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Outcomes of venetoclax combined with homoharringtonine and cytarabine in fit adults patients with de novo adverse-risk acute myeloid leukaemia: A single-centre retrospective analysis

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Abstract

Adverse-risk acute myeloid leukemia (AML) has a dismal prognosis. We aimed to investigate the activity and tolerability of venetoclax combined with homoharringtonine (HHT) plus cytarabine (VHA) regimen for de novo adverse-risk AML. Thirteen de novo AML patients with adverse-risk factors were treated with venetoclax (100 mg day 1, 200 mg day 2, 400 mg days 3-21), HHT (1 mg/m^2 days 1-5) and cytarabine (100 mg/m^2 days 1-5) (VHA regimen). Complete remission (CR) was achieved in 11/13 patient (84.6%), all of CR responders were measurable residual disease (MRD) negative detected by multi-parameter flow cytometry (MFC). Grade 3-4 neutropenia, anaemia, and thrombocytopenia occurred in most patients. Grade 3-4 non haematological adverse events (AEs) included febrile neutropenia (4/13, 30.8%). With a median follow-up of 10 months (range 4-19), median overall survival and event-free survival were not reached. VHA may be a promising and well-tolerated regimen in de novo adverse-risk AML.

KEYWORDS
Acute myeloid leukemia, Adverse-risk, Cytarabine, Homoharringtonine, Venetoclax

Adverse-risk acute myeloid leukaemia (AML) has inferior outcomes compared to other genetic subtypes of AML when treated with standard frontline regimens (such as 7+3) [1]. Patients in the adverse-risk category who received intensive chemotherapy (IC) had lower complete remission (CR) rates and poor outcomes than those in favourable- and intermediate-risk categories based on the revised 2022 European LeukemiaNet (ELN) genetic risk stratification. CR rates and 5-year overall survival (OS) for patients in the ELN-2022 adverse risk groups were 45% and 15%, meanwhile, these patients who respond to initial standard induction/consolidation chemotherapy will eventually suffer a relapse with long-term survival ranging around 51.6% [2, 3].

Venetoclax, a B-cell lymphoma 2 inhibitor, achieves encouraging results in acute myeloid leukaemia [4, 5]. The VIALE-A study (ClinicalTrials.gov Identifier: NCT02993523) showed the incidence of composite CR (CRc) was notably improved across all AML genomic risk groups, including patients with adverse cytogenetic risk [4].

Bao-quan Song, Xin Kong and Yan Pu contributed equally to this study.

TABLE 1 Patients' characteristics and outcomes of the VEN+HA therapy.

Variable	Patients ($n = 13$)
Age, year, median (range)	38 (20–58)
Sex	
Male	8
Female	5
WBC count (10^9 /L), median (range)	6.85 (0.78–125.5)
BM blast (%), median (range)	42 (22.5–91)
< 30% (*n*, %)	4 (30.7%)
≥30% to < 50% (*n*, %)	4 (30.7%)
≥50% (*n*, %)	5 (38.6%)
Adverse risk characteristics (ELN 2022), (*n*, %)	
Complex cytogenetics	4
ASXL1	4
KMT2A-rearranged	2
DEK::NUP214	2
U2AF1	1
Overall response rate, %,	
Complete remission (CR) rate, %	11 (84.6%)
MRD-Negative (MFC, %)	11 (84.6%)
No response, %	2 (15.4%)
Patients received allogeneic HSCT, %	10 (76.9%)
Event- free survival, days	NR
Overall survival, days	NR

Homoharringtonine (HHT), a Chinese medicine extracted from *Cephalotaxus* species, HHT-based induction regimens have been widely used to treat AML [6]. In vitro, HHT has been reported to have significant synergistic effects with venetoclax [7]. Moreover, a multicenter phase 2 trial showed the CRc rate was 91% after one cycle of VHA regimen (venetoclax combined with azacitidine and homoharringtonine) in relapsed/refractory AML [8]. Therefore, venetoclax combined with HHT may be a promising and well-tolerated regimen in adverse-risk AML patients.

