Meta-analysis of the efficacy of venetoclax and azacitidine combination therapy and azacitidine monotherapy for treating acute myeloid leukemia

YUQIN XIE[1,2*], XUEQIN WEI[1,2*], WEIWEI WANG[2], CHANGSHENG LIAO[2], PENGFEI HAN[3] and YANHUI YU[1]

[1]Department of Hematology, Heping Hospital Affiliated to Changzhi Medical College; [2]Graduate School, The First Clinical College of Changzhi Medical College; [3]Department of Orthopedics, Heping Hospital Affiliated to Changzhi Medical College, Changzhi, Shanxi 046000, P.R. China

Received July 25, 2023; Accepted January 31, 2024

DOI: 10.3892/etm.2024.12452

Abstract. The present study aimed to compare the efficacy of combination therapy with venetoclax and azacitidine with that of azacytidine monotherapy in the treatment of acute myeloid leukemia (AML). The Web of Science, PubMed, Embase, The Cochrane Library, Weipu Database, Wanfang Digital Periodicals, Sinomed, China National Knowledge Infrastructure, ProQuest Dissertations and Theses and Cumulative Index to Nursing and Allied Health Literature were searched for publications on the treatment of AML with venetoclax combined with azacitidine or with azacitidine monotherapy. A total of 5,271 relevant studies were retrieved, of which 10 were included. Literature quality was evaluated according to the Cochrane systematic review methodology, and data were extracted for meta-analysis using Review Manager 5.4. The combination of venetoclax and azacitidine demonstrated greater overall efficacy than azacitidine monotherapy for AML treatment. Notably, combination therapy resulted in a higher frequency of complete remission. By contrast, combined treatment and monotherapy showed no significant differences in partial remission, whereas there was a statistically significant decrease in the frequency of no remission in the combination therapy group compared with in the monotherapy group. The results also revealed a significantly higher incidence of adverse reactions when venetoclax and azacitidine were combined in the treatment of AML compared with the observed rates in response to azacitidine monotherapy. Moreover, subgroup analyses showed that no statistically significant differences were observed between the two groups regarding adverse events, including hypokalemia and liver insufficiency. In conclusion, the combination of venetoclax and azacitidine was more effective than azacitidine alone, and had a good clinical application value in the treatment of AML. Although some adverse reactions occurred in response to the combination therapy, they did not significantly affect the prognosis of AML. To better evaluate the efficacy and safety of this treatment regimen, multicenter clinical studies with larger sample sizes are required.

Correspondence to: Dr Pengfei Han, Department of Orthopedics, Heping Hospital Affiliated to Changzhi Medical College, 161 Jiefang East Street, Changzhi, Shanxi 046000, P.R. China
E-mail: 18003551149@163.com

Dr Yanhui Yu, Department of Hematology, Heping Hospital Affiliated to Changzhi Medical College, 161 Jiefang East Street, Changzhi, Shanxi 046000, P.R. China
E-mail: amilyfish@126.com

*Contributed equally

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; CI, confidence interval; OR, odds ratio; CR, complete remission; NR, no remission; PR, partial remission

Key words: acute myeloid leukemia, venetoclax, monotherapy, combination therapy, azacitidine, meta-analysis

Introduction

Acute myeloid leukemia (AML) is a malignant tumor of the hematopoietic system characterized by abnormal differentiation and excessive proliferation of hematopoietic stem cells, which may also be accompanied by invasion of the bone marrow, peripheral blood and extramedullary tissue (1). AML is the most common type of leukemia in adults, with a median age of 68 years at diagnosis, and its incidence increases with age (2). Compared with younger patients, older patients are more likely to have adverse cytogenetic risks, secondary AML, monosomal karyotypes and multidrug-resistant phenotypes, as well as more comorbidities and impaired organ function, thereby reducing their tolerance to intensive induction therapy and leading to higher rates of treatment-related mortality (3-6).

At present, the clinical treatment of AML mainly follows '3+7' induction chemotherapy and high-dose cytarabine-based consolidation chemotherapy or allogeneic hematopoietic stem cell transplantation. However, in the actual treatment, the space to improve the clinical efficacy of the single application of conventional chemotherapy for AML is limited (7). In recent years, with the rise of molecular-targeted drugs for

the treatment of leukemia, molecular-targeted therapy with novel targeted drugs, the combination of targeted drugs and their combination with intensive chemotherapy have attracted increasing attention. The BCL-2 protein is a key factor that regulates the mitochondrial apoptotic pathway, and the survival of leukemia stem cells depends on oxidative phosphorylation and BCL-2 upregulation (8). Notably, BCL-2 has recently become a target for leukemia treatment. Venetoclax is a powerful oral BCL-2 inhibitor, the efficacy and safety of which have been confirmed. The combination regimen of venetoclax with demethylated drugs (decitabine or azacytidine) was approved by the U.S. Food and Drug Administration in November 2018 for the clinical treatment of older adult patients (≥65 years old) with AML (9,10). Azacitidine, a recently developed demethylation drug, is a nucleoside metabolic inhibitor that can exert the dual effect of RNA and DNA demethylation and effectively inhibit the synthesis of proteins in tumor cells (11,12). Notably, it has been reported that venetoclax combined with azacytidine has good clinical value in patients with AML (13). Although the long-term benefits were not maintained in some patients, this regimen can significantly improve survival in patients who are not candidates for intensive chemotherapy. Most published studies are on a generally small size (14-17); therefore, the evidence for these findings is limited. To further optimize the formulation of chemotherapy regimens for patients with AML, exploration of the predictors of efficacy of combination regimens is necessary to guide clinical decision-making. Therefore, the present study focused on the efficacy of venetoclax combined with azacitidine and azacitidine monotherapy in patients with AML.

Materials and methods

Retrieval strategy. The Web of Science (https://www.webofscience.com/wos), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), Cochrane Library (https://www.cochranelibrary.com/), Weipu Database (http://www.cqvip.com), Wanfang Digital Periodicals (https://www.wanfangdata.com.cn), Sinomed (http://www.sinomed.ac.cn), China National Knowledge Infrastructure (https://www.cnki.net/), ProQuest Dissertations and Theses (http://pqdtopen.proquest.com/) and Cumulative Index to Nursing and Allied Health Literature (https://www.ebsco.com/products/research-databases/cinahl-database) were searched for relevant literature. The search was carried out from the establishment of the database to May 2023, with two researchers independently conducting literature searches. The search keywords were ('Venetoclax' OR 'ABT-199' OR 'Venclexta' OR 'RG7601' OR 'RG-7601' OR 'GDC-0199', 'leukemia, myeloid, acute' OR 'acute myeloid leukemia' OR 'AML' OR 'acute nonlymphocytic leukemia').

