European Review for Medical and Pharmacological Sciences 2024; 28: 1837-1846

The efficacy and safety of venetoclax combined with demethylating agents in elderly patients with acute myeloid leukemia: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the efficacy and adverse effects of venetoclax in combination with hypomethylating agents in elderly with acute myeloid leukemia.

MATERIALS AND METHODS: A comprehensive literature search identified related studies from PubMed, Medline, Embase, Scopus, and Cochrane Library. Overall complete remission (CR) and overall response rate (ORR) were applied to evaluate the efficacy of venetoclax in combination with hypomethylating agents in elderly with acute myeloid leukemia, and incidence of grade 3-4 adverse events were used to evaluate the safety.

RESULTS: 10 studies, including a total of 930 patients, were identified in our study and analyzed using the random-effects model. Meta-analysis showed the pooled overall CR rate of 70% (95% CI: 63-77%), the pooled ORR rate of 53% (95% CI: 39-67%), and the median overall survival ranged from 7.7 to 16.9 months. A total of 6 studies reported related adverse events, mainly including thrombocytopenia, febrile neutropenia, neutropenia, leukopenia, anemia, and pneumonia. The pooled incidence of overall adverse events was 30% (95% CI: 22-38%), and all adverse events were tolerable and resolved with treatment.

CONCLUSIONS: The combination of venetoclax and demethylating drugs has a good therapeutic effect on elderly patients with acute myeloid leukemia, but it also induces some adverse events. Although this therapy has a small impact on the quality of life, further attention is still needed to reduce the occurrence of such adverse events.

Key Words:
Acute myeloid leukemia, Elderly, Overall response, Efficacy, Adverse events.

Introduction

Acute myeloid leukemia (AML) is a malignant tumor of the hematopoietic system characterized by clonal proliferation of undifferentiated myeloid progenitor cells and resulting in the destruction of hematopoietic function[1]. AML can be life-threatening, with a particularly high mortality rate in the elderly population. In 2017, acute myeloid leukemia-related mortality in the United States was reported[2,3] to account for approximately 69.3% of elderly patients over 65 years of age, with elderly patients diagnosed with AML having a worse prognosis than younger. AML has a 5-year survival rate of 50% in younger patients of less than 50 years of age and less than 10% in patients over 70 years of age[4]. There may be many reasons for the poor efficacy in elderly patients, but the most important two aspects are the emergence of drug resistance phenomenon and patients' intolerance to traditional treatment[5-7]. For example, elderly patients are more likely to carry adverse genetic factors and have more secondary AML with increasing age, which may cause resistance to traditional treatments. On the other hand, they experience a decline in physical function and have many complications, so they cannot tolerate more aggressive treatment options[8]. Although the complete remission rate with intensive chemotherapy is not low, intensive chemotherapy increases early mortality in elderly patients. Organ dysfunction, poor general physical condition, systemic underlying diseases, and poor tolerance to drugs can all lead to reduced

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remission rates in elderly patients with AML, so it is urgent to explore the best treatment for the elderly with acute myeloid leukemia[9-11].

Demethylating drugs have been applied in the treatment of elderly patients with AML, with a certain degree of therapeutic effect and less toxicity[12]. However, its efficacy is still not very satisfactory and needs to be further improved in combination with other drugs. Venetoclax (VEN) is a small molecule targeted agent acting on B-lymphocytomas for the treatment of a variety of hematologic malignancies[13]. Studies[14,15] have shown that VEN combined with demethylating drugs can reduce drug resistance while increasing the sensitivity of acute myeloid leukemia cells to T cell-mediated cytotoxicity. However, there are only a small number of reports on the efficacy and safety of this combination regimen in the treatment of elderly patients with acute myeloid leukemia.

Therefore, we conducted this meta-analysis of related studies on the efficacy and safety of VEN combined with demethylating drugs in the treatment of elderly patients with AML to understand the efficacy and related toxic side effects of this combination and provide a reference for clinical practice.

