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Venetoclax Combination Regimens in Relapsed or Refractory Acute Myeloid Leukemia: A Systematic Review

Regímenes de combinación con Venetoclax en la leucemia mieloide aguda recidivante o refractaria: una revisión sistemática

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ABSTRACT

Purpose: This study evaluated the efficacy and safety of venetoclax combined with chemotherapy or hypomethylating agents in adult patients with relapsed or refractory acute myeloid leukemia who are ineligible for intensive chemotherapy. **Methods:** A systematic review of randomized and observational studies was conducted using MEDLINE, Embase, and the Cochrane Library through October 2024. Eligible studies included adult patients with relapsed or refractory acute myeloid leukemia treated with venetoclax-based combination regimens. Primary outcomes were overall survival, complete remission rates, and treatment-related adverse events. **Results:** Of 447 identified records, 12 studies met the inclusion criteria. Venetoclax combined with azacitidine showed improved overall survival and higher complete remission rates compared

with decitabine-based regimens and was associated with fewer severe hematologic and infectious adverse events. **Discussion:** Venetoclax combined with azacitidine demonstrated superior efficacy and tolerability compared with decitabine-based regimens in relapsed or refractory acute myeloid leukemia. These findings support its use in patients ineligible for intensive chemotherapy, although further studies are needed to define responsive subgroups and long-term outcomes.

Keywords: Leukemia, Myeloid, Acute; Antineoplastic Agents; Survival Rate; Remission Induction

RESUMEN

Objetivo: Este estudio evaluó la eficacia y la seguridad de venetoclax en combinación con quimioterapia o agentes hipometilantes en pacientes adultos con leucemia mieloide aguda recidivante o refractaria no candidatos a quimioterapia intensiva. **Métodos:** Se realizó una revisión sistemática de estudios aleatorizados y observacionales utilizando MEDLINE, Embase y Cochrane Library hasta octubre de 2024. Los estudios seleccionados incluyeron a pacientes adultos con leucemia mieloide aguda recidivante o refractaria tratados con regímenes combinados basados en venetoclax. Los resultados principales fueron la supervivencia global, las tasas de remisión completa y los acontecimientos adversos relacionados con el tratamiento. **Resultados:** De los 447 registros identificados, 12 estudios cumplieron los criterios de inclusión. La combinación de venetoclax y azacitidina mostró una mejor supervivencia global y tasas de remisión completa más elevadas en comparación con los regímenes basados en decitabina, además de asociarse con una menor incidencia de acontecimientos adversos graves de tipo hematológico e infeccioso. **Discusión:** La combinación de venetoclax y azacitidina demostró una eficacia y tolerabilidad superiores frente a los regímenes basados en decitabina en el tratamiento de la leucemia mieloide aguda recidivante o refractaria. Estos hallazgos respaldan su uso en pacientes no candidatos a quimioterapia intensiva, si bien se requieren estudios adicionales para definir los subgrupos con mejor respuesta y los resultados a largo plazo.

Palabras clave: Leucemia mieloide aguda; Agentes antineoplásicos; Tasa de supervivencia; Inducción de remisión

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INTRODUCTION

Acute myeloid leukemia (AML) is a hematologic neoplasm characterized by the clonal proliferation of immature myeloid precursors in the bone marrow, leading to rapid progression and a poor prognosis without appropriate treatment. Despite advances in initial treatment, relapse remains a significant challenge for AML patients, with limited response rates and significant toxicities associated with conventional therapies. Traditionally, intensive chemotherapy has been the cornerstone of treatment; however, high toxicity rates and limited response have driven the research for new therapies that are less toxic and more effective (11).

In recent years, the selective BCL-2 inhibitor, venetoclax, has emerged as a promising therapy in combination with hypomethylating agents (such as azacitidine and decitabine) and with conventional chemotherapies. Recent studies have demonstrated that the combination of venetoclax with hypomethylating agents significantly improves overall response rates in patients with relapsed or refractory AML, especially in those who are not candidates for intensive chemotherapy due to comorbidities or advanced age. In the combination of venetoclax with azacitidine, overall survival has shown a notable increase compared to standard treatments in patients unfit for intensive chemotherapy, achieving complete remission rates of 66.4% compared to 28.3% with azacitidine alone, according to the VIALE-A trial (2023) (2).

