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ORIGINAL RESEARCH

Superior Efficacy and Deep Molecular Remission with Venetoclax Plus Hypomethylating Agent in Elderly Acute Myeloid Leukemia: A Real-World Comparative Cohort Study

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Background: Treatment of elderly acute myeloid leukemia (AML) remains challenging, and intensive chemotherapy is often poorly tolerated in elderly patients due to comorbidities and frailty, thereby necessitating low-intensity alternatives. This study compared the efficacy and safety of venetoclax combined with a hypomethylating agent (VEN-HMA) against HMA plus low-intensity induction chemotherapy (HMA-LIIC) and low-intensity induction chemotherapy alone (LIIC) in a real-world elderly AML cohort.

Methods: In this retrospective study, 136 newly diagnosed elderly AML patients (≥60 years) were categorized into three groups: VEN-HMA (n=45), HMA-LIIC (n=38), and LIIC (n=53). LIIC was defined as low-dose cytarabine -based regimens given without a concomitant VEN or HMA. Key endpoints included morphologic response, measurable residual disease (MRD) negativity, early mortality, and overall survival (OS).

Results: The VEN-HMA group demonstrated a significantly higher overall response rate (82.2%) than the HMA-LIIC (39.4%) and LIIC (54.7%) groups (p=0.010). While the complete remission (CR) rate was comparable across groups, the VEN-HMA group had a notably higher CR with incomplete hematologic recovery (CRi) rate (33.3% vs 10.5% vs 11.3%) (p=0.007). The MRD negativity rate was significantly superior in the VEN-HMA group (65.5%) compared to HMA-LIIC (18.8%) and LIIC (41.7%) (p=0.010), an advantage particularly pronounced in intermediate-risk patients (68.8% vs 12.5% vs 30.8%, p=0.021). The VEN-HMA group also had a numerically lowest 30-day early mortality (4.44% vs 7.97% vs 17.0%). With a median follow-up, the median OS was 11.0 months in the VEN-HMA group, 7.2 months in the HMA-LIIC group, and 10.1 months in the LIIC group. The VEN-HMA group showed a numerically higher 1-year OS rate (55.0%) than the HMA-LIIC group (35.0%) and comparable to the LIIC group (47.9%) (p=0.153).

Conclusion: In this real-world analysis, VEN-HMA demonstrated superior response rates and deeper molecular remissions (MRD) compared to HMA-LIIC and LIIC in elderly AML patients, further supporting its use as an effective and feasible frontline option for this population, especially in the intermediate-risk group.

Keywords: venetoclax, hypomethylating agent, low-intensity induction chemotherapy, measurable residual disease, overall survival

Introduction

Acute myeloid leukemia (AML) is a highly heterogeneous hematological malignancy that is particularly common in older adults. Its incidence increases significantly with age. Elderly patients often present with adverse cytogenetics, comorbidities, and impaired performance status, which complicates treatment and leads to poor prognosis.[1,2] Although

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traditional intensive induction chemotherapy has established efficacy in younger patients, its use is limited in the elderly population due to high treatment-related toxicity, early mortality, and poor overall survival.

In recent years, hypomethylating agents (HMAs), such as azacitidine (AZA) and decitabine (DEC), have become important treatment options for elderly or medically unfit AML patients; however, the complete remission (CR) rates with HMA monotherapy are limited, and long-term survival benefits remain poor.[3–5] Venetoclax, a potent and selective BCL-2 inhibitor, exerts its antileukemic effect by inducing apoptosis in tumor cells. The combination of venetoclax with HMAs (VEN-HMA) has shown encouraging efficacy in clinical trials, significantly improving response rates and survival outcomes, particularly in elderly and unfit patients.[6–8] However, HMAs plus low-intensity chemotherapy or low-intensity chemotherapy alone remain widely used in many real-world settings, particularly where venetoclax is not yet universally accessible or covered by insurance. Direct comparisons between VEN-HMA and these alternative low-intensity regimens are still limited, especially regarding depth of response and early mortality. Furthermore, measurable residual disease (MRD) has been established as a powerful independent prognostic factor in AML, with MRD negativity correlating with longer relapse-free and overall survival. In elderly patients, who often cannot tolerate intensive consolidation or allogeneic transplantation, achieving deep MRD negativity may be particularly critical for durable disease control. Therefore, the differences in MRD negativity across various low-intensity treatment strategies require further clarification.

To address these questions, this retrospective study analyzed the clinical data of 136 elderly AML patients who received one of three different treatment regimens, including venetoclax plus HMA (VEN-HMA group), HMA plus low-intensity induction chemotherapy (HMA-LIIC group), or low-intensity induction chemotherapy alone (LIIC group). The study aims to compare the differences among these groups in terms of morphological remission rates, MRD negativity rates, early mortality, and overall survival (OS), thereby providing additional evidence-based insights for the rational application of venetoclax in the real-world management of elderly AML patients. We hypothesized that, in this real-world cohort of elderly AML patients, the VEN-HMA regimen would yield higher overall and complete remission rates, deeper molecular responses (MRD negativity), and a more favorable early mortality profile compared with HMA-LIIC or LIIC alone.