Materials and Methods

Studies Selection

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), systematic search in PubMed, MEDLINE, EMBASE, SCOPUS, Cochrane Library and other databases was conducted, and the literature language was limited to English. Primary search terms included ("Venetoclax" OR "VEN") AND ("acute myeloid leukemia" OR "AML") AND ("elderly" OR "old patient"). We included the full text of clinical trials according to the following inclusion criteria:

1. Patients older than 60 years and met the diagnostic criteria for acute myeloid leukemia; 2. Venetoclax combined with demethylating agents was used in the treatment regimen; 3. All studies had clear outcome measures, including but not limited to complete remission (CR), overall response rate (ORR), and median overall survival (OS); 4. Study size greater than 10 patients.
2. Exclusion criteria are as follows: 1. The types of literature were case reports and review articles; 2. Studies that recruited less than 10 patients; 3. The studies lacked outcome measures; 4. Unable to get original data.

Data Extraction

According to the established inclusion criteria, two experienced investigators screened all articles. Subsequently, the included studies were screened for duplicates using literature management software by two reviewers. All data included in this meta-analysis were independently extracted by two experienced reviewers using a standardized data extraction form. Disagreements between the two reviewers were resolved by consultation with a third reviewer. The following information was extracted from each study: 1. last name of first author; 2. published year of study; 3. number of patients enrolled in the study; 4. mean age of patients; 5. procedure of treatment; 6. overall response rate; 7. complete remission rate; 8. overall survival; 9. related adverse events.

Quality Assessment

The included articles were evaluated by two independent researchers for quality assessment according to MINORS scoring criteria. There are 8 evaluation indicators, each of which is divided into 0-2 points, 0 point means not reported; 1 point means reported but insufficient information; 2 points means that reported and sufficient information is provided.

Statistical Analysis

All data analysis in this study was performed using Revman 5.3 software. I^2 heterogeneity index was applied to calculate the heterogeneity of all included studies (25% indicating low heterogeneity, 50% moderate, and 75% high). A fixed-effect model was used to pool effect size for those with low heterogeneity, and a random-effect model was used for those with high heterogeneity. The results of the study are reported by forest plots, with all summary results represented by diamonds and 95% confidence intervals (CI) by lines on either side of the square. The significance level was set at $p<0.05$.

Results

Literature Search

A total of 644 studies were retrieved from PubMed, EMBASE, and the Cochrane Library

via literature search. After the duplication assessment, 238 studies were excluded. After browsing the titles and abstracts for eligibility, 299 studies were excluded for obvious irrelevance, while 107 articles remained. After the full-text screening, 97 studies were excluded for no primary outcome (n=61), no full text (n=21), and overlapping study populations (n=15). The selection procedure is presented in Figure 1.

Study Characteristics

A total of 10 articles[11,16-24] were included in this study, all of which treated elderly AML with a regimen of venetoclax in combination with desmethyl agents. A total of 930 patients were included, ranging from 59 to 76 years of age, with a majority of male patients. After literature quality evaluation, all included studies were high-quality articles with MINORS score ≥14 points. (Table I).

Efficacy

All 10 studies[11,16-24] included utilized VEN in combination with demethylating agents to treat elderly AML and treatment effectiveness was expressed using CR, ORR, and OS. Random effects model analysis showed that the overall CR rate of the included studies was 70% (95% CI: 63-77%, Figure 2), while the meta-analysis of ORR values showed 53% (95% CI: 39-67%, Figure 3). Median OS was reported in 9 publications[11,16-23] and ranged from 7.7 to 16.9 months.

Related Adverse Events

A total of 6 studies[16,18,20-23] reported related adverse events, mainly including thrombocytopenia, febrile neutropenia, neutropenia, leukopenia, anemia and pneumonia. In order to visually show the occurrence of different adverse events, subgroup analysis was performed for different adverse events. Subgroup analysis showed an incidence of 35% (95% CI: 20-50%) for thrombocytopenia, 49% (95% CI: 37-61%) for febrile neutropenia, 24% (95% CI: 4-43%) for neutropenia, 24% (95% CI: 14-33%) for leukopenia, 19% (95% CI: 2-36%) for anemia, 16% (95% CI: 11-20%) for pneumonia, and 30% (95% CI: 22-38%) for overall adverse events, as shown in Figure 4.