However, unresolved questions remain regarding the long-term impact of these combinations on overall survival, as well as the biological and clinical factors that predict treatment response. The biological heterogeneity of AML suggests that certain subgroups of patients may benefit more from these combinations. For example, patients with FLT3 mutations receiving venetoclax in combination with gilteritinib have demonstrated significant molecular-level tumor burden reduction, indicating the need for further studies to validate the benefit in specific subgroups (11,4).

The objective of this study is to evaluate the overall survival of patients with relapsed or refractory AML treated with venetoclax in combination with chemotherapy or hypomethylating agents.

METHODS

A systematic review of the literature was conducted to evaluate the efficacy of Venetoclax in combination with chemotherapy or hypomethylating agents on the overall survival of patients with relapsed or refractory acute myeloid leukemia (AML).

Selection Criteria

Studies

Randomized clinical trials, non-randomized studies, case series, and prospective and retrospective observational studies that assessed the use of Venetoclax in combination with chemotherapy or hypomethylating agents in patients with relapsed or refractory AML were

included. Studies that did not report overall survival data or those in which Venetoclax was not administered as part of a combination regimen were excluded.

Participants

Studies reporting data on adult patients (over 18 years of age) with a confirmed diagnosis of acute myeloid leukemia, who had relapsed or refractory disease and were treated with Venetoclax in combination with chemotherapy or hypomethylating agents, were included.

Interventions

The intervention assessed was treatment with Venetoclax administered in combination with conventional chemotherapy regimens (e.g., cytarabine, daunorubicin) or hypomethylating agents (e.g., azacitidine, decitabine). Studies where Venetoclax was used as monotherapy were not included.

Outcomes

The primary outcome was overall survival (OS), defined as the time from the initiation of Venetoclax treatment until death from any cause.

Secondary outcomes included the complete remission (CR) rate, progression-free survival (PFS), disease-free survival (DFS), and the incidence of severe adverse events (grade ≥ 3).

Search Methods for Study Identification

Systematic searches were conducted in the MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases from inception through October 2024. Search terms included combinations of keywords and MeSH terms related to "Venetoclax," "acute myeloid leukemia," "AML," "relapsed," "refractory," and "survival." Specific terms used were "Venetoclax," "acute myeloid leukemia," "relapsed," "refractory," "overall survival," "chemotherapy," and "hypomethylating agents."

A manual search of the reference lists of included studies and recent relevant reviews was conducted to identify additional studies not captured by electronic databases. Experts in the field were also contacted to identify unpublished or ongoing literature.

Data Collection and Analysis

Two reviewers independently conducted the study selection by screening titles and abstracts to identify studies that met the inclusion criteria. Full texts of potentially eligible studies were reviewed in detail. Discrepancies were resolved by consensus or by consulting a third reviewer.

Data from the included studies were independently extracted by two reviewers using a standardized form. Extracted data included study characteristics (design, sample size, type of intervention), participant characteristics, primary and secondary outcomes, and adverse event data. Discrepancies in data extraction were resolved by consensus.

The methodological quality of the included studies was assessed using the Cochrane tool for assessing the risk of bias in clinical trials (for randomized studies) and the Newcastle-Ottawa

scale for observational studies. Each study was evaluated for factors such as selection bias, confounding bias, reporting bias, and other potential biases.