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Research participants: Adult patients diagnosed with AML; ii) intervention measure: Experimental group (venetoclax combined with azacitidine), control group (azacitidine monotherapy); iii) outcome index: Complete remission (CR), partial remission (PR), no remission (NR) and adverse events (AEs); iv) Study design types: Controlled clinical trial. The exclusion criteria were as follows: i) Age <18 years, patients with non-AML; ii) reviews, systematic reviews, case reports, letters and republished studies; iii) non-case control studies; iv) incomplete or irrelevant treatment outcome reports.

Data extraction. Two independent researchers extracted data separately according to Cochrane systematic review methodology, and when there was a disagreement, it was resolved through discussion or joint evaluation with more senior researchers until a consensus was reached. The literature was scored according to the Newcastle-Ottawa scale (18). In the outcome measurement items, the follow-up time was defined as ≥1 year, the loss rate was ≤15%, and the scores were divided into low, medium and high as follows: <5, 5-8 and 8-9 points, respectively.

Statistical analysis. All extracted data were analyzed using Review Manager 5.4 (https://tech.cochrane.org/revman). Binary variables were represented according to the odds ratio (OR) and 95% confidence interval (CI) of the results. A random-effects model was used for summary analysis when I^2 was ≤50% between the study groups. When heterogeneity could not be completely eliminated, a random-effects model was adopted. A funnel plot was constructed to assess publication bias by removing studies with high heterogeneity for the sensitivity analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Search result. According to the search strategy of the present study, 5,271 relevant articles were retrieved from major databases. The inclusion and exclusion criteria were strictly implemented and 10 studies (14-17,19-24) were included.

Information included from the literature. A total of 1,988 patients were included, with 1,323 treated with venetoclax combined with azacitidine and 665 treated with azacitidine monotherapy. The included studies reported six hematological, five gastrointestinal, nine infectious and four serious AEs, as well as two studies each of hypokalemia, decreased appetite and hepatic insufficiency. CR was observed in eight studies, PR in seven studies and NR in eight studies. The literature screening process and results are shown in Fig. 1, and the basic characteristics of the included studies are listed in Table I.

Quality evaluation of the included literature. A total of 10 studies, including six prospective and four retrospective studies, were included. The Newcastle-Ottawa scale was used for quality evaluation, among which two studies scored 9 points, five studies scored 8 points, two studies scored 6 points, and one study scored 5 points. Seven studies were of high quality and three were of medium quality.

Meta-analysis results

Comparison of CR. Eight studies compared CR events between venetoclax combined with azacitidine and azacitidine monotherapy. The heterogeneity test ($I^2=0\%$) indicated no significant heterogeneity among the studies, and a random-effects model was used for classification. The results showed that CR events in patients with AML treated with azacitidine monotherapy

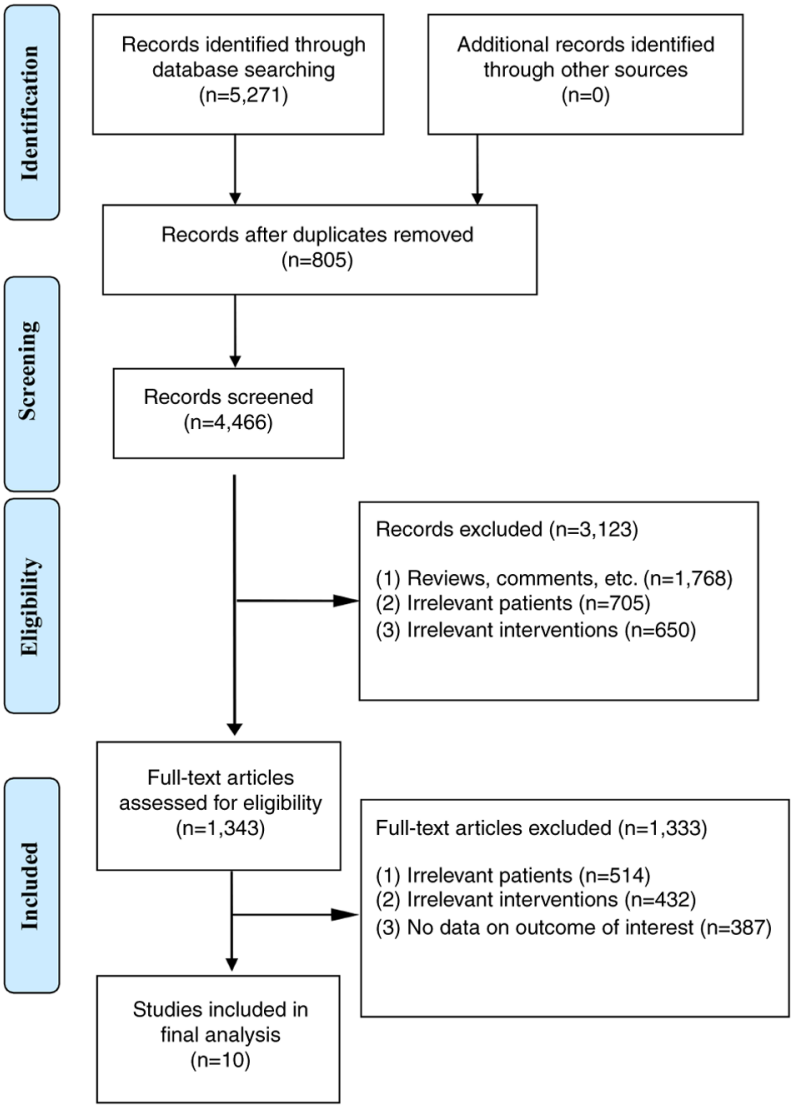

Figure 1. Flow chart showing the process for identifying relevant studies. Irrelevant patients are patients who did not meet the requirements for inclusion in the present study. Irrelevant interventions mean that the treatment regimen does not correspond to the treatment regimen required for the present study.

were significantly lower than those in patients with AML treated with venetoclax combined with azacitidine (95% CI=2.30, 4.34; P<0.00001; Fig. 2).