Methods

Patients

This study is a single-center, retrospective cohort analysis. We consecutively enrolled 136 elderly patients (age $\geq$ 60 years) with AML who were diagnosed and received initial treatment in the hematology department of our hospital from January 2019 to December 2023. All diagnoses were established according to the 5th edition of the World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms,[9] confirmed by bone marrow morphology, immunophenotyping, cytogenetic and/or molecular genetic studies. Exclusion criteria included acute promyelocytic leukemia (APL), patients treated with HMA monotherapy, concurrent active malignancies, and patients with incomplete clinical data or lost to follow-up. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (approval number:2025-RE-442) and was conducted in accordance with the Declaration of Helsinki; the written informed consent was waived due to the retrospective nature of the review; and all the data was anonymized and maintained with confidentiality.

Treatment Regimens

Based on the initial induction therapy received, patients were categorized into three groups. (1)VEN-HMA group (n=45): patients received a HMA, either DEC (20 mg/m^2 daily on days 1–5) (n=20) or AZA (75 mg/m^2 daily on days 1–7) (n=25), in combination with venetoclax; venetoclax was dose-escalated according to the standard protocol, with a target dose of 400 mg daily; each treatment cycle lasted 28 days. (2)HMA-LIIC group (n=38): 21 patients treated with DEC-based chemotherapy (15–20 mg/m^2 daily for 5 days), including 10 patients received DEC plus HAG (homoharringtonine 1 mg/m^2 daily for 7 days; low-dose cytarabine 10 mg/m^2 every 12 hours for 14 days; granulocyte colony-stimulating factor 5 μg/kg daily for 14 days); 9 patients received DEC plus low-dose IA (idarubicin 5–10 mg/m^2 daily for 3 days;

low-dose cytarabine 10 mg/m^2 daily for 7 days); 2 patients received DEC plus low-dose DA (daunorubicin 20–40 mg/m^2 daily for 3 days; low-dose cytarabine 10 mg/m^2 daily for 7 days). Another 17 patients received AZA-based chemotherapy (75 mg/m^2 daily for 7 days), consisting of 13 patients treated with AZA plus low-dose IA; 2 patients with AZA plus low-dose DA; 2 patients with AZA plus HAG. (3) LIIC group (n=53): including 48 patients treated with low-dose IA, 2 patients with low-dose DA and 3 patients with HAG. Patients who achieved CR or CR with incomplete hematologic recovery (CRi) proceeded to consolidation therapy. Consolidation regimens consisted of sequential low-dose chemotherapy, such as low-dose IA/DA, HAG, or HMA combined with above regimens.

The choice of treatment regimen was determined by the treating physician based on the patient's age, performance status, comorbidities, and personal preference.

Definitions and Statistical Analysis

Morphological remission categories included CR, CRi, and partial remission (PR).[10] The overall response rate (ORR) was defined as the proportion of patients achieving CR, CRi, or PR. MRD was detected via multiparameter flow cytometry (with a sensitivity of 10^{-4}) using bone marrow samples collected after the first induction cycle and before the start of the next cycle. MRD negativity was defined as the absence of phenotypically aberrant leukemia cells among bone marrow nucleated cells. OS was defined from initial diagnosis to death from any cause or the time until follow-up. Risk stratification was performed according to the 2022 ELN risk classification criteria, categorizing all patients into favorable, intermediate, and adverse-risk groups.[10] Safety assessments primarily focused on early mortality, defined as all-cause death occurring within 30 days after the initiation of the first induction therapy.

Categorical variables were assessed using the chi-square test or Fisher's exact test, and continuous variables were assessed using the Kruskal–Wallis *H*-test between three groups. The 1-year OS rates and their 95% confidence intervals were calculated for the three groups using the Kaplan-Meier method; and differences in survival between groups were compared using the Log rank test. The cumulative incidence curves for 30-day early mortality among the three groups were compared using Gray's test. Data analysis was performed using R software, with a p value <0.05 considered statistically significant.

Results

Clinical Characteristics

This study included 136 elderly AML patients with a median age of 69 years (range: 60–87). The VEN-HMA group comprised 45 patients with a median age of 73 years (range: 61–87), including 16 patients (35.5%) aged 75 years or older. The HMA-LIIC group consisted of 38 patients with a median age of 68 years (range: 60–84), including 9 patients (23.7%) aged 75 or older. The LIIC group included 53 patients with a median age of 66 years (range: 60–83), including 3 patients (5.7%) aged 75 or older. The detailed clinical characteristics of the three groups at initial diagnosis are presented in Table 1. According to the 2022 ELN risk stratification criteria, the VEN-HMA group included 9 (20.0%) favorable-risk, 20 (44.4%) intermediate-risk, and 16 (35.6%) adverse-risk patients. The HMA-LIIC group included 9 (23.7%) favorable-risk, 17 (44.7%) intermediate-risk, and 12 (31.6%) adverse-risk patients. The LIIC group included 13 (24.6%) favorable-risk, 23 (43.4%) intermediate-risk, and 17 (32.0%) adverse-risk patients.

