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Venetoclax combined with escalating doses of homoharringtonine, low-dose cytarabine, and granulocyte colony-stimulating factor demonstrates feasibility and tolerability for remission induction in pediatric acute myeloid leukemia

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Running heads: Venetoclax-based regimen in pediatric AML

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Advances in supportive care and intensified treatment regimens, including hematopoietic stem cell transplantation (HSCT), have markedly improved outcomes for pediatric acute myeloid leukemia (AML). However, event-free and overall survival rates have plateaued at approximately 65% and 80%, respectively.[1,2] Relapsed disease, as well as acute and long-term toxicities, remain significant challenges.

Our AML collaborative group has prioritized developing and evaluating low-dose chemotherapy (LDC) regimens for remission induction in pediatric AML.[3] A recent randomized study demonstrated that an LDC regimen for remission induction was non-inferior to standard-dose chemotherapy.[4] Nevertheless, exposure to anthracyclines and the number of patients undergoing HSCT remain high. We are currently exploring alternatives to reduce toxicity by incorporating agents with more favorable efficacy and toxicity profiles.

Homoharringtonine (HHT), a plant-derived alkaloid (from Cephalotaxus) that inhibits protein synthesis by targeting ribosomes, has been widely used in treating adult and pediatric AML in China.[5-7] Preclinical studies have shown that HHT peak plasma concentrations of 3 mg/m²/day and 5 mg/m²/day exceed levels required to inhibit 50% of HL-60 leukemia cell growth.[8] Further preclinical evidence suggests that HHT and venetoclax can synergistically promote apoptosis by inhibiting the *MAPK/ERK and PI3K/AKT* pathways while activating the p53 pathway.[9]

Clinically, HHT has been successfully integrated into standard-dose regimens of cytarabine and daunorubicin, demonstrating feasibility and efficacy.[7] Given the potential synergy between HHT, venetoclax, and cytarabine, we explored replacing mitoxantrone with venetoclax and HHT in the LDC regimen for remission induction. Based on relapse risk, patients received two to three additional courses of standard chemotherapy as consolidation therapy. Details of this new regimen (V-HAG) are provided in Supplementary Table 1. Patients at high risk of relapse (criteria outlined in Supplementary Table 1) were considered for HSCT. Homoharringtonine was administered in a 3 × 3 dose escalation design at 1 mg/m² (dose level 1), 2 mg/m² (dose level 2), and 3 mg/m² (dose level 3) daily for 10 days to determine the maximum tolerated dose within the context of this regimen. The study is registered under the identifier ChiCTR2200064901. This study was approved by the institutional review board of the Children's Hospital of Soochow University, and conducted in accordance with the Declaration of Helsinki and patient data were maintained with strict confidentiality.

Between October 2022 and June 2023, 12 consecutive patients were enrolled in this Phase I feasibility study, with three patients assigned to dose level (DL) 1, three to DL 2, and six to DL 3. The cohort included seven males and five females, with a median age of 8.3 years (range: 3.3–12.7 years). The most common fusion gene identified was *RUNX1::RUNXT1*, present in five patients, followed by *KMT2A* rearrangements in two patients, with one case each of *KMT2A::MLLT4* and *KMT2A::MLLT10*. Other detected fusion genes included *CBFB::MYH11* (n=1) and *NUP98::NSD1* (n=1). The most frequently identified gene variants were *NRAS* (n=3), *CEBPA* double mutant (n=2), and *KIT* (n=3), located in exon 17 in two cases and exon 8 in one case. Additionally, two patients had *CEBPA* single mutations (non-bZip), and two had *KRAS* mutations (Table 1).

