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Granulocyte colony-stimulating factor plus venetoclax and azacitidine in newly diagnosed acute myeloid leukemia: a multicenter phase 2 trial

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Dear Editor,

Venetoclax and azacitidine (VA) is now a leading initial therapy for elderly acute myeloid leukemia (AML) patients ineligible for intensive chemotherapy [1]. Real-world data suggests that compared with conventional intensive chemotherapy, venetoclax plus azacitidine has similar outcomes in AML patients, especially older patients [2–4]. The VA regimen is also feasible in AML patients suitable for intensive chemotherapy [5, 6]. The VIALE-A trial showed encouraging results, with 43.4% of patients reaching complete remission (CR) or CR with incomplete hematologic recovery (CRi) after one cycle. The optimal CR/CRi rate was 66.4%, and median overall survival (OS) was 14.7 months [1]. Meanwhile, many large-scale trial data showed that venetoclax and azacitidine enabled about 60% of newly diagnosed AML patients to achieve CR/Cri [2–4]. Therefore, enhancing CR rates and survival outcomes in elderly AML patients at diagnosis is essential. Granulocyte colony-stimulating factor (G-CSF), a pharmacologic agent that induces neutrophil mobilization, has shown clear efficacy in several intensive regimens, such as FLAG and CAG [7, 8]. Thus, we launched this clinical trial to assess the VAG regimen's effectiveness and safety.

A total of 38 eligible was enrolled in this single-arm, multicenter, prospective, phase 2 study (The Chinese Clinical Trial Registry: ChiCTR2200063954). The main eligibility criterion included a confirmed diagnosis of newly diagnosed AML according to the European Leukemia Net (ELN) 2022 guidelines [9]. For patients 75 or with specific comorbidities (cardiac, pulmonary, renal, or hepatic dysfunction, other conditions), standard induction therapy is not recommended. Exclusion criteria included prior hypomethylating agents, venetoclax, or chemotherapy for myelodysplastic syndrome, acute promyelocytic leukemia, myeloproliferative neoplasms, central nervous system leukemia, as well as positive for hepatitis B/C virus, and human immunodeficiency virus. The protocol was ethically approved by the First Affiliated Hospital of Xi'an Jiaotong University, with researchers following the Helsinki Declaration. All participants signed informed consent.

All patients received induction treatment with venetoclax orally once daily (escalating from 100 to 400 mg over days 1–21), azacitidine subcutaneously (75 mg/m^2, days 1–7), and G-CSF subcutaneously (5 μg/kg/d, days 1–7). Bone marrow examinations were conducted between days 28 and 42 after induction therapy. If CR or CRi was achieved, the patient continued consolidation treatment with venetoclax (400 mg, days 1–14), azacitidine (75 mg/m^2, days 1–7), and G-CSF (5 μg/kg/d, days 1–7). Consolidation therapy at least included 7 cycles.

The primary outcome was composite complete remission (CRc: CR or CRi) after one cycle of induction therapy. Responses and outcomes were defined according to the ELN 2022 guidelines [9]. Adverse events were classified using Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0). Measurable residual disease (MRD) was assessed via multi-parameter flow cytometry (sensitivity 0.01%). Baseline characteristics were analyzed using Mann–Whitney U test, the chi-squared or Fisher's exact test. The Kaplan-Meier and log-rank methods were used to test survival analysis. The follow-up data were updated in April 2025.

Baseline characteristics and treatment responses of the patients are summarized in Table 1. The median age was 68 years (range 41–81), 11 (28.9%) were ≥75 years. Fourteen (36.8%) patients were ELN favorable risk, 10 (26.3%) as intermediate and 11 (28.9%) as adverse [9]. *RUNX1::RUNX1T1* mutations were detected in 5 patients (13.2%). CRc rate was 81.6% (31/38) after one cycle of VAG induction. Twenty-four (63.2%) patients achieved CR and seven (18.4%) achieved CRi. Bone marrow was not evaluated in 1 patient. CRc rate for ELN favorable-risk, intermediate-risk, and adverse-risk was 92.9% (13/14), 80.0% (8/10), and 63.6% (7/11), respectively, with no statistically significant difference. In patients with CRc, MRD-negativity was 88.0% (22/25), 90.0% (9/10), 100.0% (8/8), and 83.3% (5/6) in overall, favorable, intermediate, and adverse-risk groups, respectively. Among five patients with *RUNX1::RUNX1T1* mutations, two reached CR and three reached CRi after one cycle of VAG re-induction. One achieved complete molecular remission (<0.01% gene expression) post allogeneic HSCT (allo-HSCT) during consolidation period.

