48)	21 (95.45)	
Mutant	2 (9.52)	1 (4.55)	
NRAS status, n (%)			0.664
Wild type	19 (90.48)	18 (81.82)	
Mutant	2 (9.52)	4 (18.18)	
IDH2 status, n (%)			0.664
Wild type	19 (90.48)	18 (81.82)	
Mutant	2 (9.52)	4 (18.18)	
IDH1 status, n (%)			>0.999
Wild type	20 (95.24)	20 (90.91)	
Mutant	1 (4.76)	2 (9.09)	
TET2 status, n (%)			0.412
Wild type	17 (80.95)	20 (90.91)	
Mutant	4 (19.05)	2 (9.09)	

Table II. Continued.

Characteristic	Off maintenance therapy, n=21	On maintenance therapy, n=22	P-value
Karyotype, n (%)			>0.999
Normal	12 (57.14)	12 (54.55)	
Favorable	2 (9.52)	3 (13.64)	
Other	7 (33.33)	7 (31.82)	
Prognostic stratification, n (%)			0.048
Favorable group	13 (61.90)	7 (31.82)	
Intermediate group	8 (38.10)	15 (68.18)	
Minimal residual disease, n (%)			0.607
Negative	14 (66.67)	13 (59.09)	
Positive	7 (33.33)	9 (40.91)	

AML, acute myeloid leukemia; ASXL1/2, transcriptional regulator 1/2; IDH1/2, isocitrate dehydrogenase [NADP(+)] 1/2; NPM1, nucleophosmin 1; CEBPA, CCAAT enhancer binding protein α; DNMT3A, DNA methyltransferase 3α.

comparisons were conducted using the Kruskal-Wallis rank-sum test. For categorical variables, proportional differences were analyzed via Fisher's exact test when any expected cell count was <10; otherwise, the χ^2 test was applied (Table II). The impact of maintenance therapy on PFS was evaluated using Kaplan-Meier survival curves and log-rank tests. Differences in PFS were assessed using univariate and multivariate Cox proportional hazards regression analysis. P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using Empower(R) (www.empowerstats.com; X&Y solutions, Inc.) and R version 3.6.1 (http://www.R-project.org).

Results

Characteristics of the cohort. The present study retrospectively analyzed 43 cases of newly diagnosed patients with intermediate-to-low-risk AML who remained in CR following the completion of induction and consolidation therapy Among them, there were 10 patients in the maintenance therapy group who received intensive treatment during the induction phase and 11 patients who received low-intensity treatment [based on hypomethylating agents (HMAs) or low-dose cytarabine]. Thus, there were 22 patients who received maintenance therapy. The median number of maintenance treatment cycles was 8 (range, 2-18). Among these patients, 59.09% (n=13) achieved MRD-negative (MRDneg) status following induction and consolidation therapy. There were 21 patients who did not receive maintenance therapy, with 66.67% (n=14) achieving MRDneg status following the induction and consolidation therapy. There was no significant difference in the MRDneg status between the off-maintenance therapy group and the maintenance therapy group at enrollment. The gene mutations with the highest frequency in the 43 patients were NPM1, CEBPA, FLT3, DNMT3A, KIT, ASXL transcriptional regulator 1 (ASXL1), ASXL2, NRAS, IDH1, IDH2 and TET2. The comparison of basic clinical characteristics between the two groups is shown in Table II. The proportion of patients with CEBPA mutations was higher in the off-maintenance therapy group (33.33% vs. 4.55%; P=0.021), and the proportion of patients in the favorable group was also higher in the off-maintenance therapy group (61.90 vs. 31.82%; P=0.048). During the study period, the most common grade 3-4 hematological adverse events in the maintenance treatment group were neutropenia (n=2) and thrombocytopenia (n=4), and the most common non-hematological adverse event was respiratory infection (Table III). Grade 3-4 adverse events were experienced by 9 patients during cycles 1-2 of treatment. No deaths occurred during the maintenance treatment period.

Table III. Adverse events of maintenance treatment in patients with acute myeloid leukemia.

Adverse event	Grade 3-4, n (%)
Neutropenia	2 (9)
Anemia	0 (0)
Thrombocytopenia	4 (19)
Digestive tract symptom	1 (4)
Fatigue	0 (0)
Respiratory infection	2 (9)
Pain	0 (0)
Heart disease	1 (4)
Liver damage	0 (0)

Prognostic value. Clinical and pathological parameters predictive of PFS were further investigated through univariate and multivariate Cox regression models. In the univariate analysis, maintenance therapy selection, WBC and age were significantly associated with PFS (Table IV). Patients with AML who did not accept maintenance therapy showed a significantly unfavorable PFS. With a median follow-up of

Table IV. Univariate analysis of progression-free survival.