All patients received at least one cycle of V-HAG and were evaluated for toxicity and response to Induction Ⅰ. One patient in DL1 was classified as a non-responder after Induction Ⅰ, with more than 20% blasts observed in the bone marrow on day 22. This patient subsequently withdrew from the trial. The remaining 11 patients completed both induction courses and achieved remission. These patients proceeded to a median of three consolidation cycles (range, 2–4 cycles), with five undergoing allogeneic HSCT. As of August 1, 2024, at a median follow-up of 18 months (range, 11–19 months), all patients were alive and disease-free, including the one patient who withdrew from the protocol. Relevant demographic data are summarized in Table 1.

No dose-limiting toxicities (DLTs) or deaths were observed within the first 30 days following the initiation of Induction Ⅰ. The most common non-hematological toxicities were febrile neutropenia, nausea or vomiting, lung infections, ECG T-wave changes (inverted T-waves, flattened T-waves, and bidirectional changes), and sinus tachycardia (Table 2). Prolongation of the QT interval was not observed in any of the patients. The median durations of neutropenia ($< 0.5 \times 10^9$/L) and thrombocytopenia ($< 20 \times 10^9$/L) during Induction Ⅰ were 22 days (14–38 days) and 16 days (10–28 days), respectively (Supplementary Table 2).

Similarly, no DLTs were observed among the 11 patients who received Induction Ⅱ. The most frequent non-hematological toxicities during Induction Ⅱ were febrile neutropenia, nausea or vomiting, ECG T-wave changes, sinus tachycardia, and lung infections (Table 2). Importantly, no impairment in cardiac ejection function was observed during Induction II. The median duration of neutropenia and platelet recovery during Induction Ⅱ were 18 days (7–34 days) and 15 days (0–29 days), respectively (Supplementary Table 2). The overall response rate after Induction Ⅱ was 100.0%. Furthermore, no severe adverse events (grade 4–5) occurred during either induction phase.

The venetoclax concentration values measured using liquid chromatography-tandem mass spectrometry and peak-to-trough concentration ratios are shown in Figure 1. Venetoclax concentrations were assessed 5–7 days after treatment initiation. The trough concentration was measured 30 minutes before the next dose, while the peak concentration was measured six hours post-administered. During Induction Ⅰ, the median venetoclax peak concentration was 1,375 ng/ml, and the median trough concentration was 415 ng/ml, yielding a peak-to-trough ratio of 4.1. During Induction Ⅱ, the median peak concentration increased to 1,740 ng/ml, while the trough concentration was 385 ng/ml, resulting in a peak-to-trough ratio of 4.86. These ratios were used to categorize patients into high- and low-ratio groups. No significant differences between the high- and low-ratio groups were observed in hematological or non-hematological toxicities. Regarding treatment response, although a higher proportion of patients in the high-ratio group achieved minimal residual disease (MRD) <1% in Induction Ⅰ, this difference was not statistically significant. (Supplementary Table 3).

Our study demonstrates the feasibility of integrating venetoclax and HHT into a regimen of low-dose cytarabine and G-CSF for remission induction in children with de novo AML. This combination was well tolerated, and the dose-limiting toxicity of HHT was not reached. Therefore, we recommend a 3 mg/m² dose over ten days for future studies. Severe complications, such as septicemia and acute cardiac toxicity, were not observed. These findings are consistent

with several multicenter clinical trials in China, which also reported the safety and efficacy of HHT in children with AML.[5,6]

Cardiovascular side effects of HHT, including heart rhythm abnormalities, transient hypotension, and chronic cardiotoxicity, are rare.[10] The incidence of these effects appears to be influenced by infusion duration and cumulative dosage. Patients receiving continuous HHT infusions experienced fewer cardiovascular complications than those receiving bolus injections.[11] Furthermore, patients administered a high cumulative dosage of HHT exhibited a higher incidence of cardiac complications than the low-dose group.[11] Our study mandated a minimum intravenous infusion time of 4 hours at a constant infusion rate (Supplementary Table 1). No abnormal left ventricular ejection fraction changes were detected on the echocardiograph throughout the treatment course. Additionally, no elevations in cardiac enzyme levels, including troponin T, were observed. These findings suggest that cumulative doses of HHT up to 30 mg/m² during remission induction are safe for pediatric patients. However, ongoing monitoring and long-term follow-up are essential to assess the potential delayed cardiac effects.