The median follow-up time was 20.5 months (95% CI 14.5–26.5). Median OS was 17.0 months (95% CI 10.4–23.6; CRc: 18.1 [16.1–20.1] vs. non-CRc: 10.3 [9.1–11.5]). Median OS in favorable, intermediate, and adverse group was 21.4 (95% CI 11.5–31.3), 25.0 (not estimated [NE]-NE), and 9.5 months (7.0–12.0), respectively (Fig. 1), with statistically significant difference ($P = 0.001$). Favorable and intermediate groups had longer OS vs. adverse ($P = 0.004$ and $P = 0.003$, respectively), with no difference between intermediate and favorable ($P = 0.848$). Median progression-free survival (PFS) was 9.0 months (7.9-10.1; CRc: 11.3 [6.2–16.4] vs. non-CRc: 4.8[1.9–7.7]). Median PFS in favorable, intermediate, and adverse group was 17.6 (7.5–27.7), 19.0 (5.0–33.0), and 5.8 months (3.6–8.0), respectively (Fig. 1), with statistically significant difference ($P < 0.001$). Both favorable and intermediate groups had longer PFS versus adverse (both $P < 0.001$), with no difference between favorable and intermediate ($P = 0.907$). The 1-year OS and PFS was 59.2% and 41.9%, respectively.

Safety analysis comprised all patients. The most common grade 3 or higher hematologic adverse events included neutropenia (27/

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Table 1. Patient characteristics and response outcomes.

Characteristics	All patients ($n = 38$)
Age	
Median (range)—yr	68(41–81)
≥75 yr—no. (%)	11(28.9)
Gender—no. (%)	
Male	22(57.9)
Female	16(42.1)
ECOG performance-status score — no. (%)[λ]	
0–1	21(55.3)
2–3	17(44.7)
Bone marrow blast count — no. (%)	
<30%[‡]	3(8.1)
≥30 to <50%	13(35.1)
≥50%	21(56.8)
Missing	1(2.6)
WBC count (range) — x 10^9/L	9.9 (0.9-184.7)
Platelet count (range) — x 10^9/L	42(3-180)
Selected molecular mutation — no. (%)	
TP53	1(2.6)
FLT3-ITD	4(10.5)
NPM1	7(18.4)
IDH1/2	10(26.3)
ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2	10(26.3)
CEBPA (bZIP in-frame)	4(10.5)
Missing	3(7.9)
ELN-2022 risk classification — no. (%)	
Favorable	14(36.8)
Intermediate	10(26.3)
Adverse	11(28.9)
Missing	3(7.9)
Response after one cycle — no. (%)	
CR	24(63.2)
CRi	7(18.4)
60-day mortality — no. (%)	1(2.6)
Median PFS— months. (95% CI)	9.0(7.9-10.1)
Median OS— months. (95% CI)	17.0(10.4–23.6)
Time to blood cell count recovery[¶] after induction—days. (IQR)	29(21–37)
Time to ANC recovery to 0.5 × 10^9/L—days. (IQR)	23(14–30)
Time to ANC recovery to 1.0 × 10^9/L—days. (IQR)	26(21–34)
Time to PLT count recovery to 20 × 10^9/L—days. (IQR)	14(0-21)
Time to PLT count recovery to 50 × 10^9/L—days. (IQR)	21(16–34)
Time to PLT count recovery to 100 × 10^9/L — days. (IQR)	22(19–45)

Data are point estimate (95% CI) [n], median (IQR), or n (%).
[λ]ECOG performance statuses, spanning 0 to 5, denote disability levels where 0 signifies absence of symptoms and each subsequent score reflects increased impairment.
[‡]Bone marrow blasts ranged from 20% to 29%.
[¶]Blood cell recovery required a neutrophil count ≥1 × 10^9/L and platelets ≥50 × 10^9/L.

38, 71.1%), thrombocytopenia (27/38, 71.1%), and anemia (24/38, 63.2%). The common grade 3 or higher non-hematologic adverse effects were pneumonia (63.2%, 24/38), febrile neutropenia (36.8%, 14/38), and sepsis (10.5%, 4/38). No tumor lysis syndrome events were observed. The median time to hematologic recovery (absolute neutrophil count [ANC] ≥1 × 10^9/L and platelets ≥50 × 10^9/L) after induction therapy was 29 days (IQR 21–37). For ANC recovery, median times were 23 days (14–30) for ≥0.5 × 10^9/L and 26 days (21–34) for 1 × 10^9/L. Platelet recovery times were 14 days (0-21) for ≥20 × 10^9/L, 21 days (16–34) for ≥50 × 10^9/L, and 22 days (19–45) for ≥100 × 10^9/L.

