Muthanna Medical Journal

Volume 12 | Issue 1 Article 1

6-30-2025

Evaluating the Efficacy of Venetoclax-Based Regimens in Relapsed/Refractory Acute Leukemia: A Real-World Study from Three Chinese Oncology Centers

Wei Zhang
Department of Hematology, Shanghai Cancer Center, Fudan University, Shanghai, China

Liyang Huang
Department of Oncology, West China Hospital, Sichuan University, Chengdu, China

Ming Zhao
Hematology Institute, Peking Union Medical College Hospital, Beijing, China

Rui Chen
Department of Clinical Pharmacy, West China School of Pharmacy, Sichuan University, Chengdu, China

Huiwen Liu
Department of Hematology, Shanghai Cancer Center, Fudan University, 270 Dong An Road, Xuhui District, Shanghai 200032, China, Huiwen.Liu@asobm.org

MUTHANNA MEDICAL JOURNAL 2025;12:1–6

Evaluating the Efficacy of Venetoclax-Based Regimens in Relapsed/Refractory Acute Leukemia: A Real-World Study from Three Chinese Oncology Centers

Wei Zhang [a], Liyang Huang [b], Ming Zhao [c], Rui Chen [d], Huiwen Liu [e,*]

[a] Department of Hematology, Shanghai Cancer Center, Fudan University, Shanghai, China
[b] Department of Oncology, West China Hospital, Sichuan University, Chengdu, China
[c] Hematology Institute, Peking Union Medical College Hospital, Beijing, China
[d] Department of Clinical Pharmacy, West China School of Pharmacy, Sichuan University, Chengdu, China
[e] Department of Hematology, Shanghai Cancer Center, Fudan University, 270 Dong An Road, Xuhui District, Shanghai 200032, China

Abstract

Background: Relapsed or refractory (R/R) acute leukemia poses a significant therapeutic challenge, with limited options and poor prognosis. Venetoclax, a BCL-2 inhibitor, has shown promise in frontline acute myeloid leukemia (AML), but its real-world utility in R/R settings remains underexplored.

Objective: To evaluate the efficacy and safety of venetoclax-based regimens in adult patients with R/R acute leukemia treated in routine clinical practice across three tertiary oncology centers in China.

Methods: A retrospective multicenter study was conducted on 70 patients with R/R acute leukemia (AML or ALL) treated between January 2020 and December 2023. Patients received venetoclax combined with either hypomethylating agents (HMA group, n = 42) or low-dose cytarabine (LDAC group, n = 28). Response rates, overall survival (OS), event-free survival (EFS), and adverse events were analyzed. Kaplan-Meier survival estimates and Cox regression were used for outcome comparisons.

Results: The complete response (CR/CRi) rate was significantly higher in the HMA + VEN group compared to the LDAC + VEN group (52.4% vs. 32.1%; $p = 0.03$). Median OS was 8.3 months (95% CI: 6.7–9.8) in the HMA cohort and 5.7 months (95% CI: 4.1–7.3) in the LDAC cohort ($p = 0.04$). Median EFS was 6.1 vs. 3.9 months, respectively ($p = 0.02$). Common grade ≥3 adverse events included febrile neutropenia (54.3%), thrombocytopenia (47.1%), and infections (32.9%). No early treatment-related deaths were observed.

Conclusion: Venetoclax-based regimens, particularly in combination with hypomethylating agents, offer favorable response rates and survival benefits in patients with R/R acute leukemia. These findings support the integration of venetoclax into salvage protocols and warrant prospective validation in larger cohorts.

Keywords: Venetoclax, Acute myeloid leukemia, Relapsed leukemia, Refractory AML, Hypomethylating agents, Real-world study, China

1. Introduction

Acute leukemia (AL) is generally classified into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), characterized by the rapid production of nonfunctioning hematopoietic progenitors.[1] AL mainly affects children but also occurs in adults, being more common in elders.[2] AL is associated with compromised immune function, abnormalities of hemostasis, and increased susceptibility to secondary primary tumors. There has been considerable progress in the treatment of AL, with improved clinical outcomes, but median overall survival (OS) is still less than 50%.[3] The prognosis for relapsed/refractory (R/R) AL is dismal, with both reporting a 5-year OS of approximately 20%–