Venetoclax, a BCL-2 inhibitor, is widely used in adults with de novo or secondary AML, typically in combination with azacitidine or low-dose cytarabine, and has shown favorable tolerability and efficacy.[12,13] Similarly, notable responses have been observed in pediatric relapsed AML when venetoclax was combined with intensive chemotherapy.[14,] A retrospective multicenter study evaluating salvage therapy with venetoclax combined with conventional chemotherapy in 31 previously treated children with AML or MDS reported an overall response rate of approximately 70% and a complete remission rate of 51%.[15] However, its use as a frontline treatment for pediatric AML remains limited.

In our protocol, venetoclax was well-tolerated at the administered doses. Although there was marked inter-patient variability in plasma concentrations, no correlation was observed between venetoclax plasma levels and toxicity. Furthermore, neutrophil and platelet recovery duration showed no association with venetoclax plasma concentrations. After two induction courses, all patients, regardless of high or low venetoclax ratios, achieved negative MRD.

In conclusion, the combination of venetoclax, homoharringtonine, low-dose cytarabine, and granulocyte colony-stimulating factor represents a safe and promising minimally myelosuppressive regimen. This anthracycline-free approach for remission induction is currently under investigation in a multicenter study of children with de novo AML.

References

1. Zeller B, Arad-Cohen N, Cheuk D, et al. Management of hyperleukocytosis in pediatric acute myeloid leukemia using immediate chemotherapy without leukapheresis: results from the NOPHO-DBH AML 2012 protocol. Haematologica. 2024;109(9):2873-2883.
2. Tomizawa D, Matsubayashi J, Iwamoto S, et al. High-dose cytarabine induction therapy and flow cytometric measurable residual disease monitoring for children with acute myeloid leukemia. Leukemia. 2024;38(1):202-206.
3. Hu Y, Chen A, Gao L, et al. Minimally myelosuppressive regimen for remission induction in pediatric AML: long-term results of an observational study. Blood Adv. 2021;5(7):1837-1847.
4. Gao L, Ju X, Jiang H, et al. Outcomes of children and adolescents with acute myeloid leukemia given a low-versus standard-dose chemotherapy regimen for remission induction (CALSIII-AML18): A multicenter, phase 3, randomized, noninferiority trial. Blood. 2023;142(Supplemental 1):729.
5. Chen X, Tang Y, Chen J, et al. Homoharringtonine is a safe and effective substitute for anthracyclines in children younger than 2 years old with acute myeloid leukemia. Front Med. 2019;13(3):378-387.
6. Tang Y, Luo C, Shen S, et al. The efficacy and safety of a homoharringtonine-based protocol for children with acute myeloid leukemia: A retrospective study in China. Pediatr Hematol Oncol. 2021;38(2):97-107.
7. Jin J, Wang JX, Chen FF, et al. Homoharringtonine-based induction regimens for patients with de-novo acute myeloid leukaemia: a multicentre, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2013;14(7):599-608.
8. Zhou DC, Zittoun R, Marie JP. Homoharringtonine: an effective new natural product in cancer chemotherapy. Bull Cancer. 1995;82(12):987-995.
9. Yuan F, Li D, Li G, Cheng C, Wei X. Synergistic efficacy of homoharringtonine and venetoclax on acute myeloid leukemia cells and the underlying mechanisms. Ann Transl Med. 2022;10(8):490.
10. Feldman E, Arlin Z, Ahmed T, et al. Homoharringtonine is safe and effective for patients with acute myelogenous leukemia. Leukemia. 1992;6(11):1185-1188.
11. Kantarjian HM, Talpaz M, Santini V, Murgo A, Cheson B, O'Brien SM. Homoharringtonine:

history, current research, and future direction. Cancer. 2001;92(6):1591-1605.
12. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617-629.
13. Karol SE, Alexander TB, Budhraja A, et al. Venetoclax in combination with cytarabine with or without idarubicin in children with relapsed or refractory acute myeloid leukaemia: a phase 1, dose-escalation study. Lancet Oncol. 2020;21(4):551-560.
14. Trabal A, Gibson A, He J, et al. Venetoclax for Acute Myeloid Leukemia in Pediatric Patients: A Texas Medical Center Experience. Cancers (Basel). 2023;15(7):1983.
15. Masetti R, Baccelli F, Leardini D, et al. Venetoclax-based therapies in pediatric advanced MDS and relapsed/refractory AML: a multicenter retrospective analysis. Blood Adv. 2023;7(16):4366-4370.

Table 1. Patient characteristics and outcome.

N	Age/ Sex	WBC at diagnosis ($\times 10^9$/L)	Fusion Genes/ Mutations	Initial[#] Risk Group	Dose Level HHT	BM blasts < 5%) Induction I/II	MRD[&] Induction II Flow cytometry/ Fusion genes RT qPCR	Consolidations Cycles	Allo-HSCT	Alive	Overall survival (months)
1	12.1 y/F	50.5	*RUNX1::RUNXT1*/ *KIT* (exon 17 p.D816Y), *ASXL2*	IR	1mg	No	NA	1	Yes	Yes	19[§]
2	11.9 y/M	7.2	Negative/ *CEBPA*-dm	LR	1mg	Yes/Yes	< 0.1%	3	No	Yes	19
3	11.9 y/F	2.6	*RUNX1::RUNXT1*/ *EZH2*	IR	1mg	Yes/Yes	< 0.1%/ Negative	3	No	Yes	18
4	6.7 y/F	9.9	*RUNX1::RUNXT1*/ *KIT* (exon 17 p.D820Y), ASXL2	IR	2mg	Yes/Yes	< 0.1%/ Negative	4	No	Yes	19
5	3.5 y/M	22.1	*NUP98::NSD1*/ *NRAS, WT1*, *CEBPA*-sm	HR	2mg	Yes/Yes	< 0.1%/ Negative	2	Yes	Yes	19

6	1.8y/ M	67.6	*CBFB::MYH 11/ KIT* (exon 8 p.T417), *KRAS*	IR	2mg	Yes/Yes	< 0.01%/ Negative	2	Yes	Yes	19
7	4.5 y/M	13.5	Negative/ *CEBPA*-dm, *CSF3R, JAK3*	IR	3mg	Yes/Yes	< 0.1%	4	No	Yes	19
8	9.7 y/F	62.8	*KMT2A::ML LT10/ NRAS*	HR	3mg	Yes/Yes	< 0.1%/ Negative	2	Yes	Yes	17
9	7.3 y/F	3.0	*RUNX1::RU NXT1/ KRAS, ASXL2*	IR	3mg	Yes/Yes	< 0.1%/ Negative	3	No	Yes	19
10	3.9 y/M	10.5	Negative, *CEBPA*-sm, GATA2, *CCND3*	IR	3mg	Yes/Yes	< 0.1%	3	No	Yes	11
11	11.7 y/M	6.7	*RUNX1::RU NXT1/ CCND2*	IR	3mg	Yes/Yes	< 0.1%/ Negative	3	No	Yes	11
12*	11.4 y/M	12.0	*KMT2A::ML LT4 NRAS, FLT3*-TKD	HR	3mg	Yes/Yes	< 0.1%/ Negative	2	Yes	Yes	11

Abbreviations: LR, low-risk; IR, intermediate-risk; HR, high-risk; Allo-HSCT, allogeneic hematopoietic stem-cell transplantation; NA, not available.

[#]None of the patients exhibited central nervous system involvement.