The VAG regimen, which combines G-CSF with venetoclax and azacitidine, was firstly used in AML patients unfit for intensive chemotherapy. It has been demonstrated a CRc rate of 81.6% after one cycle of VAG induction, which significantly improved remission rates compared to VA regimen. The VAG regimen showed superior leukemia cell clearance. Reasons for the better efficacy may be as follows. First, adding G-CSF to VA could promote the differentiation of leukemia cells into granulocytes and increase their sensitivity to venetoclax [10]. Previous data suggested that granulocytic AML is more sensitive to venetoclax and azacitidine, while monocytic AML exhibits resistance due to the absence of BCL2 expression at the venetoclax target [10, 11]. Second, both venetoclax and G-CSF can stimulate T cells to exert anti-leukemic effects [12, 13], so we assumed that G-CSF and venetoclax might play synergistic roles. In addition, we speculated that G-CSF might mobilize leukemia cells to be released from bone marrow into peripheral blood, promoting a killing effect. Specific mechanisms are under study.

In addition, the high deep response rate of VAG regimen with MRD, may also potentially improve survival outcomes in patients with AML. Our trial confirmed that VAG regimen prolonged median OS compared to VA regimen. However, no significant improvement in PFS was seen. This outcome may be associated with the delayed treatment cycle due to the COVID-19 pandemic. In this study, VAG regimen induced MRD-negative remission in 88% of patients after one cycle, demonstrating strong efficacy against leukemia cells. Evidence indicates that MRD-negative remission is the best endpoint of induction therapy, which can not only improve survival outcomes but also reduce the risk of relapse [14].

A deeper dive into the data revealed that patients with AML—whether classified as ELN favorable, intermediate, or adverse-risk—responded remarkably well to the VAG treatment. This regimen demonstrated impressive efficacy, with a significant proportion of participants achieving both CRc and MRD-negativity. The findings held true across all risk categories, underscoring VAG's potential as a therapeutic option. Sixty-three point six percent (7/11) of ELN adverse-risk patients had CRc, with 83.3% (5/6) of those achieving CRc showing negative MRD. The limited sample size in ELN intermediate and adverse-risk groups necessitates a larger randomized controlled trial to determine VAG regimen's efficacy in these patients.

A key risk of this regimen is heightened myelosuppression, which is associated with increased mortality. By day 26, ANC recovered to 1 × 10^9/L, with platelets hitting 20, 50, and 100 × 10^9/L at days 14, 21, and 22. These results were similar to the recovery time of blood cell count of about 4 weeks in previous studies. Another major concern is severe infection caused by neutropenia. Pneumonia (24/38, 63.2%) was the most common infection. Among these 24 patients, 22 were controlled after anti-infective treatment, and 2 patients ultimately died from septic shock caused by pneumonia. Hence, prompt adoption of antibiotic protocols significantly curtails the prevalence of severe, possibly fatal infections. These findings align with the side effect patterns reported in comparable studies [1, 15]. Therefore, for previously untreated patients with AML, VAG regimen appears to be safe and well tolerated, without delaying the recovery of blood cell counts.