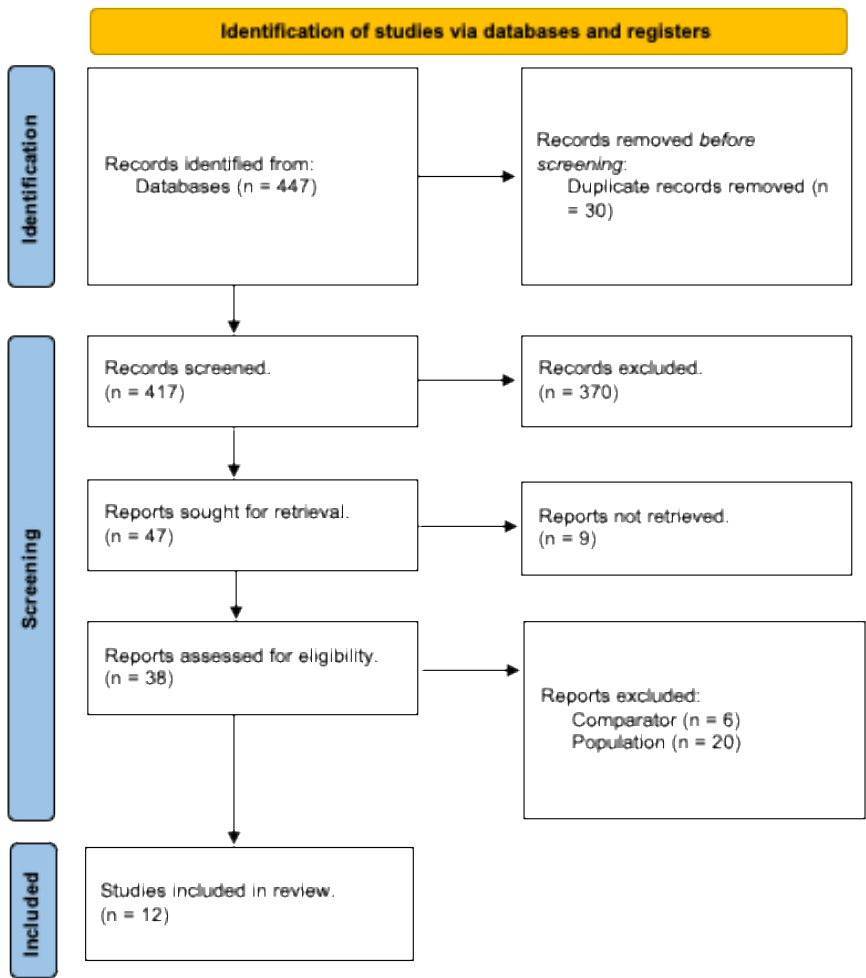
A qualitative synthesis of the findings from the included studies was conducted, describing overall survival, complete remission rates, and the incidence of adverse events.

RESULTS

Search Results

During the study selection process, 447 records were identified through database searches and specialized registries. After removing 30 duplicate studies, 417 unique studies were evaluated. Following the evaluation of titles and abstracts, 370 studies were excluded due to lack of relevance. A total of 47 full-text studies were assessed. Finally, 12 studies were included in the systematic review, providing crucial information on the effectiveness of Venetoclax in combination with other agents in the treatment of patients with relapsed or refractory AML.

Figure 1
PRISMA Flow Diagram



Primary Studies (see Table 1)

Overall Survival

Overall survival (OS) was evaluated in two primary studies. Fukumoto et al. (2023) (8) reported a median OS of 287 days in patients with relapsed/refractory acute myeloid leukemia (AML) treated with Venetoclax in combination with azacitidine or low-dose cytarabine. In the trial by DiNardo et al. (2020) (5), the median OS in refractory AML patients treated with Venetoclax and decitabine was 7.8 months, suggesting a moderate improvement in survival compared to conventional treatments.

Complete and Partial Remission Rates

Remission rates were reported in all the included studies. Fukumoto et al. (2023) (8) indicated a complete remission or complete remission with incomplete recovery (CR/CRi) rate of 73.1%, while the study by DiNardo et al. (2020) (5) reported an overall response rate (including complete and partial remission) of 62% in refractory AML patients. The study by Che et al. (2024) (4) compared Venetoclax combined with azacitidine versus Venetoclax combined with decitabine, finding a higher complete remission rate in the azacitidine group (8%) compared to the decitabine group (4%). Similarly, the partial remission rate was higher in the azacitidine group (18%) compared to the decitabine group (10%). Wang et al. (2022) (15) also reported high efficacy of Venetoclax combined with azacitidine, with an overall response rate of 90% in elderly patients with relapsed/refractory AML, compared to 40% in the control group treated with azacitidine alone.

Hematologic Parameters and Immunologic Effects

Hematologic parameters, including platelet count (PLT), white blood cells (WBC), and hemoglobin (Hb), were evaluated in the studies by Che et al. (2024) (4) and Wang et al. (2022) (15). Che et al. (2024) (4) found that the group treated with Venetoclax and azacitidine showed higher platelet levels ($89.95 \pm 15.34 \times 10^9/L$) and hemoglobin ($88.35 \pm 5.96 \text{ g/L}$) compared to the decitabine group ($81.29 \pm 12.58 \times 10^9/L$ and $74.84 \pm 7.64 \text{ g/L}$, respectively). Wang et al. (2022) (15) reported significant improvements in platelet, white blood cell, and hemoglobin levels in the group treated with Venetoclax and azacitidine compared to the control group. Additionally, a significant reduction in CD4+ and CD3+ levels was observed after treatment in both groups, with no significant differences between them.