*Complex Karyotype: 46,XY,inv(3)(q21;q26),t(4;13)(q13;q13),t(6;11)(q27;q23),t(8;16)(p11;p12)[20].

[&]MRD was performed using flow cytometry.

[§]The patient received three doses of doxorubicin (50 mg/m² daily) and 20 doses of cytarabine (100 mg/m² every 12 hours for 10 days) before proceeding to allogeneic HSCT.

Table 2. Hematologic and non-hematologic toxicities in during Induction I and II

Induction Therapy	V-HAG©								
	Level 1			Level 2			Level 3		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Induction I		**N=3**			**N=3**			**N=6**	
Hematological toxicity									
Time to recovery neutrophil count > 0.5 $\times 10^9$/L (days, median, range)		21, 22			14, 22, 38			23（16-27）	
Time to recovery platelet count > 20×10^9/L) (days, median, range)		10, 15			14, 16, 28			17（10-22）	
Infection									
Febrile neutropenia	0	**2**	0	0	**3**	0	0	**6**	0
Lung or sinus infection	**1**	**1**	0	0	**1**	0	0	**3**	0
mucositis	**1**	**0**	0	0	**0**	0	0	**0**	0
Gastrointestinal (%)									
Nausea or vomiting	**2**	0	0	**3**	0	0	2	0	0
Cardiac (%)									
Sinus tachycardic	0	0	0	1	0	0	**2**	0	0
ECG T-wave changes@	0	0	0	2	0	0	**2**	0	0
Other									
Headaches	**1**	0	0	0	0	0	0	0	0
Induction II		**N=2**			**N=3**			**N=6**	
Hematological toxicity									
Time to recovery neutrophil count > 0.5 $\times 10^9$/L (days, median, range)		7, 9			13, 22, 27			22（10-34）	
Time to recovery platelet count > 20×10^9/L) (days,		0, 6			10, 12, 21			17（14-29）	

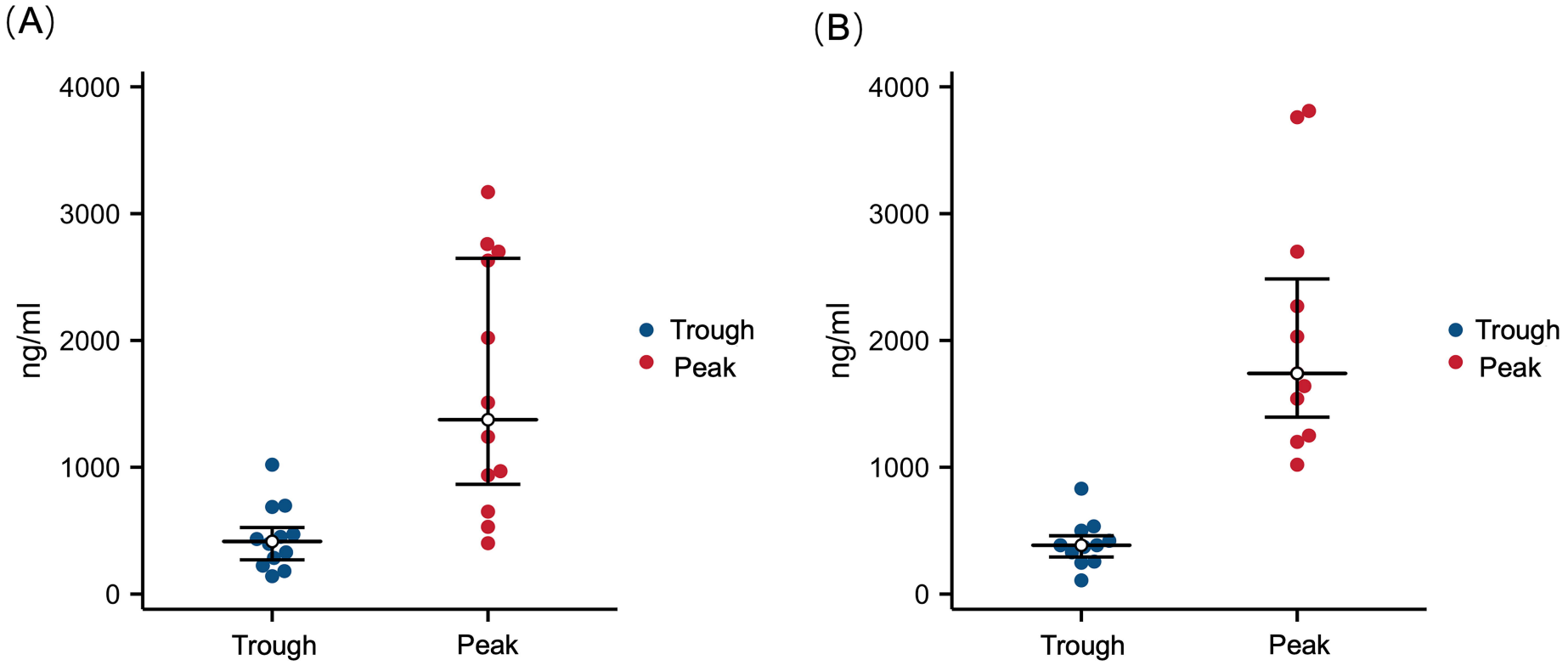
median, range)									
Infection									
Febrile neutropenia	0	0	0	0	**3**	0	0	**5**	0
Lung or sinus infection	0	0	0	0	**1**	0	0	**2**	0
mucositis	0	0	0	0	**0**	0	0	**0**	0
Gastrointestinal (%)									
Nausea or vomiting	**1**	0	0	2	0	0	**2**	0	0
Cardiac (%)									
Sinus tachycardic	0	0	0	**1**	0	0	**2**	0	0
ECG T-wave changes[@]	0	0	0	**2**	0	0	**2**	0	0