Morphologic Remission

In the overall patient population, the ORR after the first cycle of induction therapy was 59.6% (81/136), comprising a CR rate of 29.4% (40/136), a CRi rate of 18.4% (25/136), and a PR rate of 11.8% (16/136). In the VEN-HMA group, the ORR was 82.2% (37/45), with a CR rate of 28.9% (13/45), a CRi rate of 33.3% (15/45), and a PR rate of 20.0% (9/45). The HMA-LIIC group had an ORR of 39.4% (15/38), with a CR rate of 26.3% (10/38), a CRi rate of 10.5% (4/38), and a PR rate of 2.6% (1/38). The LIIC group achieved an ORR of 54.7% (29/53), with a CR rate of 32.1% (17/53), a CRi rate of 11.3% (6/53), and a PR rate of 11.3% (6/53) (Table 2).

Among the 31 favorable-risk patients, 45.2% (14/31) achieved CR after the first induction cycle; the CR rates were 44.4% (4/9) in the VEN-HMA group, 66.7% (6/9) in the HMA-LIIC group, and 30.8% (4/13) in the LIIC group (p=0.265). Of the

Table 1 Patient Demographics and Baseline Characteristics

	VEN-HMA (n=45)	HMA-LIIC (N=38)	LIIC (=53)	*p*
Age(years),median(range)	73 (61–87)	68 (60–84)	66 (60–83)	0.001
Sex(Male),n(%)	29 (64.4)	24 (65.8)	27 (51)	0.326
WBC ($\times10^9$/L),median(range)	6.28 (0.72–298)	12.94 (0.52–201.3)	14.7 (0.92–315.23)	0.284
PLT ($\times10^9$/L),median(range)	60 (5–381)	43 (6–236)	42.5 (4–243)	0.488
RBC ($\times10^{12}$/L),median(range)	2.24 (1.27–3.63)	2.2 (1.24–14.7)	2.12 (0.81–3.62)	0.633
ANC ($\times10^9$/L),median(range)	2.51 (0–42.29)	0.81 (0–45.85)	0.705 (0–113.5)	0.202
HGB (g/L),median(range)	69 (43–120)	71.5 (30–119)	72.5 (43–114)	0.813
ALT (IU/L),median(range)	14 (2.5–54.3)	19 (5–56.5)	23.15 (6–265)	0.005
AST (IU/L),median(range)	18.8 (7–118.8)	20.8 (10.6–57.5)	24.65 (3–323.3)	0.03
ALB (g/L),median(range)	36.8 (28–47.7)	34.8 (27.5–46.6)	36.45 (25.8–46.8)	0.156
UA (umol/L),median(range)	325 (156–1288)	327.8 (131–891.3)	277.6 (8.2–568.6)	0.152
CREA (umol/L),median(range)	72 (38–189)	61.8 (43–261.4)	66.6 (45–149.2)	0.148
TBIL (umol/L),median(range)	10.3 (3.9–25.4)	9.7 (3.5–29.1)	9.4 (2.3–28.8)	0.8
DBIL (umol/L),median(range)	3.6 (0–12.5)	3.2 (0–12.4)	3 (0–11.7)	0.149
IBIL (umol/L),median(range)	4.7 (1.5–15.8)	6.5 (0.5–20.6)	6.45 (1.7–28.8)	0.386
PT(second),median(range)	14.6 (10.8–19.9)	13.85 (9.8–23.5)	12.95 (10.8–53.7)	0.003
APTT(second),median(range)	36.8 (23.1–51.6)	37.45 (18.1–68.4)	30.8 (21.1–46.7)	0.009
TT (second),median(range)	16.2 (14.8–20)	15.9 (12.7–24.6)	15.8 (12.3–19.6)	0.008
INR level,median(range)	1.17 (0.92–1.66)	1.16 (0.83–3.61)	1.08 (0.88–1.88)	0.03
Comorbidities,n(%)	16 (35.6)	5 (13.2)	12 (22.7)	0.056
ELN risk assessment,n(%)				0.985
Favorable-risk	9(20)	9(23.7)	13 (24.6)	
Intermediate-risk	20 (44.4)	17 (44.7)	23 (43.4)	
High-risk	16 (35.6)	12 (31.6)	17 (32)	

Abbreviations: VEN-HMA,Venetoclax combined with a hypomethylating agent; HMA-LIIC,hypomethylating agent plus low-intensity induction chemotherapy; LIIC,low-intensity induction chemotherapy alone; WBC,white blood cell; PLT,platelet; RBC,red blood cell; ANC,absolute neutrophil count; HGB,hemoglobin; ALT,alanine aminotransferase; AST,aspartate aminotransferase; UA, uric acid; CREA,creatinine; TBIL,total bilirubin; DBIL,direct bilirubin; IBIL,indirect bilirubin; PT,prothrombin time; APTT,activated partial thromboplastintime; TT,thrombin time; INR,international normalized ratio; ELN,European Leukemia Net.

Table 2 Morphologic Remission After One Course of Induction Therapy

	VEN-HMA (n=45)	HMA-LIIC (N=38)	LIIC (n=53)	*p*
CR	13(28.9%)	10(26.3%)	17(32.1%)	0.834
CRi	15(33.3%)	4(10.5%)	6(11.3%)	0.007
PR	9(20.0%)	1(2.6%)	6(11.3%)	0.050
ORR	37(82.2%)	15(39.4%)	29(54.7%)	0.010

Abbreviations: VEN-HMA, Venetoclax combined with a hypomethylating agent; HMA-LIIC, hypomethylating agent plus low-intensity induction chemotherapy; LIIC, low-intensity induction chemotherapy alone; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; PR, partial remission; ORR, overall response rate.