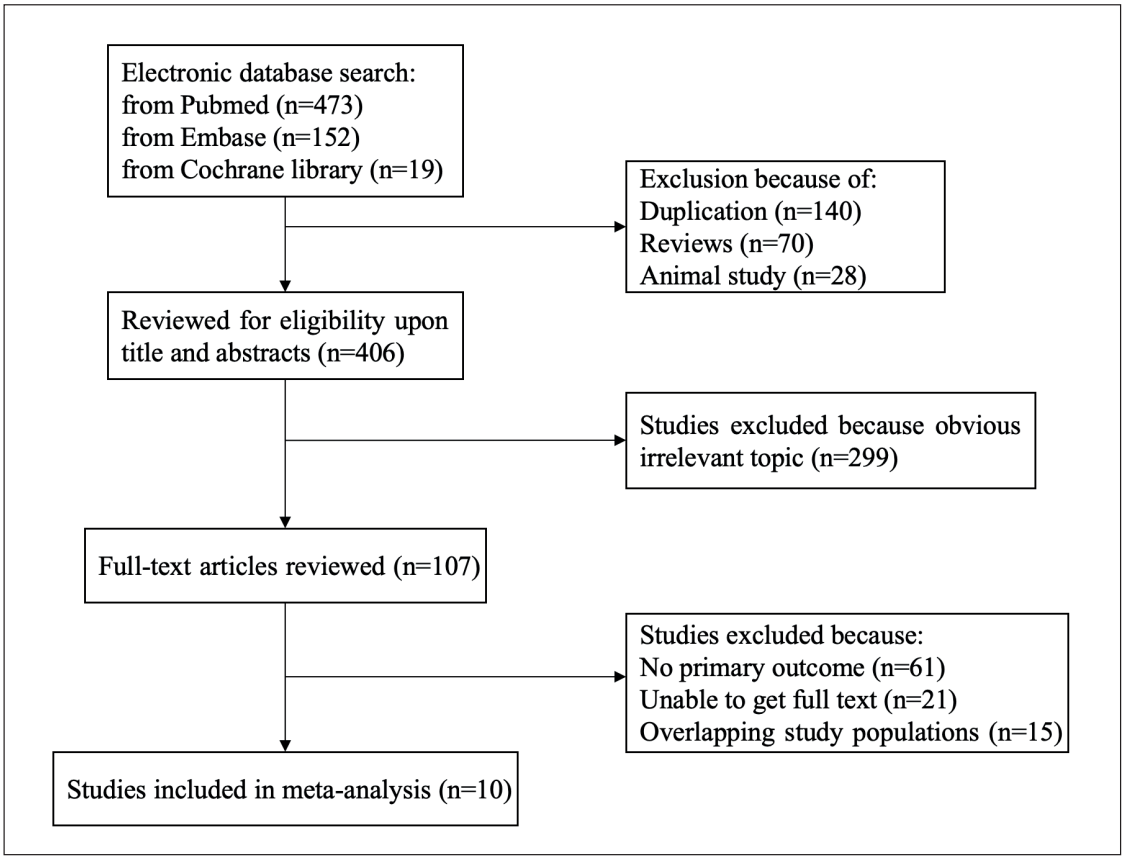

Figure 1. PRISMA flow chart of literature search and study selection.

Table I. Study characteristics of included studies.