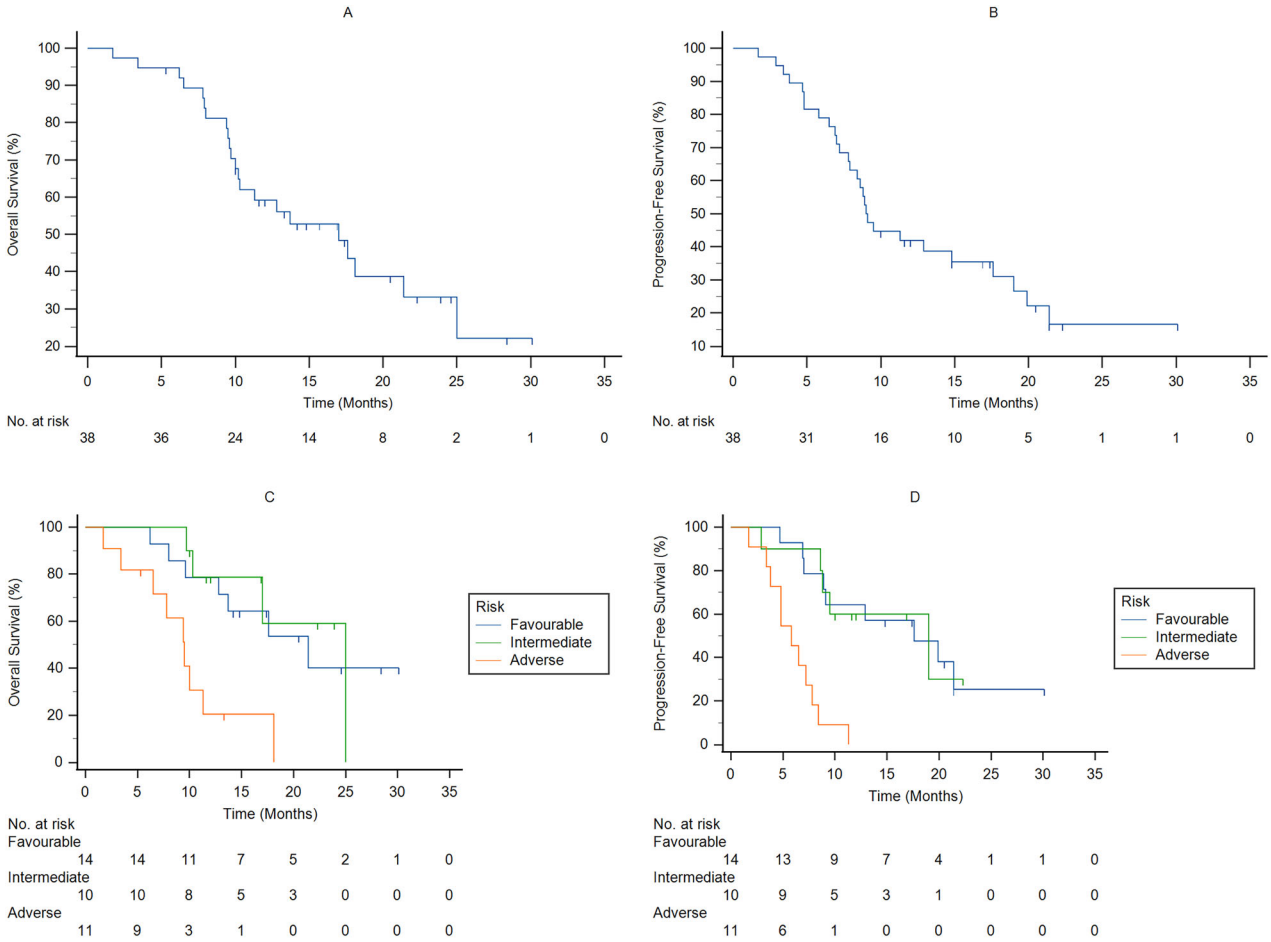

Fig. 1 Outcomes in patients. A Overall survival; **B** Progression-free survival; **C** Overall survival by ELN 2022 risk classification; **D** Progression-free survival by ELN 2022 risk classification.

The study has some limitations. Firstly, our trial limited to 38 patients with short follow-up, further research with longer-term data and larger patient groups is crucial. A randomized controlled trial (ChiCTR2300078290) is underway to compare VAG and VA regimens in newly diagnosed AML patients unfit for intensive chemotherapy. Secondly, uneven patient distribution across ELN risk groups could inflate VAG regimen's efficacy.

In conclusion, the VAG regimen achieves high remission rates and is well-tolerated in AML patients unfit for intensive chemotherapy. A randomized controlled trial with extended follow-up is in progress.

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DATA AVAILABILITY

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

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AUTHOR CONTRIBUTIONS

HW conceived and designed the study, oversaw patient management, performed data analysis, and critically reviewed the manuscript. XW was responsible for data collection and analysis, as well as drafting the initial version of the manuscript. TS contributed to data acquisition, analysis, and patient care. SW, XL, YL, and YW participated in patient management and manuscript review. MS handled patient care and data analysis. PH provided manuscript review and administrative assistance. H-HZ led the study design, conducted data analysis, reviewed the manuscript, and offered administrative support. HW, MS, PH, and H-HZ accessed and validated the dataset. All authors had complete access to the study data and jointly assumed final responsibility for the submission decision.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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