	Progression-free survival	
Characteristic	HR (95% CI)	P-value
Sex		
Male	1.0	
Female	1.6 (0.4-6.2)	0.495
Age	1.1 (1.0-1.1)	0.027
White blood cells count	1.0 (1.0-1.0)	<0.001
Hemoglobin count	1.0 (1.0-1.0)	0.487
Platelets count	1.0 (1.0-1.0)	0.575
Prognostic stratification	0.989	
Favorable group	1.0	
Intermediate group	1.0 (0.3-3.5)	
Maintenance therapy	0.021	
Off VEN-AZA	1.0	
VEN-AZA	0.1 (0.0-0.7)	
Minimal residual disease	0.107	
Negative	1.0	
Positive	2.8 (0.8-10.1)	

CI, confidence interval; HR, hazard ratio; VEN, venetoclax; AZA, azacitidine.

29.6 months (7-74), the median PFS was not reached in patients with AML receiving maintenance therapy, while the median PFS time for those not receiving maintenance therapy was 47.3 months (P=0.0034; Fig. 1D). The PFS time decreased in patients with WBC ≥50x10^9/l and those aged ≥60 (P=0.0012 and P=0.0481, respectively; Fig. 1A and B). No difference in PFS was observed between the intermediate-risk and low-risk patients (P=0.9892; Fig. 1C).

Study end points. The multivariate Cox regression model was employed to examine the association between VEN-AZA maintenance therapy and PFS, with adjustments made for potential confounding factors (Table V). In both the unadjusted and adjusted models, it was observed that patients with AML who underwent VEN-AZA maintenance treatment exhibited a decreased risk of the primary endpoint event, compared with those not receiving maintenance treatment. In the unadjusted model, the hazard ratio (HR) was determined to be 0.09, with a 95% confidence interval (CI) of 0.01-0.69. In the Adjusted I model, the adjustment factors included the age of the patients at the time of diagnosis, which was categorized as either ≥60 years old or <60 years old, and the WBC count was specified as ≥50x10^9/l or <50x10^9/l. The corresponding HR was found to be 0.1, with a 95% CI of 0.01-0.85. In the Adjusted II model, the adjustment factors comprised the age of the patients at diagnosis (≥60 years old or <60 years old), the WBC count (≥50x10^9/l or <50x10^9/l), prognostic stratification and mutations in the DNMT3A, NRAS, IDH2, IDH1, TET2, ASXL1 and ASXL2 genes, as well as MRD prior to maintenance treatment. The HR was calculated to be 0.06, with a 95% CI of 0.00-0.77.

Discussion

Maintenance therapy for AML plays a pivotal role in reducing the recurrence risk and enhancing patient survival rates. The VIALE-A study (16) demonstrated that combination treatment with VEN-AZA can significantly improve treatment outcomes. The VEN-AZA regimen is typically designed as a long-term treatment, which persists until disease progression or the emergence of unacceptable toxicity (17). In the present study, patients with intermediate-to-low-risk AML attained CR following consolidation therapy. Among those continuing VEN-AZA maintenance therapy, only 1 case experienced disease progression, with PFS not reached, showing a significantly longer PFS compared with the non-maintenance group (median PFS of 47.3 months). Even after adjusting for age, WBC count, prognostic stratification and prognosis-related gene mutations, the relapse risk of maintenance-treated patients remained significantly lower. Pratz *et al* (18) demonstrated the importance of MRD in a cohort of patients with a longer follow-up (median >20 months). Those who achieved CR without measurable residual disease also showed a longer duration of remission, OS and event-free survival compared with patients with MRD positivity. The VIALE-A study (16) demonstrated that patients responsive to VEN-AZA who achieved CR with MRD negativity had a median OS time of ~3 years. The study by Chua *et al* (19) confirmed that patients receiving VEN-based treatment for 12 months and achieving MRD negativity at the end of treatment had the potential for durable treatment-free remission (TFR).Deep remission is a key determinant of long-term survival in patients with AML. During continuous VEN-AZA treatment in the present study, the MRD of 8 patients turned negative, achieving molecular remission, with no relapses. By contrast, 7 patients had persistent positive MRD following consolidation and 6 exhibited relapse. This is consistent with previously reported results that indicated that late-stage MRDneg responses were associated with an improved prognosis (20). This suggested that intermediate- or low-risk patients may benefit from VEN-AZA maintenance, likely due to deep remission induced by continuous treatment, effectively preventing relapse.