Author	Year	No. of patients	Median age	Male/ Female	Risk stratification by genetics			CR (%)	ORR (%)	Median OS (months)	Toxicity (Gr3/4)					
					Favorable	Intermediate	Unfavorable				Thrombocytopenia	Febrile neutropenia	Neutropenia	Leukopenia	Anemia	Pneumonia
Lachowiez et al[11]	2020	28	71	NA	86%	NA	14%	89%	96%	16.9	NA	NA	NA	NA	NA	NA
Richard-Carpentier and Dinardo[16]	2019	145	74	NA	NA	74%	26%	67%	74%	12.9	24%	43%	17%	NA	25%	13%
Ravandi et al[17]	2022	37	75	20/17	NA	NA	NA	31%	53%	9.5	NA	NA	11%	NA	NA	NA
Ram et al[18]	2019	23	76	14/9	9%	48%	43%	22%	43%	12.4	NA	78%	NA	NA	NA	NA
Kwag et al[19]	2022	74	71	32/42	9.5%	67.5%	23%	35%	66%	13.4	NA	NA	NA	NA	NA	NA
Jonas and Pollyea[20]	2019	25	NA	NA	NA	NA	NA	92%	92%	12.6	26%	39%	NA	33%	31%	27%
Hu et al[21]	2023	10	71	7/3	NA	NA	NA	80%	80%	7.7	50%	NA	NA	NA	NA	NA
Dinardo et al[22]	2020	286	76	172/114	NA	64%	36%	37%	66%	14.7	46%	42%	42%	21%	5%	17%
Aldoss et al[23]	2019	90	59	46/44	68%	NA	32%	26%	46%	16.6	NA	NA	NA	NA	NA	NA
Agarwal et al[24]	2019	212	74	NA	NA	NA	NA	54%	72%	NA	NA	NA	NA	NA	NA	NA

NA, not applicable; CR, Complete response; ORR, Objective response rate; OS, Overall survival.

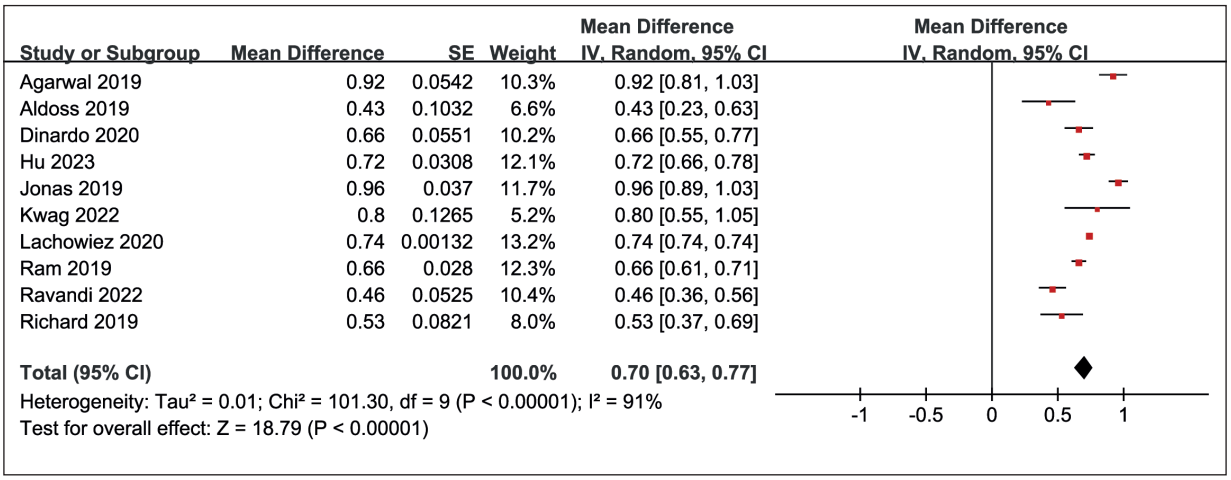

Figure 2. Forest plot of overall complete remission rate.

Publication Bias

All included studies reported CR rate, so the results of the CR rate were set for publication bias risk analysis. According to the results of the funnel plot, there was no significant publication bias in this study, and the funnel plot is shown in Figure 5.

Discussion

The incidence of acute myeloid leukemia (AML) increases gradually with age. According to previous studies[25-27], approximately 50% of AML patients have an age of onset above 60 years. Compared with younger patients, elderly patients have poor tolerance to conventional chemotherapy regimens, low response rates, and more complications. Current treatment options for AML in the elderly remain limited. The median OS of elderly AML treated with traditional chemotherapy regimens is only 5 to 6 months, and only about 15% of patients can survive for a long time. No treatment regimen has been found to be most suitable for elderly acute myeloid leukemia.