Comparison of PR. Seven studies compared PR events between venetoclax combined with azacitidine and azacitidine monotherapy. Heterogeneity was observed among the studies (I^2=38%); therefore, a random-effects model was used for classification. The results revealed no significant difference in PR events between the venetoclax combined with azacitidine group and the azacitidine monotherapy group (95% CI=1.01, 3.54; P=0.05; Fig. 3).

Comparison of NR. Eight articles compared NR events between venetoclax combined with azacitidine and azacitidine monotherapy. The heterogeneity test (I^2=0%) indicated no significant heterogeneity among the studies, and the random-effects model was used for classification. The results showed that NR events in patients with AML treated with venetoclax combined with azacitidine were significantly lower than in patients with AML treated with azacitidine monotherapy (95% CI=0.15, 0.27; P<0.00001; Fig. 4).

Comparison of AEs. Hematological, gastrointestinal, infectious and serious AEs, as well as hypokalemia, decreased appetite and hepatic insufficiency, were included (Fig. 5). Six studies compared hematological AEs between venetoclax combined with azacitidine and azacitidine monotherapy for AML. The heterogeneity test (I^2=0%) indicated no significant heterogeneity among the studies and a random-effects model was used for classification. The results showed that hematological AEs in the treatment of AML were significantly lower in patients treated with azacitidine monotherapy than those treated with venetoclax combined with azacitidine (95% CI=1.45, 2.65; P<0.0001).

Five studies compared gastrointestinal AEs in the treatment of AML between venetoclax combined with azacitidine and azacitidine monotherapy. The heterogeneity test (I^2=0%) indicated no significant heterogeneity among the studies and a random-effects model was used for classification. The results showed that in the treatment of AML, the incidence of gastrointestinal AEs in response to azacitidine alone was lower than that in response to venetoclax combined with azacitidine, and the difference was statistically significant (95% CI=1.27, 2.72; P=0.001).

Table I. Basic characteristics of the included studies.

First author, year	Research type	Nation	Year	Intervention	Case, n	Age, years (± SD)	Sex, Male/ Female	Outcome index	Quality evaluation, NOS score	(Refs.)
Cui, 2022	RCT	China	2022	VEN + AZA	15	40.23±10.58	10/5	(1-4)	8	(14)
				AZA	15	39.82±10.17	9/6			
DiNardo,	RCT	Multinational	2020	VEN + AZA	286	Median age: 76	112/174	(1)	5	(19)
				AZA	145	Median age: 76	58/87			
Fu, 2022	RCT	China	2022	VEN + AZA	30	77.9±4.9	13/17	(1-4)	8	(20)
				AZA	30	78.6±4.6	12/18			
Jonas, 2020	Retrospective cohort study	America	2020	VEN + AZA	293	-	-	(1-4)	8	(21)
				AZA	146	-	-			
Pollyea, 2020	Retrospective cohort study	America	2020	VEN + AZA	306	-	-	(1,2)	6	(22)
				AZA	127	-	-			
Pollyea, 2022	Retrospective cohort study	America	2022	VEN + AZA	308	-	182/126	(1,4)	6	(23)
				AZA	127	-	76/51			
Wang, 2022	RCT	China	2022	VEN + AZA	10	70.21±8.39	5/5	(1-4)	9	(15)
				AZA	10	70.44±7.61	6/4			
Xia, 2023	RCT	China	2023	VEN + AZA	21	-	14/7	(1-4)	8	(16)
				AZA	14	-	7/7			
Yamamoto, 2021	RCT	Japan	2021	VEN + AZA	24	-	14/10	(1-4)	8	(17)
				AZA	13	-	9/4			
Yang, 2022	Retrospective cohort study	China	2022	VEN + AZA	30	68.13±7.42	18/12	(1-4)	9	(24)
				AZA	38	67.82±5.55	24/14			

Outcome indexes: (1) Adverse event; (2) complete remission; (3) partial remission; (4) no remission. RCT, randomized controlled trial; VEN, venetoclax; AZA, azacitidine; NOS, Newcastle-Ottawa scale.

Two studies compared the decreased appetite events between venetoclax combined with azacitidine and azacitidine monotherapy in patients with AML. The heterogeneity test (I^2=0%) indicated no significant heterogeneity among the studies and a random-effects model was used for classification. The results showed that in the treatment of AML, the incidence of decreased appetite in response to azacitidine alone was lower than that in response to venetoclax combined with azacitidine, and the difference was statistically significant (95% CI=1.06, 2.77; P=0.03).

In addition, no significant differences were observed regarding infectious AEs, serious AEs, hypokalemia or hepatic insufficiency between the two groups [(95% CI=0.86, 2.26; P=0.17), (95% CI=0.98, 2.62; P=0.06), (95% CI=0.64, 1.51; P=0.94), (95% CI=0.21, 8.27; P=0.77), respectively].

Publication bias and sensitivity analysis. Review Manager 5.4 statistical software was used to analyze publication bias for four outcome indicators: CR, PR, NR and AEs. References were individually excluded for sensitivity analysis, and the results were stable. The data were also considered stable and reliable after the sensitivity analysis. The results showed that the funnel plots were symmetric, suggesting no significant publication bias (Fig. 6).

Discussion

AML is a hematological disease with a relatively high incidence, which is characterized by rapid onset and progression. Most patients have several notable symptoms after the onset of the disease, which can have a serious impact on the life and health of patients if not treated in a timely manner (25). AML is characterized by clonal proliferation of malignant bone marrow stem cells, and is often accompanied by infection, anemia and bleeding (26). Currently, combination chemotherapy is the preferred treatment for clinically naïve patients with AML. However, conventional chemotherapy regimens may lead to drug resistance, whereas high-dose chemotherapy leads to severe myelosuppression (27). In recent years, the emergence of novel targeted drugs has provided innovative options for patients with AML not eligible for intensive induction chemotherapy, effectively improving the response and survival rates.