The maintenance treatment regimen for AML should effectively prevent recurrence while avoiding severe chemotherapy-related adverse reactions. A previous study reported that the incidence of any-grade infections was 84% in the combination therapy group and 67% in the single-agent AZA group. The incidence of severe adverse events was 83% in the combination therapy group, higher than the 73% in the single-agent AZA group (21). Of note, in the present study, no deaths or severe adverse events occurred during the maintenance treatment of patients. The most common grade 3-4 adverse events were neutropenia, thrombocytopenia and respiratory tract infections. Most adverse reactions occurred in the first two cycles of maintenance treatment, and then the frequency gradually decreased, which may have been associated with the dose reduction of VEN or the adjustment of the administration time. As demonstrated in the retrospective analysis by Xin *et al* (22), in patients who responded to the combination therapy of HMAs and VEN, the incidence of infectious complications was relatively high, and the infection-related mortality was also at a high level. The infection-related mortality has an adverse impact on the

Table V. Association between VEN-AZA maintenance therapy and the endpoint of acute myeloid leukemia recurrence in multivariate Cox proportional-hazards analysis.

	Non-adjusted		Adjust I[a]		Adjust II[b]	
Therapy	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Off VEN-AZA	1.0	0.0205	1.0	0.0354	1.0	0.0309
VEN-AZA	0.09 (0.01-0.69)		0.10 (0.01-0.85)		0.06 (0.00-0.77)	

[a]The Adjust I model adjusts for age ≥60 years and WBC ≥50x10^9/l, <50x10^9/l. [b]The Adjust II model adjusts for adjust I plus prognostic stratification, mutations in the DNA methyltransferase 3α, NRAS proto-oncogene, GTPase, IDH2, IDH1, tet methylcytosine dioxygenase 2 and ASXL transcriptional regulator 1. HR, hazard ratio; CI, confidence interval; MRD, before maintenance treatment; VEN, venetoclax; AZA, azacitidine; IDH1/2, isocitrate dehydrogenase [NADP(+)] 1/2.