Recently, B-cell lymphoma (BCL) inhibitors have shown promising clinical applications as novel agents recommended for AML. Venetoclax, an inhibitor of the anti-apoptotic protein BCL-2, was approved in 2018 in combination with demethylating agents for the treatment of elderly AML[20,28]. Previous studies[29-31] have shown that venetoclax combined with demethylating drugs can block the uptake of amino acids by leukemia cells, thereby interfering with the oxidative phosphorylation process of leukemia cells. Byrne et

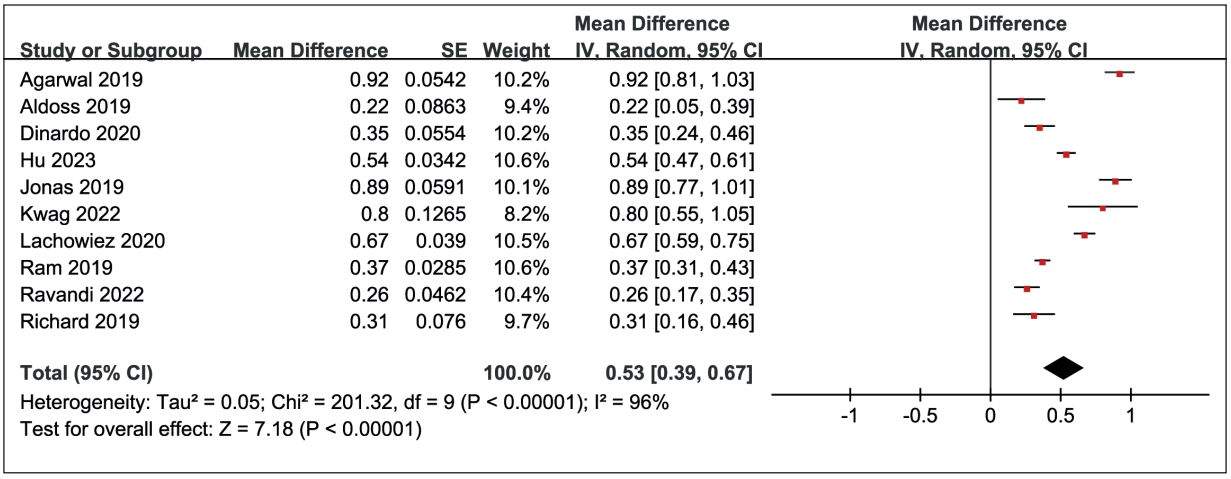

Figure 3. Forest plot of overall response rate.