60 intermediate-risk patients, 25.0% (15/60) achieved CR after the first induction cycle; the CR rates were 25.0% (5/20) in the VEN-HMA group, 11.8% (2/17) in the HMA-LIIC group, and 34.8% (8/23) in the LIIC group (p=0.440). Among the 45 adverse-risk patients, 24.4% (11/45) achieved CR after the first induction cycle; the CR rates were 25.0% (4/16) in the VEN-HMA group, 16.7% (2/12) in the HMA-LIIC group, and 29.4% (5/17) in the LIIC group (p=0.831) (Supplementary Table 1).

Molecular Remission

MRD was assessed in 69 patients following the first treatment cycle. In the VEN-HMA group (n=29), the MRD negativity rate was 65.5% (19/29). In the HMA-LIIC group (n=16), the MRD negativity rate was 18.8% (3/16). In the LIIC group (n=24), the MRD negativity rate was 41.7% (10/24) (p=0.010) (Figure 1A).

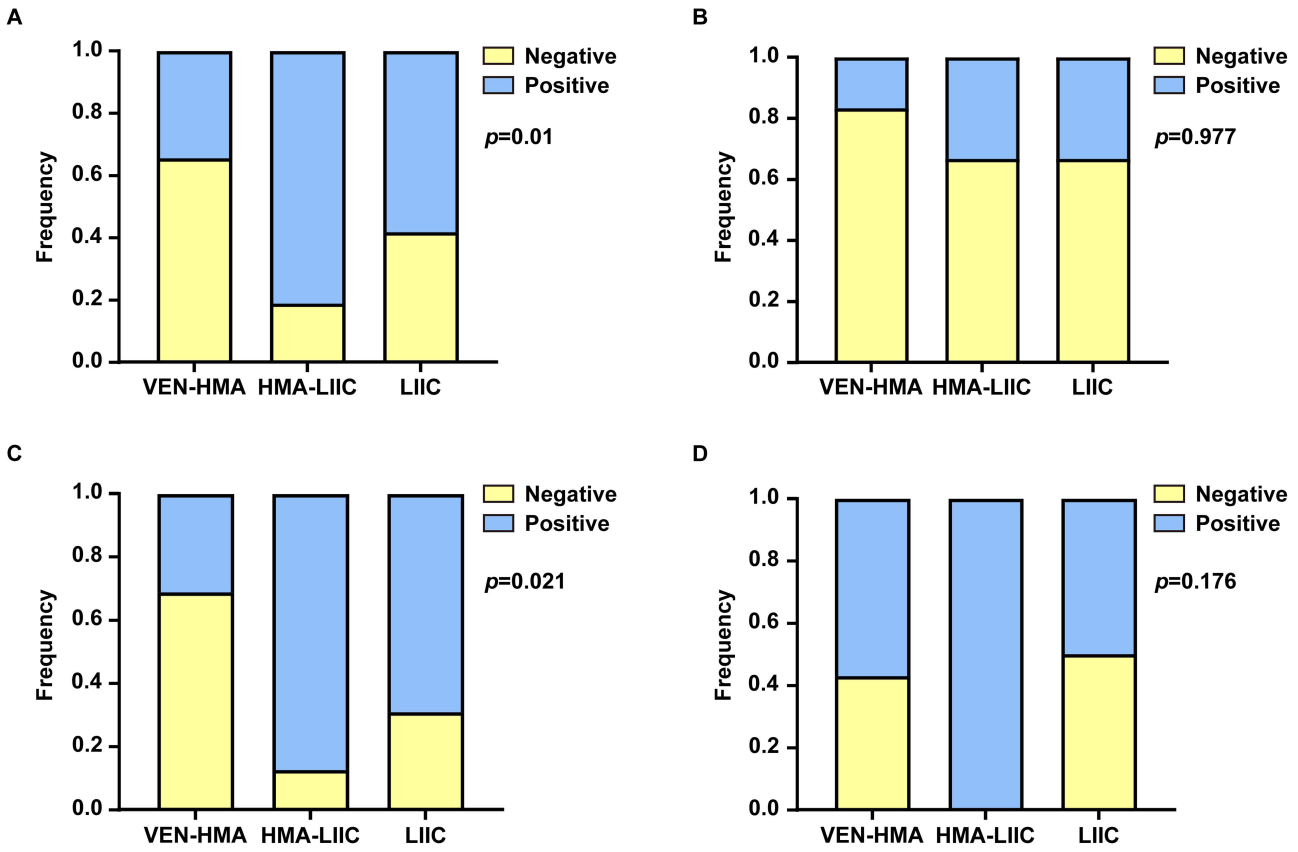

Figure 1 Molecular response analysis. Among all patients, the MRD-negative rates were 65.5% in the VEN-HMA group, 18.8% in the HMA-LIIC group, and 41.7% in the LIIC group (p=0.010) (**A**). In subgroup analyses, no significant differences were found among the treatment groups for patients with favorable prognosis (83.3% vs 66.7% vs 66.7%) (p=0.977) (**B**). However, for patients with intermediate prognosis, the MRD-negative rates were 68.8%, 12.5%, and 30.8% in the three groups respectively (p=0.021) (**C**). No significant differences were also found among the treatment groups for patients with adverse prognosis (42.9% vs 0% vs 50%) (p=0.176) (**D**).