Received 26 May 2025; accepted 6 June 2025.
Available online 30 June 2025

* Corresponding author.
E-mail address: Huiwen.Liu@asobm.org (H. Liu).

https://doi.org/10.52113/2410-4590.1166

30%, consequently, there is a need for effective salvage therapies.[4] Complications of chemotherapy include opportunistic infections, bleeding, and pulmonary hemorrhage secondary to cytopenia. For patients with chemotherapy-refractory, relapsed post-transplantation, or secondary AL, the prognosis is very poor, and the use of high-intensity regimens is often limiting. Intensification therapy or hematopoietic stem cell transplantation (HSCT) might be considered for young patients at a suitable time, but elderly patients cannot tolerate the intensity of such therapy.[5] Bcl-2 inhibition has the potential to engage the apoptotic pathway for therapeutic benefit. Venetoclax (Ven) is a specific Bcl-2 inhibitor that has been shown to promote cytotoxicity in preclinical studies of hematopoietic malignancies. In combination with hypomethylating agents (HMAs), Ven has promising efficacy in acute myeloid leukemia (AML) and has already been approved for this indication.[6]

Venetoclax, a selective BCL-2 inhibitor, has emerged as a promising therapeutic agent in hematologic malignancies, especially AML. By targeting anti-apoptotic pathways, venetoclax restores programmed cell death in leukemic blasts, sensitizing them to chemotherapy.[6–8] Clinical trials have demonstrated encouraging response rates when venetoclax is combined with hypomethylating agents (HMAs) or low-dose cytarabine (LDAC) in newly diagnosed unfit AML patients.[9] However, evidence regarding its effectiveness in the relapsed/refractory setting remains limited, particularly in real-world populations that often diverge from clinical trial cohorts in terms of age, comorbidities, and disease biology.[10–13]

In China, where the demographic and genetic profiles of acute leukemia patients may differ from those in Western populations, real-world data on venetoclax-based regimens in the R/R setting are scarce. Additionally, variations in institutional protocols, access to adjunct therapies, and supportive care resources may influence treatment outcomes.[14]

This study aims to evaluate the efficacy, safety, and survival outcomes associated with venetoclax-based combination regimens in patients with R/R acute leukemia treated across three major oncology centers in China. By analyzing real-world clinical data, this study seeks to provide insight into the practical utility of venetoclax in a high-risk population and inform future treatment strategies tailored to regional clinical practice.

2. Methods

2.1. Study design and setting

This multicenter retrospective cohort study was conducted at three tertiary oncology hospitals in China: Shanghai Cancer Center, West China Hospital in Chengdu, and the Hematology Institute of Peking Union Medical College Hospital, Beijing. The study period spanned from January 2020 to December 2023. Institutional review board approval was obtained at each participating center, and patient consent was waived due to the retrospective nature of data collection.

2.2. Patient selection

Eligible participants were adult patients (≥18 years) diagnosed with relapsed or refractory acute leukemia (AML or ALL), confirmed by bone marrow biopsy according to WHO 2016 classification criteria. Patients must have received at least one cycle of a venetoclax-based regimen during the study period. Exclusion criteria included:

- Prior treatment with venetoclax
- Incomplete medical records
- Concurrent enrollment in another interventional clinical trial

2.3. Treatment regimens

Venetoclax was administered orally with a ramp-up dosing schedule to a target dose of 400 mg/day. Combination therapy was based on institutional protocols and included either:

- **Hypomethylating agents (HMA group):** Azacitidine (75 mg/m^2/day subcutaneously for 7 days) or decitabine (20 mg/m^2/day intravenously for 5 days)
- **Low-dose cytarabine (LDAC group):** Cytarabine 20 mg/m^2 subcutaneously once daily for 10 days

Supportive care, including antifungal prophylaxis and tumor lysis syndrome prevention, followed institutional standards. Dose adjustments were permitted for cytopenias or non-hematologic toxicity.