[©] This V-HAG regimen consists of venetoclax, HHT, low-dose cytarabine, and granulocyte colony-stimulating factor (G-CSF).

[@] During Induction I, two patients in the Level 2 group exhibited T wave abnormalities, including flattened T waves in leads I and II and inverted T waves in lead III. In the Level 3 group, two patients also showed flattened T waves. During Induction II, all patients in the Level 2 group demonstrated flattened T waves in leads II and III. In the Level 3 group, one patient displayed bidirectional T waves in leads V2 and V3, while another presented with inverted T waves in leads V3 and V4. Importantly, none of the electrocardiograms (ECGs) showed QT interval prolongation.

Figure legends

Figure 1. Venetoclax concentration in plasma during Induction therapies. (A) Venetoclax concentration in plasma during Induction I. (B) Venetoclax concentration in plasma during Induction II.


(A)
4000
3000
2000
1000
0
ng/ml
Trough
Peak
Trough
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(B)
4000
3000
2000
1000
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ng/ml
Trough
Peak
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Peak

Supplementary Tables

Supplementary Table 1. Chemotherapy regimens of V-HAG and indications for HSCT

	Drug	Dose	Schedule	Duration
Induction I/II	HHT	1 mg/m^2	Once daily, intravenously, infusion over ≥ 4 hours	Day1-10
		2 mg/m^2		
		3 mg/m^2		
	Cytarabine	10 mg/m^2	Every 12 hours, intravenously	Day1-10
	Venetoclax	120 mg/m^2 (max 400 mg)	Once daily, orally	Day 0
		240 mg/m^2 (max 400 mg)	Once daily, orally	Day1-10
	G-CSF	5 μg/kg	Once daily, subcutaneously	Day1-10
Consolidations				
I	Cytarabine	3 g/m^2	Every 12 hours, intravenously	Day 1-3
	HHT	3 g/m^2	Once daily, intravenously	Day 1-5
II	Cytarabine	3 g/m^2	Every 12 hours, intravenously	Day 1-3
	Etoposide	150 mg/m^2	Once per day, intravenously	Day1-3
III	Cytarabine	3 g/m^2	Every 12 hours, intravenously	Day 1, 2, 8, 9
	L-asparaginase	6000 U/m^2	Once per day, intramuscularly	Day 3,10
Criteria for HSCT	**Numeric changes:** Complex karyotype, or chromosome 5, 7 or 17p abnormalities. **Fusion genes:** *NUP98*-rearranged, *KMT2A*-rearranged (except *KMT2A*::*MLLT11* and *KMT2A*::*MLLT3*), *KMT2A*-PTD, *MECOM*-rearranged, *CBFA2T3*-rearranged, *DEK*::*NUP214*, *ETV6*::*HLXB9*, *BCR*::*ABL*, *KAT6A*::*CREBBP*, *FUS*::*ERG, PICALM*::*MLLT10.* **Pathogenic gene variants:** *FLT3-ITD, TP53, KIT* (exon 17), *UBTF-ITD, ASXL1, BCOR, EZH2, RUNX1*, *SF3B1, SRSF2, STAG2, U2AF1, ZRSR.* **MRD:** ≥ 0.1% after induction II.			After consolidation I or II

Abbreviations: HHT, homoharringtonine; V-HAG, venetoclax, HHT, cytarabine, granulocyte colony-stimulating factor; G-CSF; HSCT, hematopoietic stem cell transplantation; MRD, measurable residual disease.

Supplementary Table 2. Adverse events of HAGV treatment regimens during Induction I and II

	V-HAG group
Induction I (N)	12 cases
Hematological toxicity	
Time to recovery neutrophil count > 0.5 $\times 10^9$/L (days, median, range)	22 (14-38)
Time to recovery platelet count > 20×10^9/L) (days, median, range)	16 (10-28)
Non-hematological toxicity	
Gastrointestinal events (all grades, N, %)	7 (58.3%)
Cardiac events (all grades, N, %)	6 (50.0%)
Grade 3-5 Cardiac events (N, %)	0
Infection events (all grades, N, %)	11 (91.7%)
Grade 3-5 Infection events (N, %)	11 (91.7%)
Induction II (N)	11 cases
Hematological toxicity	
Time to recover neutrophil count > 0.5 $\times$ 10^9/L (days, median, range)	18 (7-34)
Time to recover platelet count > 20×10^9/L (days, median, range)	15 (0-29)
Non-hematological toxicity	
Gastrointestinal events (all grades, N, %)	5 (41.2%)
Cardiac events (all grades, N, %)	4 (33.3%)
Grade 3-5 Cardiac events (N, %)	0
Infection events (all grades, N, %)	6 (54.5%)
Grade 3-5 Infection events (N, %)	6 (54.5%)

Abbreviations: V-HAG, venetoclax, homoharringtonine, cytarabine, and granulocyte colony-stimulating factor.

Supplementary Table 3. Comparison of selected adverse events and treatment responses between low- and high-ratio venetoclax concentrations

	Induction I		**Induction II**	
	Low ratio concentration N=6	High ratio concentration N=6	Low ratio concentration N=6	High ratio concentration N=5
Gastrointestinal events	2	2	1	2
Cardiac events	3	3	0	1
Infection events	6	5	4	2
Grade 3-5 Infection events	6	5	4	2
Time to neutrophil recovery (> 0.5 x10^9/L), days	23.5 (16-38)	21(18-27)	16 (3-34)	16 (0-27)
Time to platelet recovery (>20 x10^9/L), in days	17.5 (11-28)	14 (10-19)	3 (0-29)	3 (0-13)
CR	4	6	6	5
Negative MRD♦	2	6	6	5

♦ During Induction I, the cut-off for negative MRD was set at <1%**,** while during Induction II, the threshold was <0.1% for negative MRD.