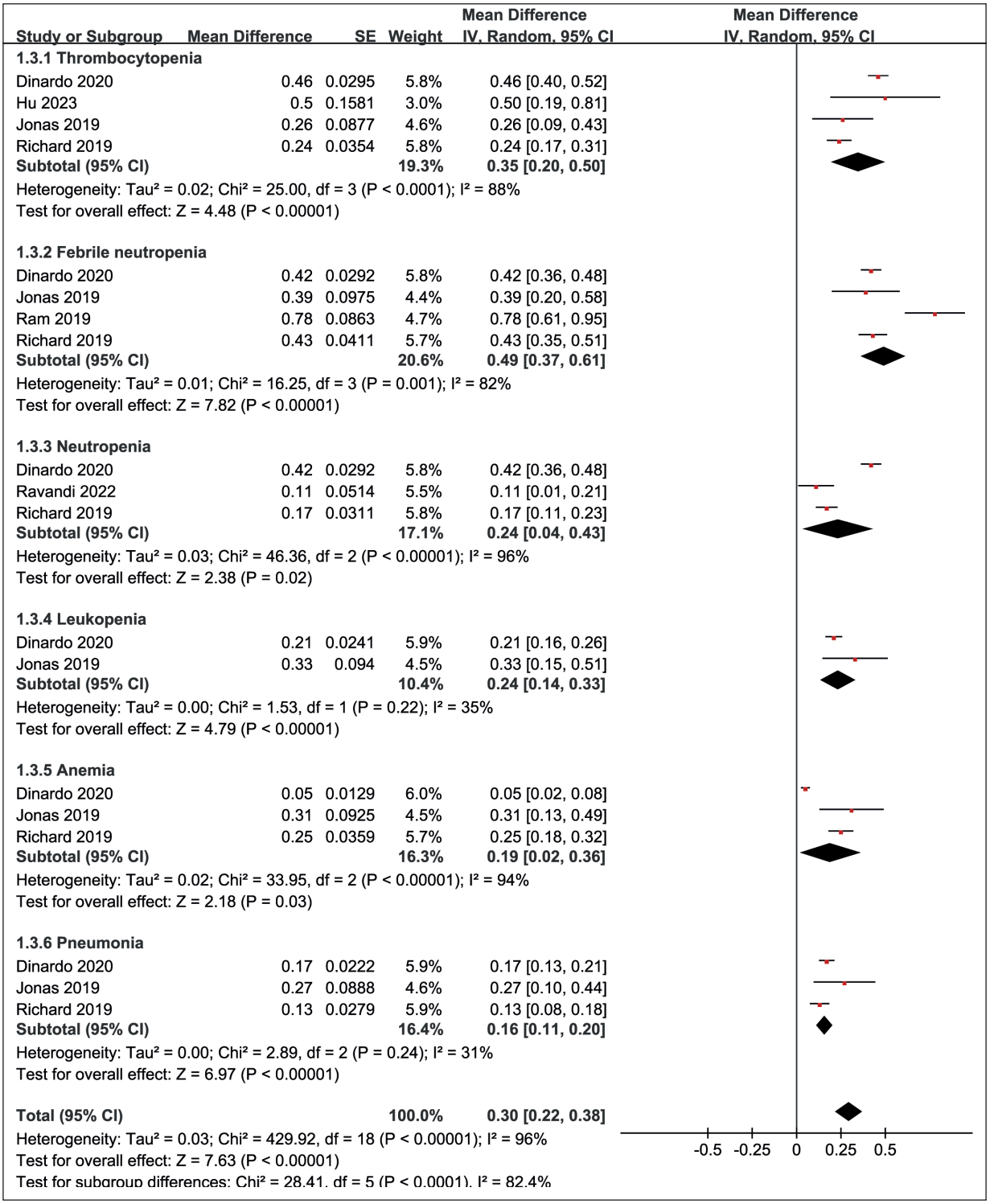

Figure 4. Forest plot of related adverse events.

al[32] retrospectively reviewed 21 elderly patients with AML who relapsed after transplantation and were treated with a VEN combined regimen, of whom 5 achieved CR and 3 achieved CRi, with an ORR of 38% and median OS of 7.8 months. While another study[33] retrospectively analyzed 29 patients who received VEN-based combination regimens for post-transplant relapse, the ORR