Among favorable-risk patients, the MRD negativity rates were 83.3% (5/6) in the VEN-HMA group, 66.7% (2/3) in the HMA-LIIC group, and 66.7% (2/3) in the LIIC group (p=0.977) (Figure 1B). Among intermediate-risk patients, the MRD negativity rates were 68.8% (11/16) in the VEN-HMA group, 12.5% (1/8) in the HMA-LIIC group, and 30.8% (4/13) in the LIIC group (p=0.021) (Figure 1C). Among adverse-risk patients, the MRD negativity rates were 42.9% (3/7) in the VEN-HMA group, 0% (0/5) in the HMA-LIIC group, and 50% (4/8) in the LIIC group (p=0. 176) (Figure 1D).

Early Mortality

The overall 30-day early mortality rate after the first induction therapy was 10.3% (95% CI:5.12–15.5%). The 30-day mortality rates were 4.44% (95% CI: 1.13–16.6%) in the VEN-HMA group, 7.97% (95% CI:2.64–22.7%) in the HMA-LIIC group, and 17.0% (95% CI:9.22–30.1%) in the LIIC group (p=0.10) (Figure 2A).

In the favorable-risk subgroup, the 30-day mortality rates were 0% in the VEN-HMA group, 0% in the HMA-LIIC group, and 23.1% (95% CI:8.09–55.8%) in the LIIC group (p=0.108) (Figure 2B). In the intermediate-risk subgroup, the rates were 5.0% (95% CI: 0.7–30.5%) in the VEN-HMA group, 11.8% (95% CI:3.08–39.4%) in the HMA-LIIC group, and 13.0% (95% CI:4.04–35.2%) in the LIIC group (p=0.638) (Figure 2C). In the adverse-risk subgroup, the rates were 6.25% (95% CI: 0.91–36.8%) in the VEN-HMA group, 8.3% (95% CI: 1.22–46.1%) in the HMA-LIIC group, and 17.7% (95% CI:6.06–45.3%) in the LIIC group (p=0.510) (Figure 2D).

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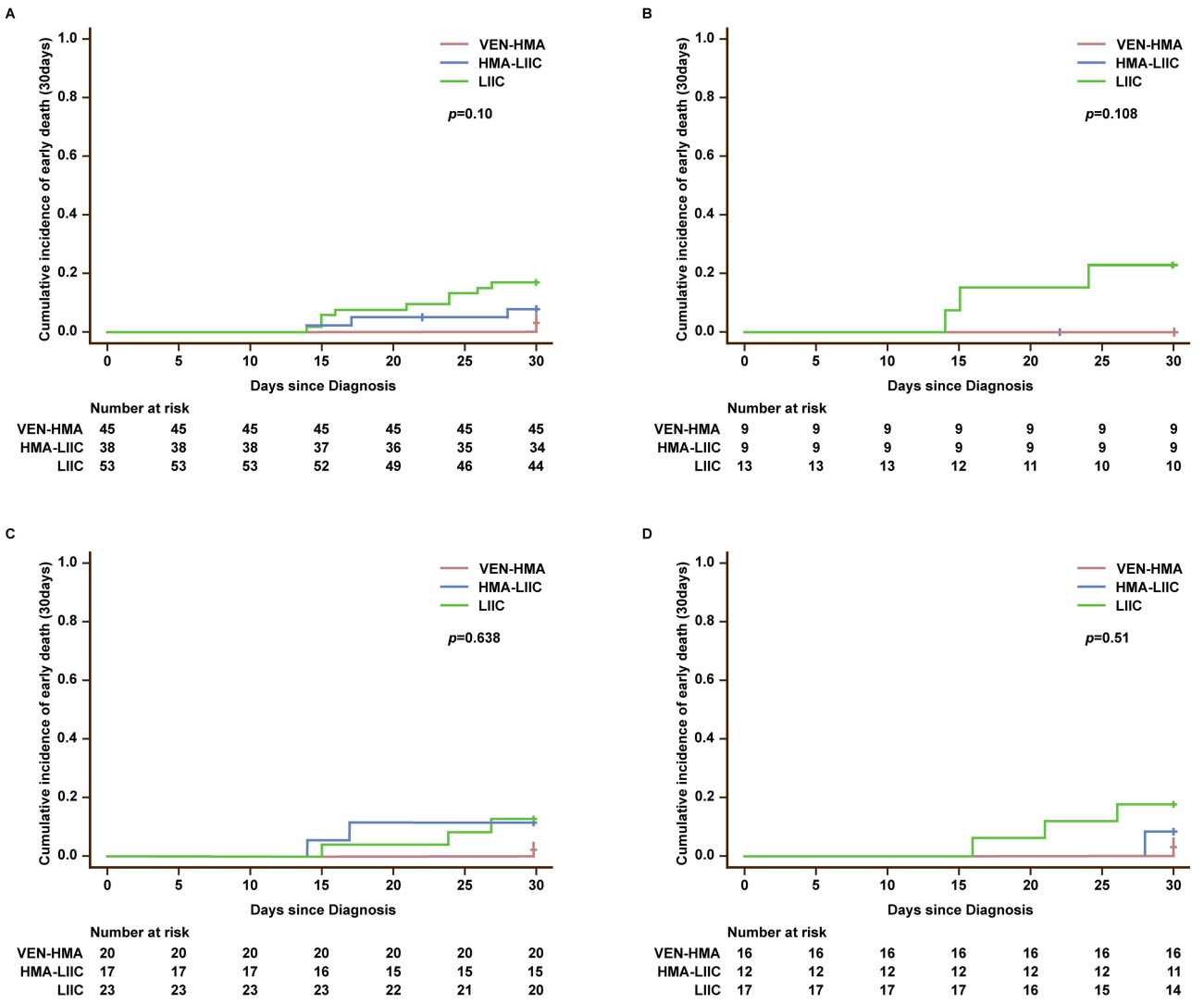