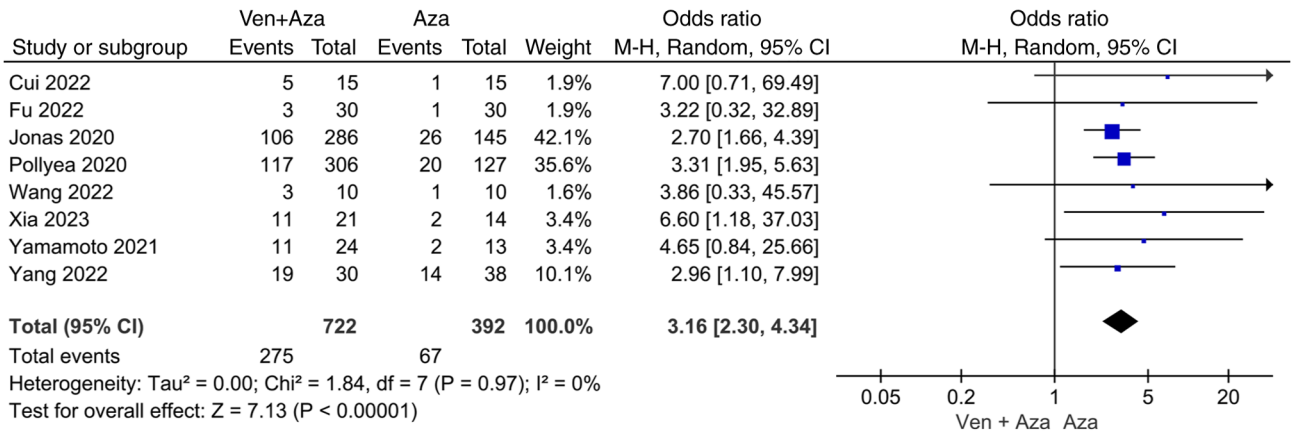

Figure 2. Analysis of the frequency of complete remission of patients with AML treated with Ven + Aza combination therapy or Aza monotherapy using a random-effects model. The I^2 and P-value were regarded as criteria of heterogeneity. The blue squares indicate the relative risk and their 95% CI. The black diamonds indicate the pooled relative risk and 95% CI. CI, confidence interval; Ven, venetoclax; Aza, azacitidine; M-H, Mantel-Haentzel; df, degrees of freedom.

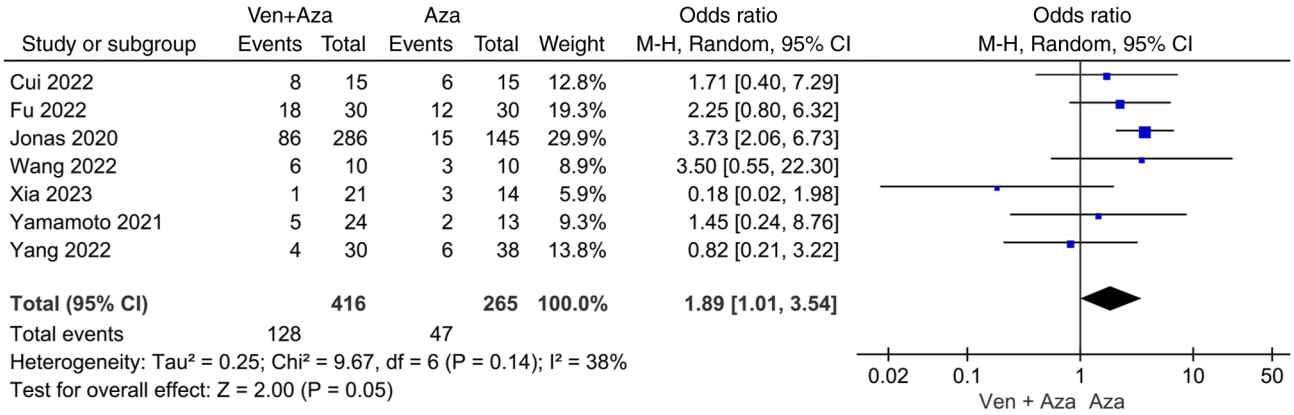

Figure 3. Analysis of the frequency of partial remission of patients with AML treated with Ven + Aza combination therapy or Aza monotherapy using a random-effects model. The I^2 and P-value were regarded as criteria of heterogeneity. The blue squares indicate the relative risk and their 95% CI. The black diamonds indicate the pooled relative risk and 95% CI. CI, confidence interval; Ven, venetoclax; Aza, azacitidine; M-H, Mantel-Haentzel; df, degrees of freedom.

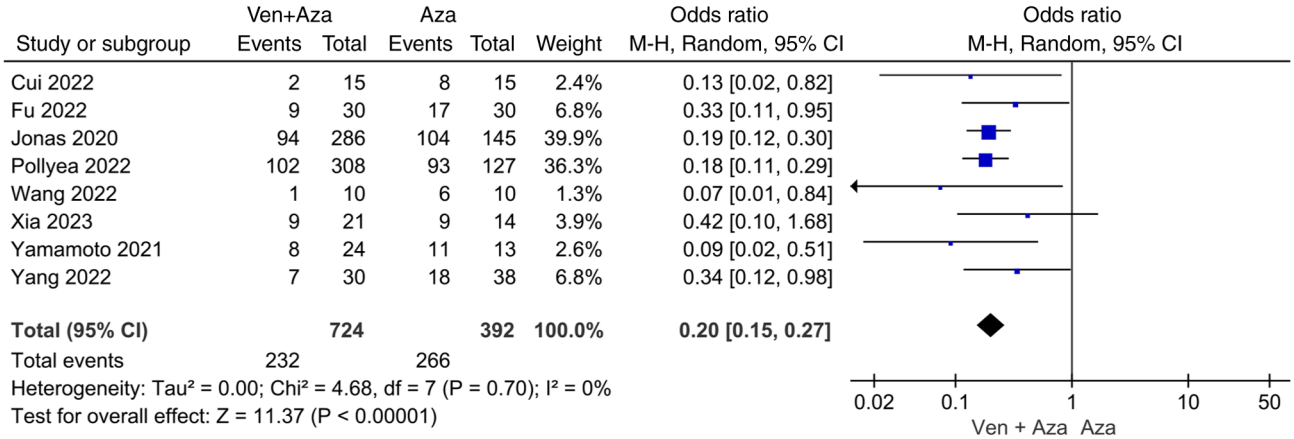

Figure 4. Analysis of the frequency of no remission of patients with AML treated with Ven + Aza combination therapy or Aza monotherapy using a random-effects model. The I^2 and P-value were regarded as criteria of heterogeneity. The blue squares indicate the relative risk and their 95% CI. The black diamonds indicate the pooled relative risk and 95% CI. CI, confidence interval; Ven, venetoclax; Aza, azacitidine; M-H, Mantel-Haentzel; df, degrees of freedom.