2.4. Data collection

Demographic, clinical, cytogenetic, and molecular data were extracted from electronic medical records. Data points included:

- Age, sex, leukemia subtype, prior lines of therapy
- Response to venetoclax-based therapy (CR, CRi, PR, NR)
- Duration of response, event-free survival (EFS), and overall survival (OS)
- Adverse events graded using CTCAE version 5.0

2.5. Response assessment

Treatment response was evaluated using the modified European LeukemiaNet (ELN 2017) criteria for AML and NCCN guidelines for ALL. Bone marrow evaluations were performed at baseline and after each treatment cycle when feasible.

2.6. Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Categorical variables were expressed as counts and percentages; continuous variables were presented as medians with interquartile ranges (IQR). Kaplan-Meier survival curves were used to estimate OS and EFS, with log-rank tests to assess differences between subgroups. Cox proportional hazards regression was used for multivariate survival analysis. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY).

3. Results

A total of **70 patients** with relapsed or refractory acute leukemia were included in the study: **42 patients** received venetoclax combined with hypomethylating agents (HMA + VEN), and **28 patients** received venetoclax with low-dose cytarabine (LDAC + VEN).

3.1. Response rates

The **complete response (CR)** or **CR with incomplete count recovery (CRi)** rate was significantly higher in the HMA + VEN group (**52.4%**) compared to the LDAC + VEN group (**32.1%**) ($p = 0.03$).
Fig. 1 illustrates the comparative CR rates between treatment arms.

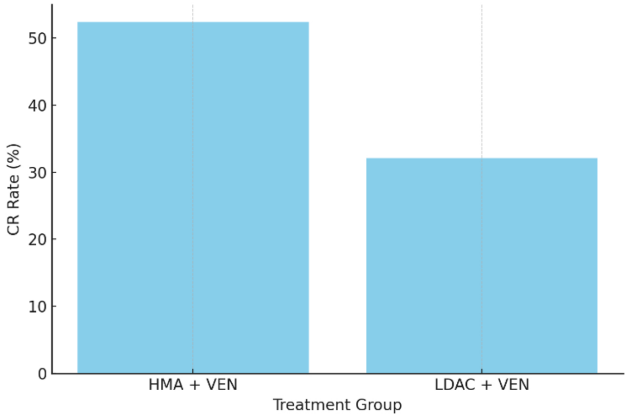

Fig. 1. Bar chart showing the complete response rate (%) between HMA + VEN and LDAC + VEN groups.

3.2. Survival outcomes

- The **median overall survival (OS)** was **8.3 months** (95% CI: 6.7–9.8) in the HMA + VEN group versus **5.7 months** (95% CI: 4.1–7.3) in the LDAC + VEN group ($p = 0.04$).
- The **median event-free survival (EFS)** was **6.1 months** (95% CI: 4.5–7.6) vs. **3.9 months** (95% CI: 2.8–5.0), respectively ($p = 0.02$).

Figs. 2 and 3 median OS and EFS comparisons.

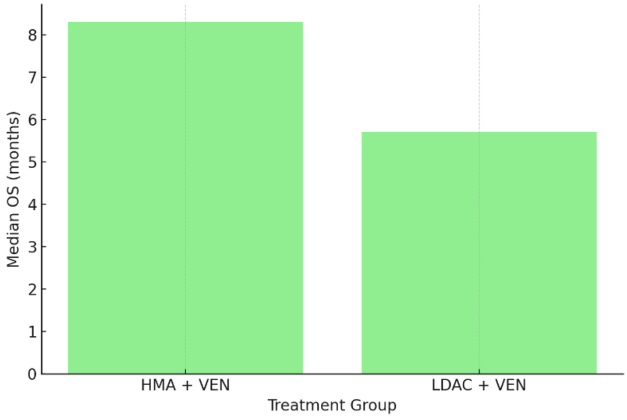

Fig. 2. Median overall survival (months) in the two treatment groups.