Figure 2 The 30-day early mortality. The 30-day mortality rates were 4.44% (95% CI: 1.13–16.6%) for VEN-HMA, 7.97% (2.64–22.7%) for HMA-LIIC, and 17.0% (9.22–30.1%) for LIIC overall (p=0.10; **A**). In the favorable-risk subgroup, rates were 0% for VEN-HMA, 0% for HMA-LIIC, and 23.1% (8.09–55.8%) for LIIC (p=0.108; **B**). For intermediate-risk, rates were 5.0% (0.7–30.5%), 11.8% (3.08–39.4%), and 13.0% (4.04–35.2%) respectively (p=0.638; **C**). In adverse-risk, rates were 6.25% (0.91–36.8%), 8.3% (1.22–46.1%), and 17.7% (6.06–45.3%) respectively (p=0.510; **D**).

Long-Term Survival

As of the follow-up cutoff date of December 31, 2024, the median OS was 11.0 months (range: 1–46.1 months) in the VEN-HMA group, 7.2 months (range: 0.47–63.5 months) in the HMA-LIIC group, and 10.1 months (range: 0.40–69.7 months) in the LIIC group.

For the overall patient population, the 1-year OS rates were 55.0% (95% CI: 38.3–68.9%) in the VEN-HMA group, 35.0% (95% CI: 19.4–51.1%) in the HMA-LIIC group, and 47.9% (95% CI: 33.5–61.0%) in the LIIC group (p=0.153) (Figure 3A). Among favorable-risk patients, the 1-year OS rates were 74.1% (95% CI: 28.9–93.0%) in the VEN-HMA group, 72.9% (95% CI: 27.6–92.5%) in the HMA-LIIC group, and 69.2% (95% CI: 37.3–87.2%) in the LIIC group (p=0.805) (Figure 3B). Among intermediate-risk patients, the 1-year OS rates were 53.6% (95% CI: 28.2–73.6%) in the VEN-HMA group, 21.8% (95% CI: 5.49–45.0%) in the HMA-LIIC group, and 54.2% (95% CI: 31.6–72.2%) in the LIIC group (p=0.02) (Figure 3C). Among adverse-risk patients, the 1-year OS rates were 46.9% (95% CI: 21.4–68.9%) in the VEN-HMA group, 27.8% (95% CI:6.68–54.5%) in the HMA-LIIC group, and 25.9% (95% CI:8.13–48.3%) in the LIIC group (p=0.441) (Figure 3D).