Adverse Effects

Adverse effects were reported in all included studies. Fukumoto et al. (2023) (8) reported a grade ≥ 3 neutropenia incidence of 92.6% in patients treated with Venetoclax in combination with azacitidine or low-dose cytarabine, indicating a high incidence of myelosuppression. In the study by Che et al. (2024) (4), the group treated with Venetoclax and decitabine showed a higher incidence of thrombocytopenia (16%), red blood cell depletion (11%), and pulmonary infections (6%) compared to the azacitidine group. Wang et al. (2022) (15) found similar incidences of

adverse effects between the groups treated with Venetoclax and azacitidine and the control group, with no significant differences.

Table 1
Results of the Included Primary Studies

Author, Year	Objective	Country	Population	Design	N	Intervention	Comparator	Outcomes	Key Results
DiNardo, 2020 (5)	Assess safety/efficacy of VEN + DEC in ND and R/R AML	USA	≥60 yrs, ND or R/R AML	Phase II	168	VEN + DEC	–	ORR, OS, DOR, safety	ORR 62% (R/R AML); median OS 7.8 mo
Che, 2024 (4)	Compare VEN + AZA vs VEN + DEC in R/R AML	China	R/R AML	RCT	200	VEN + AZA	VEN + DEC	Response, CR, PR, labs, AEs	ORR: 50% vs 28%; CR 8% vs 4%; PR 18% vs 10%. PLT 89.9 vs 81.3×10 ⁹ /L; Hb 88.3 vs 74.8 g/L (p<0.01). Higher AEs with DEC (thrombocytopenia 16%, infection 6%)
Wang, 2022 (15)	Evaluate AZA + VEN in elderly R/R AML	China	≥60 yrs, R/R AML	RCT	20	AZA + VEN	AZA	ORR, PLT, WBC, Hb, CD markers, AEs	ORR 90% vs 40% (p<0.05). ↑ PLT & WBC both groups. ↓ CD4+, CD3+. Similar AEs
Fukumoto, 2023 (8)	Real-world VEN combinations in AML	Japan	ND & R/R AML	Retrospective	41	VEN + AZA or LDAC	–	OS, CR/CRi, safety	Median OS 287 d; CR/CRi 73.1%; grade ≥3 neutropenia 92.6%

Secondary Studies (see Table 2)

Eight secondary studies were analyzed that investigated the efficacy and safety of Venetoclax in the treatment of relapsed or refractory acute myeloid leukemia (AML). The studies included combinations of Venetoclax with hypomethylating agents (HMA) and low-intensity chemotherapy, with the goal of evaluating key clinical outcomes such as complete remission (CR) rate, overall response rate (ORR), overall survival (OS), and the incidence of adverse events.

Complete Remission (CR) Rate and Overall Response Rate (ORR)

The complete remission (CR) rate showed considerable variability across studies, depending on the therapeutic combinations used and the characteristics of the patient population.

In the VIALE-A trial, reported by Hu et al. (2023) (9), the combination of Venetoclax with azacitidine resulted in a CR rate of 66.4%, compared to 28.3% in the placebo group. Aldoss (2021) (3) reported a CR rate of 46% in relapsed/refractory AML patients treated with Venetoclax and hypomethylating agents. Similarly, Bewersdorf (2020) (2) reported a CR rate of 26.7% in patients treated with Venetoclax in combination with HMA or low-dose cytarabine (LDAC). The overall response rate (ORR) also varied significantly, ranging from 31.1% to 56.6%, being higher when Venetoclax was administered in combination with hypomethylating agents (Shimony, 2022; Bewersdorf, 2020) (12,15).

Overall Survival (OS)

The median overall survival (OS) also showed considerable variability across studies. In the study by Hu et al. (2023) (9), the combination of Venetoclax with azacitidine was associated with a median OS of 14.7 months, compared to 9.6 months in the placebo group. Aldoss (2021) (3) reported a mean OS of 7.8 months in relapsed/refractory AML patients treated with Venetoclax and hypomethylating agents. Bewersdorf (2020) (2) reported a median OS ranging from 3 to 6.6 months for those treated with Venetoclax in combination with HMA or LDAC. Overall, the data suggest improved survival for patients treated with Venetoclax combinations compared to conventional therapies.

Adverse Events

In terms of safety, the most common adverse events reported included febrile neutropenia, grade 3/4 hematological toxicity, and early mortality. Lasica (2021) (10) indicated that 42% of patients experienced febrile neutropenia when treated with Venetoclax in combination with hypomethylating agents. Shimony (2022) (12) reported a 38.6% incidence of febrile neutropenia in relapsed/refractory AML patients. Additionally, 30-day mortality was 6.1% in patients treated with Venetoclax combinations, highlighting the importance of close monitoring during the early stages of treatment.