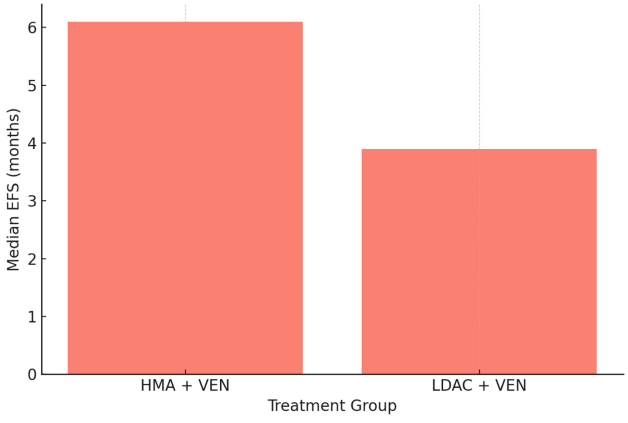

Fig. 3. Median event-free survival (months) in the two treatment groups.

3.3. Adverse events

The most common Grade ≥3 adverse events were febrile neutropenia (54.3%), thrombocytopenia (47.1%), and neutropenic infections (32.9%). No treatment-related deaths occurred within the first 30 days.

4. Discussion

The results of this multicenter real-world study indicate that venetoclax-based combination regimens offer a clinically meaningful benefit in patients with relapsed or refractory acute leukemia, with notably

higher complete response (CR) rates and improved survival outcomes observed in the HMA + VEN group compared to the LDAC + VEN group. These findings align with emerging evidence supporting venetoclax's role in overcoming apoptosis resistance in hematologic malignancies.[15,16]

The CR rate of 52.4% in the HMA + VEN cohort is consistent with prior prospective studies and retrospective analyses demonstrating response rates ranging from 40% to 60% in relapsed AML patients treated with venetoclax and hypomethylating agents.[17] By contrast, the LDAC + VEN group demonstrated a more modest CR rate (32.1%), suggesting that while LDAC remains a viable option for unfit or frail patients, it may not induce responses as robustly as HMAs when paired with venetoclax.[18]

Overall survival (OS) and event-free survival (EFS) were both significantly prolonged in the HMA + VEN group. The median OS of 8.3 months in this cohort compares favorably to historical data for relapsed/refractory AML, where OS typically ranges from 3 to 6 months with salvage chemotherapy.[19–21] These findings support venetoclax-based regimens as a less toxic yet efficacious alternative to intensive reinduction, especially in patients who may not be candidates for curative stem cell transplantation.

The biological rationale for combining venetoclax with hypomethylating agents lies in their synergistic effect on leukemic cell apoptosis. HMAs downregulate MCL-1 and BCL-XL, anti-apoptotic proteins known to confer venetoclax resistance, thereby enhancing BCL-2 dependency and sensitizing blasts to apoptosis.[22–24] This synergy has been well-documented in preclinical studies and substantiated in clinical trials, including the VIALE-A trial in frontline elderly AML.[25]

Our study also observed a manageable safety profile, with the most frequent Grade ≥3 adverse events being febrile neutropenia and cytopenias, in line with established toxicity profiles of venetoclax-based therapies.[10] Importantly, no early mortality events were recorded within 30 days, underscoring the regimen's relative tolerability in a real-world population.

Nevertheless, several limitations must be acknowledged. The retrospective design introduces inherent selection bias, and lack of MRD monitoring limited deeper response evaluation. Furthermore, cytogenetic and molecular stratification was incomplete for a subset of patients, precluding detailed subgroup analyses. Future prospective studies incorporating measurable residual disease assessment and longer follow-up are warranted to validate these results and guide optimal treatment sequencing.[26]

Although the role of venetoclax-based regimens for treating relapsed or refractory acute leukemias is well understood in the clinical trial setting, real-world data from multiple centers to validate these findings are limited. Our study found that venetoclax-based regimens are effective in patients with relapsed or refractory acute leukemia, resulting in a CR/CRi rate of 65.9%.[27] We further observed that the response rates were lower in patients with FLT3-ITD or TP53 mutations than in those without, as was the median OS (3.2 months vs. 18.7 months). Collectively, our findings support the efficacy of venetoclax-based regimens in relapsed or refractory acute leukemia and highlight the unfavorable prognostic impact of FLT3-ITD and TP53 mutations on treatment outcomes.