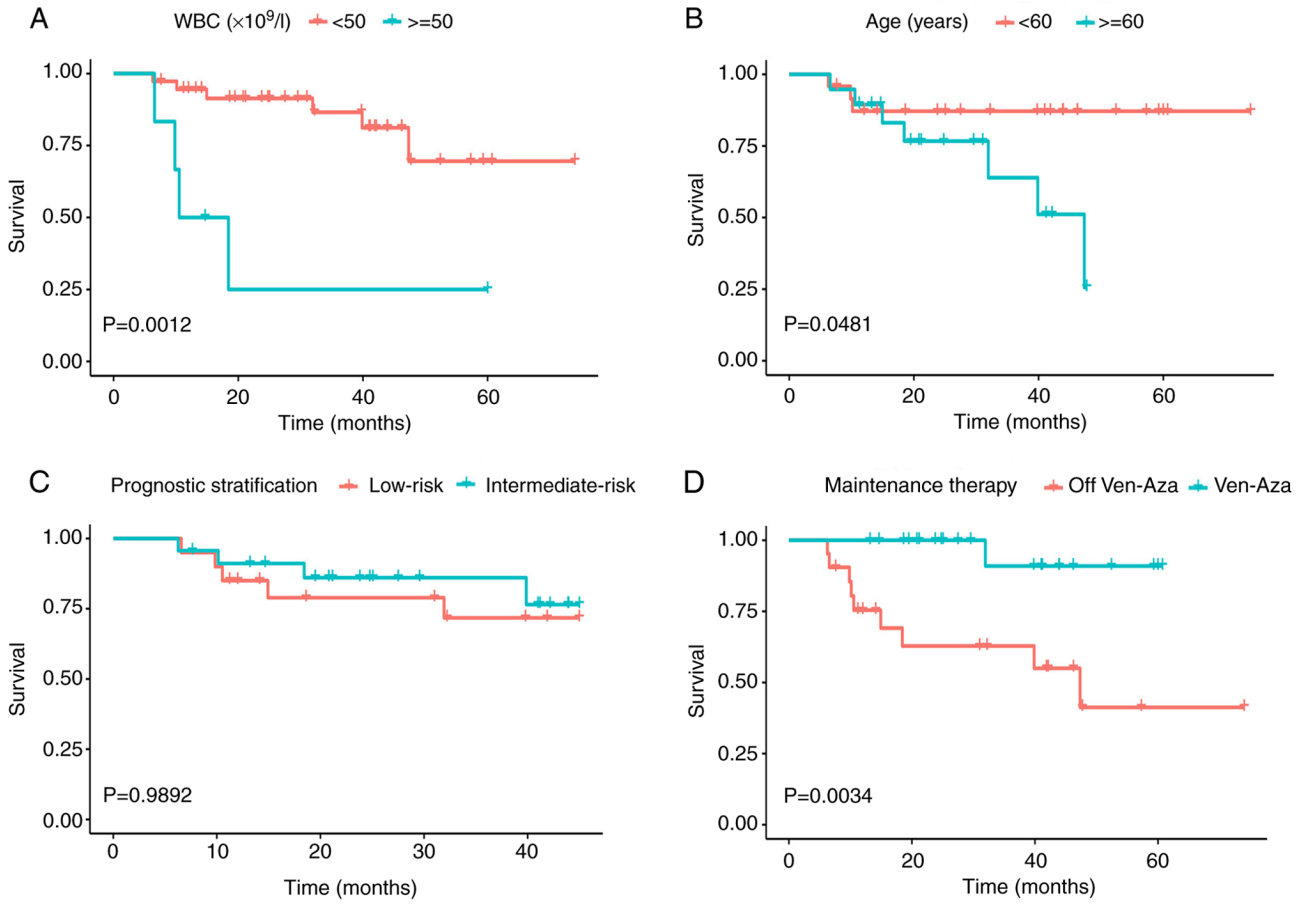

Figure 1. (A) Relationship between PFS and WBC count. (B) PFS in age groups above and below 60 years. (C) PFS in the low-risk and intermediate risk groups. (D) PFS according to VEN-AZA maintenance therapy. PFS, progression-free survival; WBC, white blood cell; VEN, venetoclax; AZA, azacitidine.

OS of this vulnerable patient population with AML. Elderly patients with AML or those unfit for intensive chemotherapy are more likely to be affected by treatment-related toxicities during long-term treatment (23). Therefore, for patients with intermediate- or low-risk AML who achieve deep (MRD ≤0.01%) and sustained CR, attempting to discontinue treatment and obtaining the benefits of treatment-free survival (TFS) could be a feasible strategy.

However, whether discontinuing treatment is the best strategy for achieving an improvement in quality of life and TFR remains controversial (24). In the present study, the median number of maintenance treatment cycles was 8 (range, 2-18), yet we were unable to determine the minimum number of VEN-AZA treatment cycles associated with a longer TFR. As reported in the study by Garciaz *et al* (25), patients who had received >10 previous cycles of treatment had the longest TFS, and a minimum of 5 cycles were associated with an acceptable TFR. Therefore, further exploration to determine the optimal number of cycles and dosage for maintenance therapy is needed.

Although the present study demonstrated the advantages of VEN-AZA maintenance therapy in reducing the recurrence

risk and prolonging survival in patients with intermediate- or low-risk AML, it should be noted that the study has limitations. The small sample size increases the likelihood of failing to detect true treatment effects. As a retrospective study, a number of confounding factors, including prior consolidation chemotherapy regimens and prophylactic antibiotic choices, were not included, which may have inflated the observed treatment benefits. Additionally, the limited follow-up duration might have led to an underestimation of late toxicities. Future research should focus on conducting large-scale, long-term and strictly controlled clinical trials to accurately determine the minimum number of VEN-AZA maintenance treatment cycles required to achieve durable TFR without compromising treatment efficacy. Additionally, given that existing studies have shown that molecular changes, such as NPM1 and IDH mutations, are associated with a higher benefit from VEN-AZA treatment (26), identifying predictive biomarkers to accurately screen out patients who are most likely to benefit from VEN-AZA maintenance therapy will lay the foundation for developing truly individualized treatment strategies.

Acknowledgements

Not applicable.

Funding

The present study was funded by Youth Support Project of Luhe Hospital (grant no. LHYH2024-LC07).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DZ and XD conceptualized the study, designed the methodology and interpreted data. DZ and HZ conducted the statistical analyses and validated the analytical models. XD drafted the manuscript and coordinated revisions. YZ, XC and JQ completed the acquisition and preliminary interpretation of clinical data. TC participated in the study design. HZ adjudicated clinical endpoints, resolved discrepancies in adverse event attribution and critically revised the manuscript for scientific accuracy. HZ and XC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Beijing Luhe Hospital of Capital Medical University (Beijing, China; approval no. 2024-KY-108). Given the retrospective nature of the study and the use of de-identified patient data, the requirement for informed consent was waived by the Institutional Review Board. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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