Table 2

Results of the Included Systematic Reviews

Author, Year	Objective	Country	Population	Intervention	Comparator	Outcomes	Key Results
Lasica, 2021 (10)	Review VEN in hematologic malignancies	Australia	CLL, AML, MM	VEN ± HMA	Standard therapy	ORR, CR, OS, toxicity	AML: OS 14.7 vs 9.6 mo (HMA alone); CR 66.4%; FN 42%
Guerra, 2019 (8)	Review VEN combos in AML	USA	ND & R/R AML	VEN + HMA/chemo	—	CR/CRi, OS	R/R AML: CR/CRi 48–53%; OS 3–6 mo
Hu, 2023 (9)	Review VEN-based AML therapy	China	Adult AML	VEN + HMA/chemo	Placebo/HMA	CR/CRi, OS	CR/CRi 66.4% vs 28.3%; OS 14.7 vs 9.6 mo

Author, Year	Objective	Country	Population	Intervention	Comparator	Outcomes	Key Results
Aldoss, 2021 (1)	Review VEN in AML	USA	Unfit & R/R AML	VEN + HMA/LDAC	HMA/LDAC	CR, OS, MRD	CR/CRi 46%; OS 7.8 mo (16.6 mo if CR); MRD–64%
Du, 2023 (6)	VEN + HMA post-transplant	USA	R/R AML/MDS post-allo	VEN + HMA	Prior tx	CR/CRi, ORR, survival	CR/CRi 32%; ORR 48%; 6-mo OS 42%; 12-mo 23%
Shimony, 2022 (12)	VEN combinations in AML	USA	ND & R/R AML	VEN combos	Subgroups	ORR, CR, MRD, FN	R/R AML: ORR 56.6%; CR 24.4%; MRD– 57.8%; FN 38.6%; 30-d mortality 6.1%
Wei, 2024 (16)	VEN + demethylating agents in elderly AML	China	>60 yrs AML	VEN + HMA	–	CR, ORR, OS	CR 70%; ORR 53%; OS 7.7–16.9 mo
Bewersdorf, 2020 (2)	VEN in R/R AML	USA	R/R AML	VEN ± HMA/LDAC	–	ORR, CR/CRi, OS	ORR 31.1% (38.7% combo); CR/CRi 26.7%; OS 1.8–7.8 mo (mono), 3–6.6 mo (combo)

Risk of Bias Assessment of Included Studies

Cohort Studies: The study by Fukumoto et al. (2023) (8) on the safety and efficacy of Venetoclax for acute myeloid leukemia (AML) in real-world clinical practice presents a "fair quality" risk of bias rating, with a total score of 6. The representativeness of the exposed cohort is considered adequate, but the lack of an unexposed cohort and the absence of comparability between cohorts limit the comparative analysis. The verification of drug use and outcome assessment were well-documented, with secure records and independent blind evaluation, respectively. Additionally, the study is notable for complete follow-up and sufficient duration for observing outcomes. However, the absence of a comparison group reduces the ability to assess the differential impact of the treatment.

Clinical Trials: The studies by Che et al. (2024) (4) and Wang et al. (2022) (15) evaluated the use of Venetoclax in combination with azacitidine or decitabine in relapsed/refractory acute myeloid leukemia. Both studies show a low risk of bias in the domains related to the randomization process, missing outcome data, and outcome measurement, indicating good methodological quality in these areas. However, "some concerns" were identified in the domains related to deviations from the intended interventions and selection of the reported outcome, which

could limit the interpretation of the treatment effects. The presence of these concerns highlights the importance of transparency in outcome reporting and the need to minimize potential biases in outcome selection.

Table 3
Risk of Bias Assessment of Clinical Trials

Domain	Che, 2024 (4)	Wang, 2022 (15)
Domain 1: Risk of bias arising from the randomization process	Low	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Some concerns	Some concerns
Domain 3: Risk of bias due to missing outcome data	Low	Low
Domain 4: Risk of bias in measurement of the outcome	Low	Low
Domain 5: Risk of bias in selection of the reported result	Some concerns	Some concerns

Systematic Reviews

Table 4 shows the risk of bias in the systematic reviews conducted by different authors. The studies by Lasica (2021) (10), Guerra (2019) (8), Hu (2023) (9), and Aldoss (2021) (1) presented a high risk of bias across all evaluated domains, including study eligibility criteria, study identification and selection, data collection and evaluation, and synthesis and findings. This suggests significant methodological issues that could affect the validity of their conclusions. In contrast, the studies by Du (2023) (6), Shimony (2022) (12), Wei (2024) (16), and Bewersdorf (2020) (2) presented a low risk of bias across all evaluated domains, indicating better methodological quality and greater confidence in their results.