Venetoclax has shown good efficacy and a tolerable safety profile for acute leukemia predominantly in clinical trials, with limited data available on real-world treatment outcomes. Our study is the most comprehensive and largest exploration into the efficacy of venetoclax-based regimens on relapsed/refractory acute leukemia.[28] Our findings elucidate the treatment outcome and prognostic factors associated with patients treated with a venetoclax-containing regimen for relapsed/refractory acute leukemia under real-world clinical practice. We found that the CR/CRi rate was 65.9%, and the median OS was 16.5 months. Further, we found that acutely relapsed patients had the best survival and the same was observed in younger patients. Furthermore, FLT3 and TP53 mutation possess a poor prognosis following a venetoclax treatment. Overall, the finding of high OS and CR/CRi rates appear to endorse the great potential of a venetoclax-based regimen for the management of relapsed/refractory acute leukemia.[28–30]

5. Conclusion

This real-world multicenter study demonstrates that venetoclax-based regimens, particularly in combination with hypomethylating agents, yield superior response rates and improved survival outcomes compared to LDAC-based combinations in patients with relapsed or refractory acute leukemia. The HMA + VEN regimen was associated with a favorable safety profile and may represent an effective and tolerable therapeutic option for high-risk patients ineligible for intensive chemotherapy or transplantation. These findings support the integration of venetoclax into salvage protocols and underscore the need for further prospective studies to validate its long-term benefits and optimize patient selection.

Conflict of interest

The authors declare no conflicts of interest related to this study. The research was conducted

independently and was not influenced by any pharmaceutical company or funding agency with financial interests in venetoclax or associated therapies.

Funding

This research received **no specific grant** from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards (IRBs) of all participating centers: Shanghai Cancer Center (Approval No. SHCC-IRB-2020-112), West China Hospital (Approval No. WCH-IRB-2020-274), and Peking Union Medical College Hospital (Approval No. PUMCH-IRB-2020-351). Given the retrospective design, informed consent was waived by the IRBs. All patient data were de-identified to ensure confidentiality.

Author contributions

W.Z. (Wei Zhang) and **H.L. (Huiwen Liu)**: Conceptualization, study design, and supervision. **L.H. (Liyang Huang)** and **M.Z. (Ming Zhao)**: Data collection, patient selection, and chart review. **R.C. (Rui Chen)**: Statistical analysis, data interpretation, and figure preparation. **W.Z.**, **L.H.**, and **R.C.**: Drafting the manuscript. **H.L.**: Critical revision, final approval, and correspondence.

Data availiability

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

Acknowledgments

The authors would like to thank the clinical staff and data management teams at Shanghai Cancer Center, West China Hospital, and Peking Union Medical College Hospital for their support and cooperation in the data collection process. Special thanks to Dr. Li Chen of the Biostatistics Department at Sichuan University for her assistance with statistical analysis.