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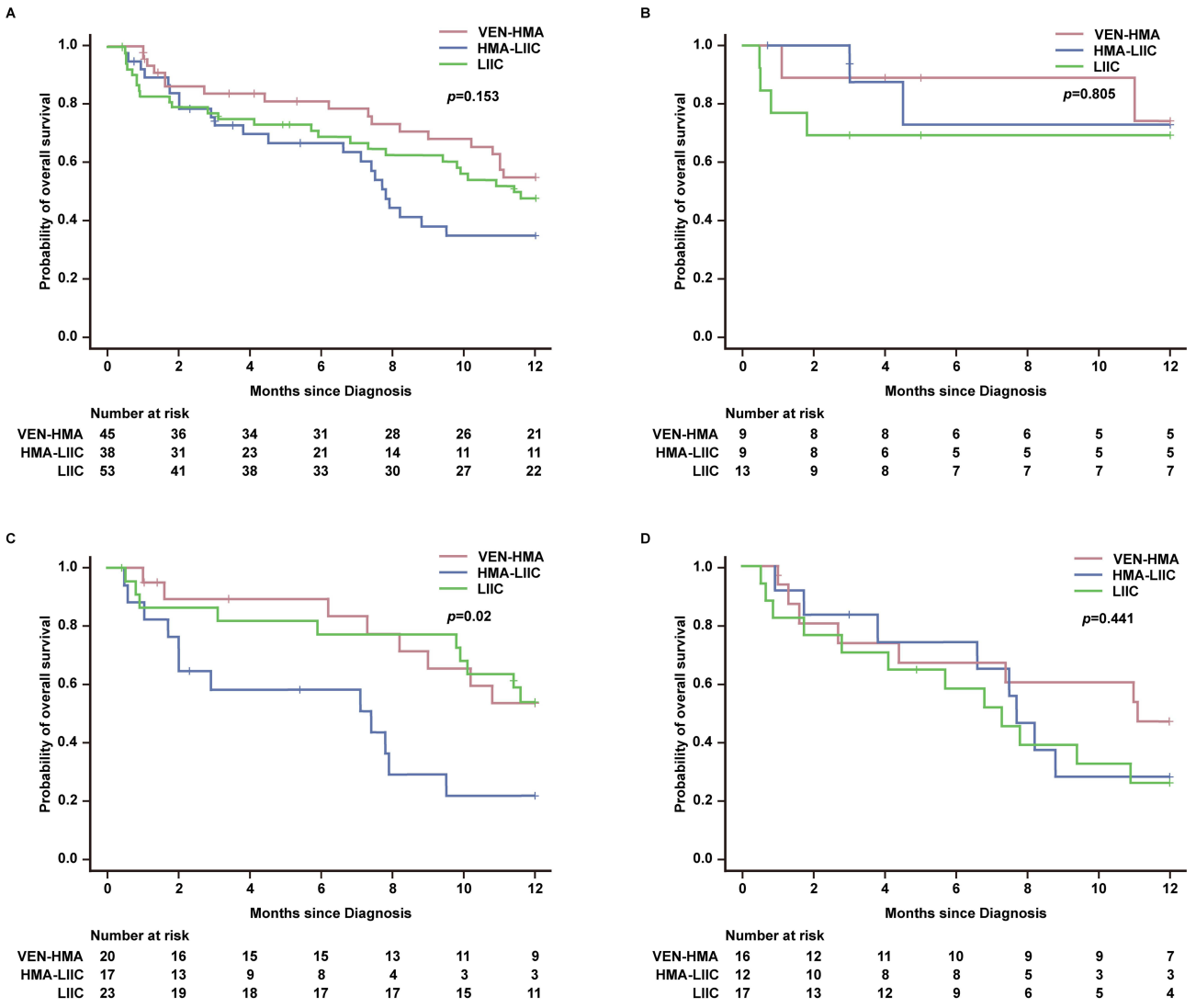

Figure 3 Overall survival. In the overall population, 1-year OS was 55.0% (95% CI: 38.3–68.9) with VEN-HMA, 35.0% (95% CI:19.4–51.1) with HMA-LIIC, and 47.9% (95% CI:33.5–61.0) with LIIC (p=0.153) (**A**). For favorable-risk patients, rates were 74.1% (95% CI:28.9–93.0), 72.9% (95% CI:27.6–92.5), and 69.2% (95% CI:37.3–87.2), respectively (p=0.805) (**B**). Among intermediate-risk patients, rates were 53.6% (95% CI:28.2–73.6), 21.8% (95% CI:5.49–45.0), and 54.2% (95% CI:31.6–72.2) (p=0.02) (**C**). For adverse-risk patients, rates were 46.9% (95% CI:21.4–68.9), 27.8% (95% CI:6.68–54.5), and 25.9% (95% CI:8.13–48.3) (p=0.441) (**D**).

Discussion

This retrospective analysis of 136 elderly AML patients treated with different regimens (VEN-HMA, HMA-LIIC, LIIC) provides a comprehensive evaluation of the efficacy and safety of venetoclax-based combinations in real-world clinical practice. Our findings demonstrate across multiple dimensions that the VEN-HMA regimen offers significant advantages in elderly AML patients, particularly those unsuitable for or unable to tolerate traditional intensive chemotherapy, especially in enhancing the depth of treatment response. These findings are consistent with recent Phase III trials such as VIALE-A, which demonstrated superior response and survival with venetoclax-azacitidine compared to azacitidine alone.[11]

Regarding morphologic remission, our study found a notable superiority for the VEN-HMA regimen. The ORR in this group reached 82.2%, substantially higher than in the other two groups. A finding warranting further discussion is the unique response pattern observed in the VEN-HMA group: while its CR rate (28.9%) was comparable to the other groups, its CRi rate (33.3%) was significantly higher. This observation holds important clinical implications. Historically,

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CRi has been considered an inferior response category compared to CR.[12,13] However, within venetoclax-based regimens, a higher CRi rate may reflect the unique mechanism of action of BCL-2 inhibition, which efficiently clears leukemic cells from the bone marrow but may concurrently delay the recovery of normal hematopoiesis, potentially impacting hematopoietic precursor cells.[14,15] Crucially, multiple studies have confirmed that among patients receiving venetoclax-based therapy, those achieving CRi derive similar survival benefits to those achieving CR.[16–18] Therefore, the high ORR and high CRi rate collectively underscore the efficacy of the VEN-HMA regimen in controlling leukemia.