BCL-2 is a key molecule in the regulation of apoptosis of tumor cells and is a novel target for the treatment of leukemia (28). The BCL-2 protein family is an important regulator of endogenous apoptotic pathways. Notably, BCL-2 is upregulated in AML and its stem cells, thereby mediating the survival of AML cells, and their resistance to chemotherapy and targeted therapies (29,30).

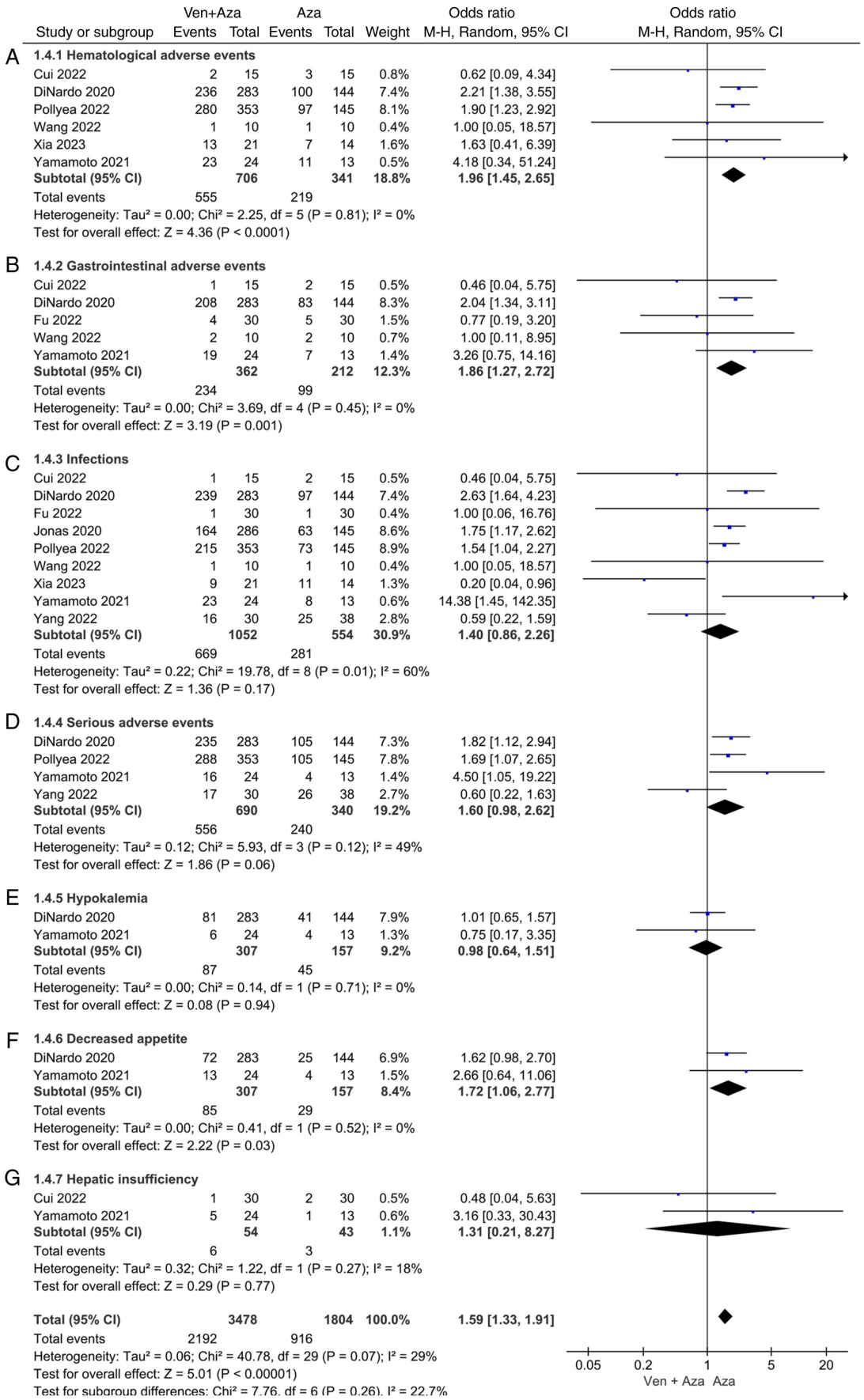

Figure 5. Analysis of the frequency of adverse events in patients with AML treated with Ven + Aza combination therapy or Aza monotherapy using a random-effects model. (A) hematological adverse events; (B) gastrointestinal adverse events; (C) infections; (D) serious adverse events; (E) hypokalemia; (F) decreased appetite; (G) hepatic insufficiency. The I^2 and P-value were regarded as criteria of heterogeneity. The blue squares indicate the relative risk and their 95% CI. The black diamonds indicate the pooled relative risk and 95% CI. CI, confidence interval; Ven, venetoclax; Aza, azacitidine; M-H, Mantel-Haentzel; df, degrees of freedom.