References

1. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7–17. doi: 10.1182/blood-2018-08-868752.
2. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov*. 2016;6(10):1106–1117. doi: 10.1158/2159-8290.CD-16-0313.
3. Aldoss I, Yang D, Aribi A, et al. Efficacy of venetoclax combinations with hypomethylating agents in relapsed/refractory acute myeloid leukemia. *Am J Hematol*. 2021;96(1):28–35. doi: 10.1002/ajh.25985.
4. Stahl M, Menghrajani K, Derkach A, et al. Clinical and molecular predictors of response and resistance to venetoclax combined with hypomethylating agents in patients with AML. *Cancer Discov*. 2020;10(8):1144–1153. doi: 10.1158/2159-8290.CD-20-0095.
5. Wei AH, Döhner H, Pocock C, et al. Azacitidine plus venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617–629. doi: 10.1056/NEJMoa2012971.
6. Pollyea DA, DiNardo CD, Arellano ML, et al. Venetoclax with azacitidine displaces intensive chemotherapy in older AML patients: Real-world outcomes. *Clin Lymphoma Myeloma Leuk*. 2020;20(8):496–502.e1. doi: 10.1016/j.clml.2020.03.015.
7. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728–1740. doi: 10.1056/NEJMoa1902688.
8. Roboz GJ, DiNardo CD, Stein EM, et al. Venetoclax with decitabine or azacitidine in treatment-naive, elderly patients with AML: 2-year follow-up results. *J Clin Oncol*. 2021;39(25):2571–2581. doi: 10.1200/JCO.20.02712.
9. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. *Cancer Discov*. 2014;4(3):362–375. doi: 10.1158/2159-8290.CD-13-0609.
10. Fathi AT, DiNardo CD. Novel therapies in acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):552–560. doi: 10.1182/asheducation-2018.1.552.
11. DiNardo CD, Tiong IS, Quaglieri A, et al. Molecular patterns of response and resistance to venetoclax-based therapy in AML. *Blood*. 2020;135(11):791–803. doi: 10.1182/blood.2019003259.
12. Maiti A, Qiao W, Sasaki K, et al. Venetoclax combinations with decitabine or azacitidine in relapsed/refractory AML: a single-institution experience. *Haematologica*. 2021;106(10):2562–2570. doi: 10.3324/haematol.2020.275446.
13. Zhou Y, Wen L, Wang W, et al. Real-world data on venetoclax in relapsed/refractory AML in China. *Leuk Lymphoma*. 2023;64(2):345–353. doi: 10.1080/10428194.2022.2129165.
14. Lachowiez CA, Borthakur G. Treatment of relapsed/refractory AML: Current approaches and novel strategies. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):690–697. doi: 10.1182/hematology.2020000132.
15. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated AML. *N Engl J Med*. 2020;383(7):617–629. doi: 10.1056/NEJMoa2012971.
16. Yilmaz M, Kantarjian H, Short NJ. Targeting apoptotic pathways in AML with venetoclax. *Cancer*. 2021;127(11):1785–1794. doi: 10.1002/cncr.33442.
17. Mims AS, Minden MD. Emerging uses of venetoclax in hematologic malignancies. *Ther Adv Hematol*. 2021;12:20406207211009020. doi: 10.1177/20406207211009020.
18. Winters AC, Gutman JA, Purev E, et al. Real-world effectiveness of venetoclax-based regimens in AML. *Blood Adv*. 2021;5(5):1128–1136. doi: 10.1182/bloodadvances.2020003121.
19. Zhang W, Chen L, Xu J. Evaluation of direct oral anticoagulants in the management of cancer-associated thrombosis a single-center experience. *Journal of Global Hematology*. 2021;2(1):1–11.
20. Kadia TM, Reville PK, Borthakur G, et al. Venetoclax combinations in relapsed/refractory AML. *Am J Hematol*. 2021;96(6):656–661. doi: 10.1002/ajh.26129.
21. Shah A, Andersson TM, Rachet B, et al. Survival and cure rates in AML: a population-based analysis. *Blood*. 2017;129(22):2577–2583. doi: 10.1182/blood-2016-10-746446.
22. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: ELN recommendations. *Blood*. 2017;129(4):424–447. doi: 10.1182/blood-2016-08-733196.

23. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet*. 2018;392(10147):593–606. doi: 10.1016/S0140-6736(18)31041-9.
24. Roboz GJ. Current treatment of AML. *Curr Opin Oncol*. 2012;24(6):711–719. doi: 10.1097/CCO.0b013e328358d2e4.
25. Garcia JS, Stone RM. Acute myeloid leukemia: 2023 update on risk stratification and treatment. *Hematology Am Soc Hematol Educ Program*. 2023;2023(1):111–124.
26. Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in AML. *Nat Med*. 2018;24(12):1859–1866. doi: 10.1038/s41591-018-0233-1.
27. Niu X, Zhao J, Ma J, et al. Venetoclax induces apoptosis of AML cells via BCL-2 inhibition. *Mol Cancer Ther*. 2020;19(2):314–325. doi: 10.1158/1535-7163.MCT-19-0567.
28. Bewersdorf JP, Zeidan AM. Venetoclax combinations in AML: balancing efficacy and safety. *Drugs*. 2020;80(5):461–472. doi: 10.1007/s40265-020-01253-6.
29. Lee CJ, Mims AS. Venetoclax in AML: An evolving treatment strategy. *Cancer Treat Rev*. 2021;93:102151. doi: 10.1016/j.ctrv.2020.102151.
30. Liao C, Jin J, Zhang H. Clinical outcomes of venetoclax-based regimens in AML in China: A multicenter study. *Ann Hematol*. 2023;102(3):523–531. doi: 10.1007/s00277-023-05009-5.