MRD status has become a pivotal biomarker for assessing treatment efficacy and predicting long-term outcomes in AML. Achieving MRD negativity is strongly associated with longer relapse-free survival and overall survival.[19] One of the most striking findings of our study was the superior performance of the VEN-HMA group in terms of MRD negativity. Among the overall patient population, the MRD negativity rate in the VEN-HMA group was 65.5%, significantly higher than that in the HMA-LIIC group (18.8%) and the LIIC group (41.7%) (p=0.01). This result aligns closely with the findings of the global phase III VIALE-A trial,[11,16] which established azacitidine plus venetoclax as a new standard of care for elderly or unfit AML patients. Our real-world data further validate the potent ability of this regimen to induce deep molecular remission. Further risk-stratified analysis revealed that this advantage was particularly pronounced in the intermediate-risk patients (68.8% vs 12.5% vs 30.8%, p=0.021). This suggests that for this heterogeneous intermediate-risk group, the synergistic effect of HMA and venetoclax may more effectively eradicate leukemic cells and overcome treatment resistance associated with certain intermediate-risk genetic abnormalities; however, it requires prospective validation in larger cohorts before clinical application. Although no statistically significant differences in MRD negativity rates were observed among the three groups within the favorable and adverse-risk categories, we noted a trend towards the highest MRD negativity rate in the VEN-HMA group among favorable-risk patients (83.3%). This indicates that the regimen may potentially offer deeper disease remission across all risk strata, although statistical significance was not reached, likely limited by sample size.

A major challenge in treating elderly AML is balancing efficacy and safety. Early mortality is a key indicator of treatment safety. In this study, the VEN-HMA group had the lowest 30-day early mortality rate (4.44%); although the difference among the three groups was not statistically significant (p=0.10), this numerical advantage suggests a favorable safety profile. Notably, within the favorable-risk subgroup, the early mortality rate was 0% in both the VEN-HMA and HMA-LIIC groups, compared to 23.1% in the LIIC group. This strongly implies that for relatively frail elderly patients, even those with favorable-risk disease who might theoretically tolerate chemotherapy better, non-chemotherapy targeted combination regimens can significantly reduce treatment-related mortality risk without compromising efficacy. This favorable safety profile makes the VEN-HMA regimen a preferable option for older patients with multiple comorbidities or poor performance status, thereby expanding the population eligible for effective treatment.

Unlike response and MRD outcomes, we did not observe a statistically significant OS benefit for VEN-HMA in this cohort. The median OS in the VEN-HMA group was 11.0 months, similar to the LIIC group (10.1 months) but slightly superior to the HMA-LIIC group (7.2 months). Although the comparison of 1-year OS rates among all patients did not reach statistical significance (p=0.153), we observed a numerically higher rate in the VEN-HMA group (55.0%) compared to the HMA-LIIC group (35.0%), and it was comparable to or slightly better than the LIIC group (47.9%), which included potentially younger, more chemotherapy-fit patients. Considering that the median age of the VEN-HMA group (73 years) was significantly higher than that of the LIIC group (66 years), and the proportion of very elderly patients (≥75 years) was greater (35.5% vs 5.7%), achieving such survival outcomes is noteworthy. Risk-stratified OS analysis provided deeper insights. For instance, in the intermediate-risk group, the VEN-HMA group showed a clear trend towards superior survival (1-year OS rate 53.6%), markedly higher than the HMA-LIIC group (21.8%). This reinforces the pattern revealed by the MRD data, suggesting that this regimen may be particularly beneficial for the intermediate-risk patient population. Among adverse-risk patients, although the 1-year OS rates were poor across all groups, the VEN-HMA group still maintained the highest numerical rate (46.9%), indicating its potential value even for patients with very poor prognosis.

This study has several limitations. First, its single-center, retrospective design limits the generalizability of the findings; furthermore, treatment selection was non-randomized and potentially influenced by physician preference and patient-specific factors, introducing the possibility of selection bias. Second, the sample size was relatively limited,

particularly for subgroup analyses based on risk stratification, where some subgroups had small patient numbers, reducing statistical power and potentially masking clinically meaningful differences. Additionally, we were unable to perform a systematic analysis of the patients' mutational profiles; differential sensitivity to venetoclax based on specific mutations (eg, IDH1/2, FLT3-ITD, TP53) could explain some of the heterogeneity in response observed, especially within the adverse-risk group, and future studies focusing on specific molecular subtypes will help to more precisely define the patient populations that benefit most.

In conclusion, based on real-world data, this study demonstrates that in elderly AML patients, the HMA plus venetoclax regimen, compared to other combination therapies or traditional induction chemotherapy, can induce higher rates of deep molecular and morphologic remission and is associated with a trend towards lower early mortality. Although no statistically significant difference in overall survival was observed, the survival data achieved in older and chemotherapy-ineligible patients are encouraging, particularly the potential survival benefit suggested in intermediate-risk patients. Our study provides robust local evidence supporting the use of venetoclax in Chinese elderly AML patients. Future prospective, large-scale studies incorporating comprehensive molecular genetic analysis will be crucial to further optimize patient selection and explore novel strategies combining this regimen with other targeted agents to address the challenge of treating high-risk AML.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (approval number: 2025-RE-442) and was conducted in accordance with the Declaration of Helsinki; and all the data was anonymized and maintained with confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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