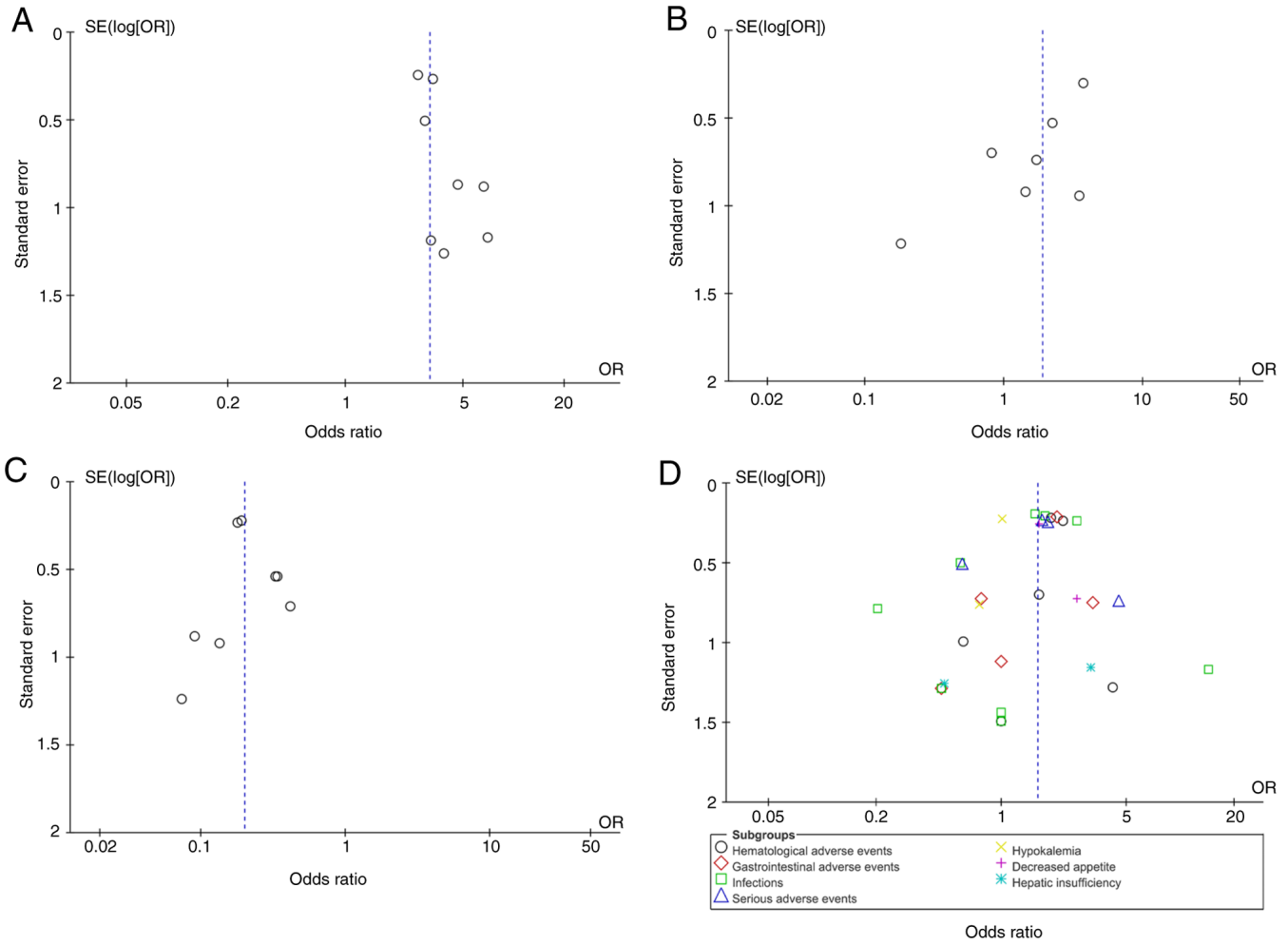

Figure 6. Funnel plots of the odds ratios reported in the included studies. Funnel plots were constructed to assess the existence of publication bias regarding (A) complete remission events; (B) partial remission events; (C) no remission events and (D) adverse events. OR, odds ratio.

Venetoclax was the first marketed BCL-2 inhibitor (1); this drug induces the apoptosis of tumor cells and improves AML treatment sensitivity by targeting BCL-2. It has previously been shown that a combination of venetoclax and hypomethylating agents can delay the development of drug resistance, and improve the remission and survival rates of patients with AML (31). Azacitidine, a recently developed demethylation drug, is a nucleoside metabolic inhibitor that can exert the dual effect of RNA and DNA demethylation and effectively inhibit the synthesis of proteins in tumor cells (31,32). Relevant clinical trials have shown that compared with the traditional treatment regimen, azacitidine can effectively optimize the treatment effect and prolong the survival of patients with AML (33). Moreover, azacitidine is an effective and low-toxicity alternative for patients with AML who have lost the opportunity for transplantation and have difficulty tolerating traditional chemotherapy regimens (33,34). However, in untreated patients with AML aged ≥65 years, azacitidine monotherapy has a response rate of ≤30% and results in survival time of <1 year (35). Preclinical studies (11,36,37) have shown that azacitidine enhances the antitumor effect of venetoclax by activating the transcription of the pro-apoptotic protein NOXA, and that the combination of azacitidine and venetoclax induces deep and long-lasting anti-leukemia effects by blocking the energy metabolism of leukemia stem cells.

To evaluate the therapeutic effect of venetoclax combined with azacitidine, and provide more evidence for the selection of clinical treatment plans, the present study conducted a meta-analysis using venetoclax combined with azacitidine as the observation group and azacitidine alone as the control group. The aim was to observe the effects of these two treatment regimens on clinical efficacy and the AEs of patients with AML. Through data analysis, the present meta-analysis confirmed that azacitidine + venetoclax combination therapy exhibited a significant advantage in improving the CR rate of patients with AML (95% CI=2.30, 4.34; P<0.00001). Significant heterogeneity was not observed (I^2=0%). DiNardo *et al* (19) reported that the composite CR rate of patients in the azacitidine + venetoclax group was 66.4%, which was significantly higher than that of patients in the azacitidine monotherapy group. The results of Cui *et al* (14) also showed that the total effective rate of the azacitidine + venetoclax group (86.67%) was significantly higher than that of the azacitidine group (46.67%) (P<0.05).

In the present study, no statistically significant difference was observed between the azacitidine + venetoclax combination treatment and azacitidine monotherapy groups regarding the occurrence of PR events in patients with AML (95% CI=1.01, 3.54; P=0.05). However, there was a statistically significant difference between the venetoclax + azacitidine

combination treatment and azacitidine monotherapy groups regarding the occurrence of NR events (95% CI=0.15, 0.27; P<0.00001), with no significant heterogeneity (I^2=0%), suggesting that venetoclax combined with azacitidine resulted in a lower incidence of NR events than azacitidine monotherapy in the treatment of AML. Therefore, it was concluded that azacitidine + venetoclax combination therapy may be superior to azacitidine monotherapy, and that combination therapy can significantly improve the incidence of CR in patients with AML. The present results are consistent with those of previous clinical studies (14-17,20-22,24) and practical experience, supporting the clinical feasibility and effectiveness of this treatment regimen. In addition, it is worth noting that the present meta-analysis observed that the overall incidence of AEs in patients with AML treated with venetoclax combined with azacitidine was significantly higher than those in patients treated with azacitidine monotherapy (95% CI=1.33, 1.91; P<0.000001); however, there was heterogeneity (I^2=29%). The studies by Xia *et al* (16) and Yang *et al* (24) showed a significant impact on the incidence of AEs. Moreover, the most common AEs in both groups were hematological (pooled OR=1.96; 95% Cl=1.45, 2.65; P<0.0001) and gastrointestinal (pooled OR=1.86; 95% Cl=1.27, 2.72; P=0.001). These findings are consistent with those of previous studies (17,23).