This retrospective analysis included 13 newly diagnosed AML patients (aged ≤ 60 years) with adverse-risk AML (European LeukemiaNet 2022 classification) who presented to First Hospital of Soochow University between July 2021 and December 2022. Table 1 summarizes the patients and their clinical information. Patients were treated with VHA induction chemotherapy (VEN 100 mg day 1, 200 mg day 2, 400 mg days 3–21, orally; HHT 1 mg/m^2 days 1–5, intravenously; cytarabine, 100 mg/m^2 days 1–5, intravenously) (Figure 1A). After reaching complete remission, patients received two cycles of intermediate-dose cytarabine (1-2 g/m^2, every 12 h, for a total of six doses) ± idarubicin (8 mg/m^2, daily for 2 days). Subsequently, patients received allogeneic haematopoietic stem cell transplantation (allo-HSCT) if a suitable donor was available (Figure 1B). Dose interactions between venetoclax and concomitant medications were considered. All patients received supportive care measures per institutional guidelines including prophylactic anti-infective agents, blood product transfusions, and growth factor support. All patients provided written informed consent in accordance with the Declaration of Helsinki. Response assessments were performed according to the National Comprehensive Cancer Network (NCCN) guidelines for AML (version 2. 2022). Event-free survival (EFS) was defined as the time interval from treatment initiation to the first observation of induction failure, relapse, or death. OS was defined as the time interval from treatment initiation to death from any cause.

A total of 13 patients with de novo adverse-risk AML received the VHA regimen, including eight males and five females, with a median age of 38 years (range 20–58). According to European LeukemiaNet (ELN 2022) [9] risk stratification, the adverse risk genetic mutations were: complex cytogenetics (four of 13), ASXL1 mutations (four of 13), KMT2A-rearranged (two of 13), t(6;9)(p23.3;q34.1)/DEK::NUP214 (two of 13) and U2AF1 mutations (one of 13). Patients' demographic, cytogenetic and molecular features are summarised in Table 1 and Table S1. With a median follow-up of 10 months (range 4–19), median EFS and OS were not reached (Figure 2A,B). The last follow-up date is 20 April 2023.

After one cycle of the VHA regimen, 11 of 13 patients (84.6%) achieved CR, in CR responders, all of the patients were measurable residual disease (MRD) negative detected by multi-parameter flow cytometry (MFC). Only two patients showed no response after one cycle of VHA induction therapy. One patient (P13) received salvage treatment with gilteritinib combined with azacitidine and achieved CR. Unfortunately, the patient (P13) relapsed during one cycle of consolidation therapy, who currently undergoing salvage treatment and delayed HSCT due to relapse. The other no-response patient (P4) achieved CR with incomplete haematologic recovery (CRi) after one cycle of selinexor plus azacitidine and then received hapllo-HSCT, who died 3 weeks after HSCT due to a serious pulmonary infection. Among 11 CR patients, 10 patients received two cycles of consolidation treatment, except one patient (P3) received an azacitidine consolidation regimen due to poor physical condition caused by VHA induction therapy. There were 10 patients (76.9%) who eventually proceeded to allo-HCT after receiving consolidation chemotherapy. Two of 13 patients (P3 and P11) chose consolidation/maintenance therapy instead of transplantation due to unavailable donors or economic pressure (Figure 1C).

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). The AEs observed during the VHA regimen induction are summarized in Table S2. Grade 3–4 neutropenia, anaemia, and thrombocytopenia occurred in most patients during the induction. The most common Grade 3–4 non-haematological AEs included febrile neutropenia (4/13, 30.8%). Other serious AEs included pneumonia (3/13, 23.1%), sepsis (2/13, 15.4%), fatigue (2/13, 15.4%), oesophagitis (1/13, 7.7%), diarrhoea (1/13, 7.7%), fungal infection (1/13, 7.7%), hypertension (1/13, 7.7%), dizziness (1/13, 7.7%) and gastrointestinal bleeding(1/13, 7.7%). No tumour lysis syndrome or death occurred during VHA induction chemotherapy.