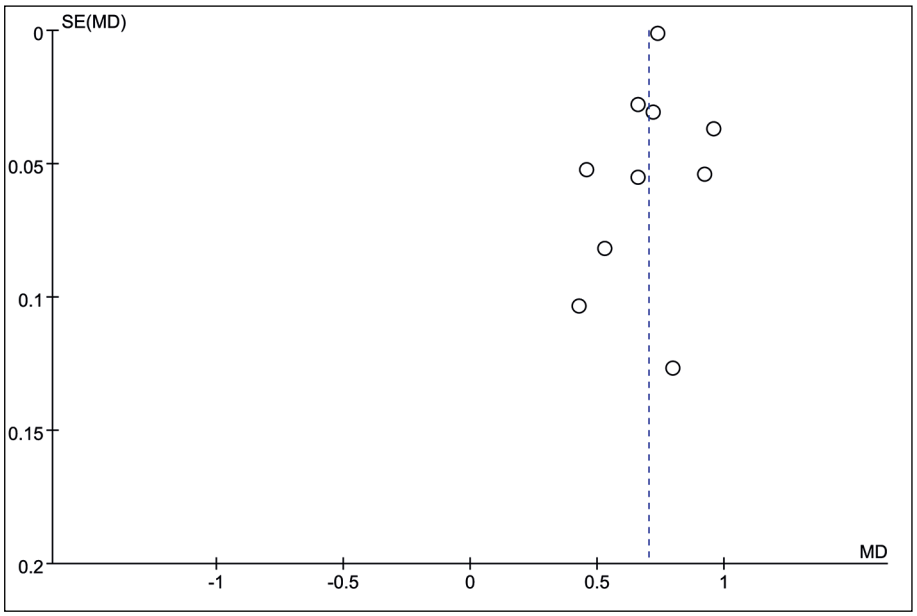

Figure 5. Funnel plot of overall complete remission rate.

was 38%, 28% achieved CR, the median OS was 2.6 months, and the OS of patients who achieved CR reached 13.4 months.

To evaluate the efficacy and safety of combined treatment with venetoclax and demethylating agents in elderly patients with AML, we performed this analysis and included a total of 10 relevant articles. Aberrant DNA methylation promotes tumorigenesis by affecting the expression of genes involved in the cell cycle, apoptosis, DNA repair, and maintaining genomic stability, which is one of the important mechanisms of AML pathogenesis, and this is why we studied the combination of venetoclax and demethylating drugs. Relevant studies[34-36] have shown that although elderly AML patients respond less frequently to hypomethylating agents (HMA) monotherapy than intensive chemotherapy, overall survival is similar to or even better than intensive chemotherapy regimens, especially in patients with TP53 mutations.

Our findings showed an overall CR rate of 70% and an ORR of 53% for venetoclax combined with demethylating agents. According to previous studies in the literature, the CR rate of elderly patients with AML after high-intensity chemotherapy is only about 65% and has strong adverse events. In our study, the CR rate of venetoclax combined with demethylating drugs was similar to that of high-intensity chemotherapeutic drugs, and the incidence of adverse events was about 30%, most of which could be relieved spontaneously and had no significant effect on the quality of life of patients. Subgroup analysis of adverse events revealed that febrile neutropenia had the highest incidence of approximately 49%, which is frequently present in acute myeloid leukemia. Such adverse events have also occurred in other previous treatments, and have had a good coping regimen. In general, the combination of venetoclax and demethylating agents is relatively safe for elderly patients with AML, especially those who cannot tolerate high-intensity chemotherapy, with good response rates and adverse events within an acceptable range[37,38].

Limitations

This study also has some limitations. Firstly, there are few studies on the combination of venetoclax and demethylating drugs. The number of studies and cases we included is relatively limited, and there is a certain degree of heterogeneity. Secondly, not every included study reports the relevant adverse events, so the comprehensive analysis of data on the incidence of adverse events is not sufficient.

Conclusions

For elderly patients with AML, venetoclax combined with demethylating drugs has a better

therapeutic effect, with a lower incidence of adverse events and better tolerance. Subsequently, a large-sample multicenter randomized controlled trial study is needed to confirm the clinical efficacy of this treatment further so that it can be reasonably popularized and applied in clinical practice.

Data Availability
All datasets generated during and/or analyzed during the current study are available in the manuscript.

Ethics Approval and Informed Consent
Not applicable.

Conflict of Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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Funding
This study was supported by Luzhou Municipal Government—Southwest Medical University Cooperation Application Foundation (grant No. 2023LZXNYDJ045) and Academic Research Projects of Southwest Medical University (grant No. 2023QN042).

Authors' Contributions
Mengyu Wei conceived the study, assessed the data and wrote the draft. Jun Yin and Yun Liao assessed the data. Jiayue Liu made the figures. Yu Zhao and Xiaomin Chen contributed to the methodological framework. Yang Liu and Xuemei Wang revised the manuscript. Chunlan Huang edited the manuscript and polished the language. All authors read and approved the final version of the manuscript.

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