Compared with previous similar studies, such as those by Du *et al* (38) and Bewersdorf *et al* (39), the present study has several advantages. First, few randomized controlled trials were included in the previous studies, and there was a lack of prospective studies that could affect the reliability of the results. The present meta-analysis included six randomized controlled trials, including prospective studies, which increased the reliability of the results. Second, more than half of the participants in previous studies were from the U.S.; therefore, there is insufficient evidence on whether the results of previous studies can be generalized to other populations. The present study included research on Chinese patients and patients from other countries, further demonstrating the efficacy and safety of azacitidine + venetoclax for treating patients with AML from different countries. Third, the data in previous meta-analyses were highly heterogeneous, and it was difficult to determine the cause of the heterogeneity. However, the current study showed low heterogeneity in the statistical data, demonstrating the reliability of the results.

Although the results of the present meta-analysis showed the advantages of azacitidine + venetoclax in AML treatment, some limitations should be noted. First, because the data sources were mainly clinical trials and literature reports, there may have been selective reporting and publication bias. Second, the dose and course of treatment used in the different studies may have produced some heterogeneity, affecting the reliability of the results. Based on the findings of the present study, we recommend that azacitidine + venetoclax combination therapy for AML be further promoted in clinical practice. However, more large-scale multicenter clinical studies are needed to better evaluate the efficacy and safety of this treatment regimen. We encourage further exploration of other potential combination treatment options to improve the survival and quality of life of patients with AML.

In conclusion, the present study observed that, despite some adverse reactions, the combination regimen of azacitidine and venetoclax did not lead to a deterioration in the prognosis of patients with AML, which is of great significance for the long-term treatment and quality of life of patients. Notably, azacitidine monotherapy is often associated with relapse and a series of side effects and AEs, such as bone marrow suppression and liver function abnormalities (35). Therefore, the addition of venetoclax serves a positive role in delaying disease recurrence and alleviating adverse reactions in patients. In summary, azacitidine + venetoclax has significant efficacy in AML treatment and can improve the overall response rate of patients with high safety.

Acknowledgements

Not applicable.

Funding

The present study was funded by the Scientific and Technological Innovation Programs of Higher Education Institutions in Shanxi (grant no. 2021L353) and the Natural Science Foundation for Young Scientists of Shanxi Province (grant no. 20210302124089).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YQX and XQW were responsible for the design of the current study, and both performed the statistical analysis. YQX and XQW confirm the authenticity of all the raw data. WWW and CSL were responsible for the acquisition and sorting of data. PFH and YHY performed the interpretation of the data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Konopleva M, Pollyea DA, Potluri J, Chyla B, Hogdal L, Busman T, McKeegan E, Salem AH, Zhu M, Ricker JL, *et al*: Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. Cancer Discov 6: 1106-1117, 2016.
2. Kadia TM, Reville PK, Wang X, Rausch CR, Borthakur G, Pemmaraju N, Daver NG, DiNardo CD, Sasaki K, Issa GC, *et al*: Phase II study of venetoclax added to cladribine plus low-dose cytarabine alternating with 5-azacitidine in older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 40: 3848-3857, 2022.