Table 4
Risk of Bias Assessment of Included Systematic Reviews

Domain	Lasica, 2021 (10)	Guerra, 2019 (8)	Hu, 2023 (9)	Aldoss, 2021 [12]	Du, 2023 [4]	Shimony, 2022 [13]	Wei, 2024 [14]	Bewersdorf, 2020 [15]
Domain 1: Study eligibility criteria	High	Low	High	Low	Low	Low	Low	Low
Domain 2: Identification and selection of studies	High	High	High	High	Low	Low	Low	Low
Domain 3: Data collection and study appraisal	High	High	High	High	Low	Low	Low	Low
Domain 4: Synthesis and findings	High	High	High	High	Low	Low	Low	Low
Overall Risk of Bias	High	High	High	High	Low	Low	Low	Low

Table 5
Abbreviations

Abbreviation	Definition
AML	Acute Myeloid Leukemia
BCL-2	B-cell Lymphoma 2
CR	Complete Remission

Abbreviation	Definition
CRi	Complete Remission with Incomplete Recovery
DFS	Disease-Free Survival
FN	Febrile Neutropenia
Hb	Hemoglobin
HMA	Hypomethylating Agent
IRB	Institutional Review Board
LDAC	Low-Dose Cytarabine
MDS	Myelodysplastic Syndrome
MRD	Minimal Residual Disease
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PLT	Platelet Count
PR	Partial Remission
R/R	Relapsed or Refractory
WBC	White Blood Cell Count

The following abbreviations are used in this manuscript:

DISCUSSION

This study evaluated the efficacy of Venetoclax combined with hypomethylating agents and chemotherapy in patients with relapsed or refractory acute myeloid leukemia (AML). The findings showed improved overall survival (OS) and high complete remission (CR) rates, particularly with Venetoclax plus azacitidine, especially in elderly patients and those with comorbidities who are not candidates for intensive chemotherapy. A recent meta-analysis reported a CR/CRi rate of 32%, an overall response rate (ORR) of 48%, and a 6-month survival of 42%, supporting the benefit of Venetoclax-based combinations in high-risk patients.

A lower incidence of severe adverse events was observed with Venetoclax plus azacitidine compared with Venetoclax plus decitabine. Although both regimens are viable, azacitidine-based combinations demonstrated superior safety and tolerability, supporting their use in patients unfit for intensive chemotherapy (6).

These results are consistent with previous studies, including the VIALE-A trial, which reported higher CR rates (66.4% vs 28.3%) and longer median OS (14.7 months) with Venetoclax plus azacitidine compared with azacitidine alone, findings comparable to those reported by

Fukumoto et al. (2023) (8). High response rates have also been observed in elderly populations treated with this combination (14).

In contrast, Venetoclax combined with decitabine showed lower remission rates and a higher frequency of adverse events, including thrombocytopenia and pulmonary infections, limiting its applicability in certain subgroups (6,7,13). These differences highlight the importance of selecting the appropriate hypomethylating agent based on patient characteristics and treatment tolerability.

This study has limitations related to the heterogeneity of included study designs, populations, and inclusion criteria, which may affect comparability and limit definitive conclusions. However, this heterogeneity reflects real-world clinical practice and enhances the external applicability of the findings.

Strengths of this review include the inclusion of diverse patient populations and real-world data, as well as the integration of randomized and observational studies, providing a comprehensive assessment of Venetoclax-based combinations in relapsed or refractory AML.

Clinically, Venetoclax combined with hypomethylating agents, particularly azacitidine, represents a valuable therapeutic option for patients unfit for intensive therapy. Further research should focus on identifying predictive biomarkers, including genetic subgroups such as FLT3-ITD, and on evaluating long-term survival and quality-of-life outcomes (4).

CONCLUSION

This study provides robust evidence on the efficacy and safety of Venetoclax in combination with hypomethylating agents in the treatment of relapsed or refractory AML. Combinations with azacitidine proved to be superior in terms of remission rates and adverse effects compared to decitabine, suggesting that this combination should be considered as a first-line option in these patients. Future research should focus on optimizing patient selection and addressing remaining questions about the long-term impact of these therapies, as well as exploring new combinations that could improve outcomes in AML patients and other hematologic malignancies.

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