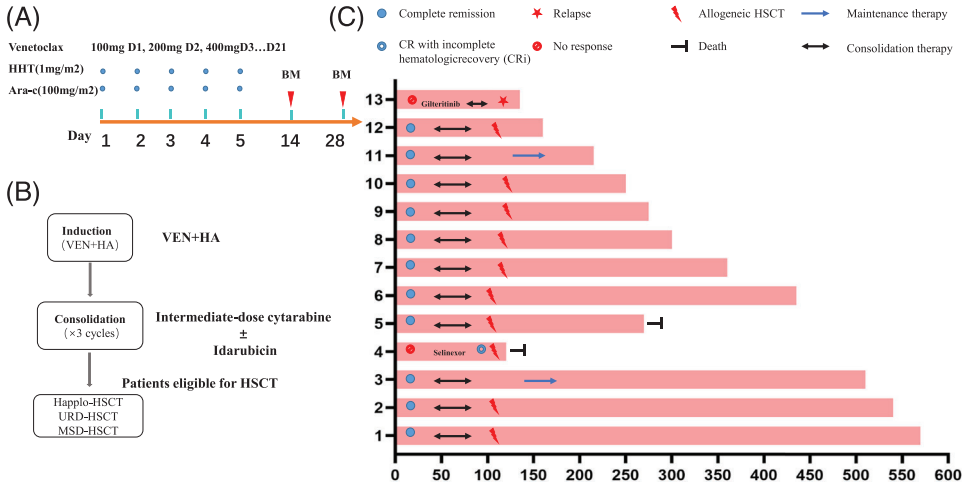

FIGURE 1 Effect of VHA regimen in patients. (A, B) Treatment schedule of our modified VHA regimen. (C) Swimmer plot showing the clinical response and follow-up of individual patients treated with VHA regimen. Each bar represents one patient.

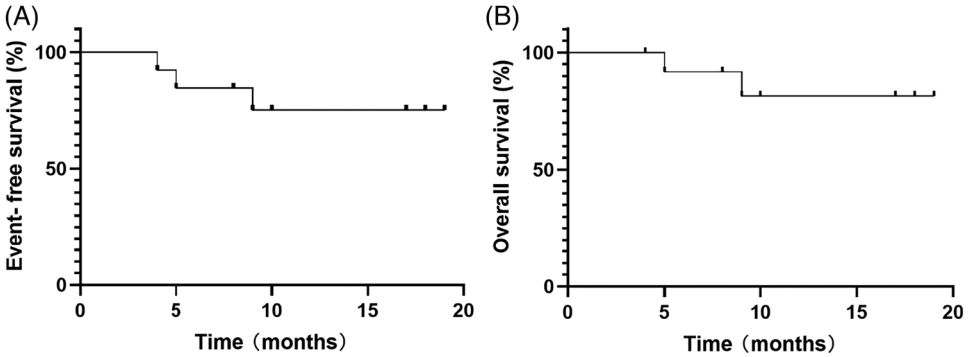

FIGURE 2 Clinical and response characteristics of all patients enrolled in the study. (A) Event-free survival of all patients. (B) Overall survival of all patients.

The venetoclax-based regimen has led to improved outcomes among newly diagnosed fit or unfit AML patients [10, 11]. However, few studies have reported the efficacy of a venetoclax-based regimen in newly diagnosed adverse-risk AML. In this retrospective analysis, we reported the real-world outcomes in de novo AML patients with high risk, who received VHA induction chemotherapy in the frontline. In our study population, we saw a very promising CR rate of 84.6% and MFC- MRD negative rates of 100% in patients with response, accompanied by low treatment-related mortality. Although median EFS and OS were not reached for CR1 patients, the estimated 1-year EFS and OS rates suggest that the VHA regimen improves survival. Overall, our research demonstrated that the VHA regimen may be as potentially the preferred choice to induce newly diagnosed adverse-risk AML patients considering its high response rate and low toxicity. The limitations of our study include the retrospective design, small sample size, and lack of long-term follow-up data. A well-designed randomised trial with long-term follow-up is needed to confirm this finding.

AUTHOR CONTRIBUTIONS

Hui-Ying Qiu, Jian Zhang and De-Pei Wu designed the research; all authors collected, assembled, analyzed, and interpreted data, Yan Pu and Yin Liu performed the statistical analysis, Bao-Quan Song and Xin Kong wrote the manuscript; and all authors approved the final version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PATIENT CONSENT STATEMENT

All patients (13) provided written informed consent in accordance with the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

All relevant data are within the manuscript and its additional files.

ETHICS STATEMENT

Our study was approved by the ethical committee of the First Affiliated Hospital of Soochow University (No2021-026).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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