3. Richard-Carpentier G and DiNardo CD: Venetoclax for the treatment of newly diagnosed acute myeloid leukemia in patients who are ineligible for intensive chemotherapy. Ther Adv Hematol 10: 2040620719882822, 2019.
4. Pollyea DA, Amaya M, Strati P and Konopleva MY: Venetoclax for AML: Changing the treatment paradigm. Blood Adv 3: 4326-4335, 2019.
5. Wei AH, Strickland SA Jr, Hou JZ, Fiedler W, Lin TL, Walter RB, Enjeti A, Tiong IS, Savona M, Lee S, *et al*: Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: Results from a phase Ib/II study. J Clin Oncol 37: 1277-1284, 2019.
6. DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, Arellano M, Frattini MG, Kantarjian H, Popovic R, *et al*: Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: A non-randomised, open-label, phase 1b study. Lancet Oncol 19: 216-228, 2018.
7. Vasu S, Kohlschmidt J, Mrózek K, Eisfeld AK, Nicolet D, Sterling LJ, Becker H, Metzeler KH, Papaioannou D, Powell BL, *et al*: Ten-year outcome of patients with acute myeloid leukemia not treated with allogeneic transplantation in first complete remission. Blood Adv 2: 1645-1650, 2018.
8. Singh R, Letai A and Sarosiek K: Regulation of apoptosis in health and disease: The balancing act of BCL-2 family proteins. Nat Rev Mol Cell Biol 20: 175-193, 2019.
9. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, Frankfurt O, Konopleva M, Wei AH, Kantarjian HM, *et al*: Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 133: 7-17, 2019.
10. Choi JH, Bogenberger JM and Tibes R: Targeting apoptosis in acute myeloid leukemia: Current status and future directions of BCL-2 inhibition with venetoclax and beyond. Target Oncol 15: 147-162, 2020.
11. Pollyea DA, Stevens BM, Jones CL, Winters A, Pei S, Minhajuddin M, D'Alessandro A, Culp-Hill R, Riemondy KA, Gillen AE, *et al*: Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med 24: 1859-1866, 2018.
12. Yue X, Chen Q and He J: Combination strategies to overcome resistance to the BCL2 inhibitor venetoclax in hematologic malignancies. Cancer Cell Int 20: 524, 2020.
13. Garciaz S, Hospital MA, Alary AS, Saillard C, Hicheri Y, Mohty B, Rey J, D'Incan E, Charbonnier A, Villetard F, *et al*: Azacitidine plus venetoclax for the treatment of relapsed and newly diagnosed acute myeloid leukemia patients. Cancers (Basel) 14: 2025, 2022.
14. Cui H, Liu Z, Jin M, Wang D and Liu L: Efficacy and safety of azacytidine and BCL-2 inhibitors in the treatment of acute myeloid leukemia. Syst Med 7: 4-7, 2022.
15. Wang W, Luo Q, Chen Q, Pang A and Fang K: Analysis of the clinical efficacy of azacytidine + venetoclax in the treatment of elderly patients with relapsed refractory acute myeloid leukemia. Evid Based Complement Alternat Med 2022: 8691835, 2022.
16. Xia L, Tian W, Zhao Y, Jiang L, Qian W, Jiang L, Ge L, Li J, Jin F and Yang M: Venetoclax and azacitidine in Chinese patients with untreated acute myeloid leukemia ineligible for intensive chemotherapy. Signal Transduct Target Ther 8: 176, 2023.
17. Yamamoto K, Shinagawa A, DiNardo CD, Pratz KW, Ishizawa K, Miyamoto T, Komatsu N, Nakashima Y, Yoshida C, Fukuhara N, *et al*: Venetoclax plus azacitidine in Japanese patients with untreated acute myeloid leukemia ineligible for intensive chemotherapy. Jpn J Clin Oncol 52: 29-38, 2022.
18. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25: 603-605, 2010.
19. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, *et al*: Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 383: 617-629, 2020.
20. Fu L, Liao X and Xiong M: Efficacy of venetoclax combined with azacytidine in the treatment of elderly patients with acute myeloid leukemia and its effect on immune function. Gerontol Health Care 28: 125-128, 134, 2022.
21. Jonas BA, Dinardo CD, Fracchiolla N, Pristupa A, Ishizawa K, Jin J, Konopleva M, Ofran Y, Montesinos P, Kovacsovics T, *et al*: CYP3A inhibitors and impact of these agents on outcomes in patients with acute myeloid leukemia treated with venetoclax plus azacitidine on the VIALE-A study. Blood 136 (Suppl 1): S50-S52, 2020.
22. Pollyea DA, Dinardo CD, Arellano ML, Pigneux A, Fiedler W, Konopleva M, Rizzieri DA, Smith BD, Shinagawa A, Lemoli RM, *et al*: Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with IDH 1/2 mutations. Blood 136 (Suppl 1): S5-S7, 2020.
23. Pollyea DA, DiNardo CD, Arellano ML, Pigneux A, Fiedler W, Konopleva M, Rizzieri DA, Smith BD, Shinagawa A, Lemoli RM, *et al*: Impact of venetoclax and azacitidine in treatment-naïve patients with acute myeloid leukemia and IDH1/2 mutations. Clin Cancer Res 28: 2753-2761, 2022.
24. Yang L, Wang S, Hu W and Zhang W: Clinical efficacy of azacytidine combined with Veneckla in the treatment of elderly patients with acute myeloid leukemia. J Clin Hematol 35: 512-516, 521, 2022.
25. Shallis RM, Wang R, Davidoff A, Ma X and Zeidan AM: Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. Blood Rev 36: 70-87, 2019.
26. Shimony S, Stahl M and Stone RM: Acute myeloid leukemia: 2023 Update on diagnosis, risk-stratification, and management. Am J Hematol 98: 502-526, 2023.
27. Naqvi K, Konopleva M and Ravandi F: Targeted therapies in acute myeloid leukemia: A focus on FLT-3 inhibitors and ABT199. Expert Rev Hematol 10: 863-874, 2017.
28. Kwag D, Cho BS, Bang SY, Lee JH, Min GJ, Park SS, Park S, Yoon JH, Lee SE, Eom KS, *et al*: Venetoclax with decitabine versus decitabine monotherapy in elderly acute myeloid leukemia: A propensity score-matched analysis. Blood Cancer J 12: 169, 2022.
29. Lagadinou ED, Sach A, Callahan K, Rossi RM, Neering SJ, Minhajuddin M, Ashton JM, Pei S, Grose V, O'Dwyer KM, *et al*: BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells. Cell Stem Cell 12: 329-341, 2013.
30. Ball S and Borthakur G: Apoptosis targeted therapies in acute myeloid leukemia: An update. Expert Rev Hematol 13: 1373-1386, 2020.
31. Zhang Y and Zhou H: B-cell lymphoma/leukemia-2 inhibitor combined with azacytidine in the treatment of acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation in two cases. Chin J Transplant (Electron Ed) 15: 45-48, 2021.
32. Wang WM, Wang J, Zhu MX, Wang YF, Liu YY and Jing HM: Inductive effect of 5-azacitidine on apoptosis of multiple myeloma cell lines and its mechanism. Zhongguo Shi Yan Xue Ye Xue Za Zhi 24: 110-116, 2016 (In Chinese).
33. Zheng Y, Zheng H and Hu J: Clinical observation on reinduction of azacytidine combined with CAG regimen in the treatment of recurrent refractory acute myeloid leukemia in children. Leuk Lymphoma 30: 470-474, 2019.
34. Miu W, Sha X and Liu Y: Treatment of four cases of newly diagnosed aged acute myeloid leukemia with azactidine and review of literature. Chin J Prim Med 28: 291-293, 2019.
35. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, Kumar R, Cavenagh J, Schuh AC, Candoni A, *et al*: International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 126: 291-299, 2015.
36. Jin S, Cojocari D, Purkal JJ, Popovic R, Talaty NN, Xiao Y, Solomon LR, Boghaert ER, Leverson JD and Phillips DC: 5-azacitidine induces NOXA to prime AML cells for venetoclax-mediated apoptosis. Clin Cancer Res 26: 3371-3383, 2020.
37. Cojocari D, Smith BN, Purkal JJ, Arrate MP, Huska JD, Xiao Y, Gorska A, Hogdal LJ, Ramsey HE, Boghaert ER, *et al*: Pevonedistat and azacitidine upregulate NOXA (PMAIP1) to increase sensitivity to venetoclax in preclinical models of acute myeloid leukemia. Haematologica 107: 825-835, 2022.
38. Du Y, Li C and Yan J: The efficacy and safety of venetoclax and azacytidine combination treatment in patients with acute myeloid leukemia and myelodysplastic syndrome: Systematic review and meta-analysis. Hematology 28: 2198098, 2023.
39. Bewersdorf JP, Giri S, Wang R, Williams RT, Tallman MS, Zeidan AM and Stahl M: Venetoclax as monotherapy and in combination with hypomethylating agents or low dose cytarabine in relapsed and treatment refractory acute myeloid leukemia: A systematic review and meta-analysis. Haematologica 105: 2659-2663, 2020.