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ARTICLE

Effects of Venetoclax Combined with Azacitidine on the Immune Function and Quality of Life in Patients with Relapsed Acute Myeloid Leukemia

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Abstract

Aims/Background Patients with relapsed acute myeloid leukemia (AML) have a poor prognosis and limited treatment options. The combination of azacitidine and venetoclax has demonstrated some efficacy in relapsed AML. This study aimed to investigate the effects of venetoclax combined with azacitidine on immune function and quality of life in patients with relapsed AML.

Methods This study retrospectively analyzed the clinical data of 104 patients with relapsed AML who were admitted to the First People's Hospital of Fuyang from January 2020 to January 2024. The patients were divided into a combination group (n = 53, treated with a combination of venetoclax and azacitidine) and an azacitidine group (n = 51, treated with azacitidine) according to the treatment protocol. Hematological parameters (proportion of bone marrow progenitor cells [PBMPC], white blood cell count [WBC], platelet count [PLT], neutrophil count [NEUT], and hemoglobin [Hb]), serum immunoglobulin (immunoglobulin G [IgG], IgA, and IgM) and inflammatory factor (interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]) levels, as well as European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) scores were compared between the two groups, and adverse reactions were recorded.

Results The remission rate in the combination group (66.0%) was significantly higher than that in the azacitidine group (45.1%, $p < 0.05$). Both azacitidine monotherapy and the combination therapy with venetoclax improved hematological indicators and quality of life while reducing serum immunoglobulin levels and inflammatory factors. Compared with the azacitidine group, the combination group demonstrated a significant reduction in PBMPC ($p < 0.05$), alongside an increase in WBC, PLT, NEUT, and Hb ($p < 0.05$). Additionally, combination therapy led to a greater reduction in serum levels of IgG, IgA, IgM, IL-6, and TNF-α compared to azacitidine alone ($p < 0.05$). Moreover, combination therapy significantly improved scores for physical, emotional, cognitive, social function, and general health status ($p < 0.05$), while reducing scores for nausea, dyspnea, insomnia, pain, and constipation ($p < 0.05$). Importantly, there was no significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$).

Conclusion The combination of venetoclax and azacitidine could regulate the immune function, improve hematological indicators and quality of life, without increasing the incidence of adverse reactions in patients with relapsed AML.

Key words: venetoclak; azacitidine; relapsed acute myeloid leukemia; immune function; quality of life

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Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy, accounting for approximately 80% of acute leukemia cases (Chaurasiya et al, 2023). AML has a rapid onset, with clinical manifestations such as fever, bleeding, and anemia (Pelcovits and Niroula, 2020). Despite major advances in AML treatment, the prognosis remains poor, and many patients still face a high risk of relapse after remission. Reports indicate that approximately 40–50% of younger AML patients and the majority of elderly patients experience relapse (Thol and Ganser, 2020). AML relapse compromises treatment efficacy and leads to poor outcomes. Statistics show that the three-year survival rate of relapsed AML patients after hematopoietic stem cell transplantation is around 20–30% (Leotta et al, 2022).

Relapse in AML is associated with animmune function imbalance (Sauerer et al, 2023). Williams et al (2019) compared immune cell phenotypes in bone marrow between newly diagnosed and relapsed AML patients, revealing that programmed cell death protein 1 (PD1) expression in cluster of differentiation 8 positive ($CD8^+$) T cells was higher in patients with multiple relapses than in those newly diagnosed. Additionally, compared to AML patients in remission, the proportion of $CD8^+CD28^+$ T cells in the peripheral blood of refractory/relapsed AML patients was lower, while the proportion of $CD8^+CD57^+$ and $CD8^+CD28^-CD57^+$ T cells increased (Tang et al, 2020). Furthermore, serum levels of immunoglobulin A (IgA) were found to be lower in relapsed pediatric AML patients compared to those in remission (Bansal et al, 2014).

The quality of life in patients with relapsed AML is also an important consideration in treatment strategies, as different therapies can significantly impact the quality of life of patients (Yan et al, 2022). Venetoclax, a highly selective oral small-molecule inhibitor of B-cell lymphoma-2 (Bcl-2), inhibits the anti-apoptotic protein Bcl-2 and has promising therapeutic effects on malignant tumors (Pollyea et al, 2019). Azacitidine (AZA), when combined with venetoclax, synergistically inhibits the pro-survival proteins myeloid cell leukemia 1 (MCL1) and B-cell lymphoma-extra large (Bcl-XL), inducing apoptosis in AML cells (DiNardo et al, 2020; Jin et al, 2020). Clinical studies have shown that the combination of venetoclax and the demethylating agent AZA has therapeutic potential in patients with refractory/relapsed AML (Aldoss et al, 2018).

However, there are limited studies on the effects of venetoclax combined with AZA on immune function and quality of life in patients with relapsed AML. Therefore, this study aimed to investigate the impact of venetoclax combined with AZA on immune function and quality of life in relapsed AML patients, providing a reference for evaluating the efficacy and prognosis of this combination therapy.

Methods

General Information

The clinical data of 104 relapsed AML patients who received treatment at the First People's Hospital of Fuyang from January 2020 to January 2024 were retrospectively analyzed. Based on the treatment regimens, patients were divided into

two groups: the combination group (n = 53), treated with venetoclax and azacitidine, and the azacitidine group (n = 51), treated with azacitidine alone. General patient information, including age, gender, French-American-British (FAB) classification, number of relapses, prognostic risk stratification, and prior chemotherapy before relapse, was collected. This study was approved by the Ethics Committee of the First People's Hospital of Fuyang (2024-LW-075), and all procedures complied with the Declaration of Helsinki. All patients provided informed consent.

Inclusion criteria were: (1) patients meeting the diagnostic criteria of AML (Arber et al, 2016) with confirmation through bone marrow cytomorphology and molecular tests; (2) patients meeting the definition of relapsed AML, characterized by a 5% or greater increase in proportion of bone marrow progenitor cells (PBMPC) after achieving complete remission (CR) (Leukemia and Lymphoma Group of the Hematology Branch of the Chinese Medical Association, 2021); and (3) completeness of clinical information. Exclusion criteria included: (1) presence of other hematologic diseases; (2) expected survival time of less than two months; (3) coexisting severe diseases such as central nervous system disorders, liver and kidney dysfunction, or cardiovascular and cerebrovascular diseases; (4) incomplete clinical information; and (5) patients who did not receive azacitidine or venetoclax treatment. Fig. 1 showed the flow of patient selection.

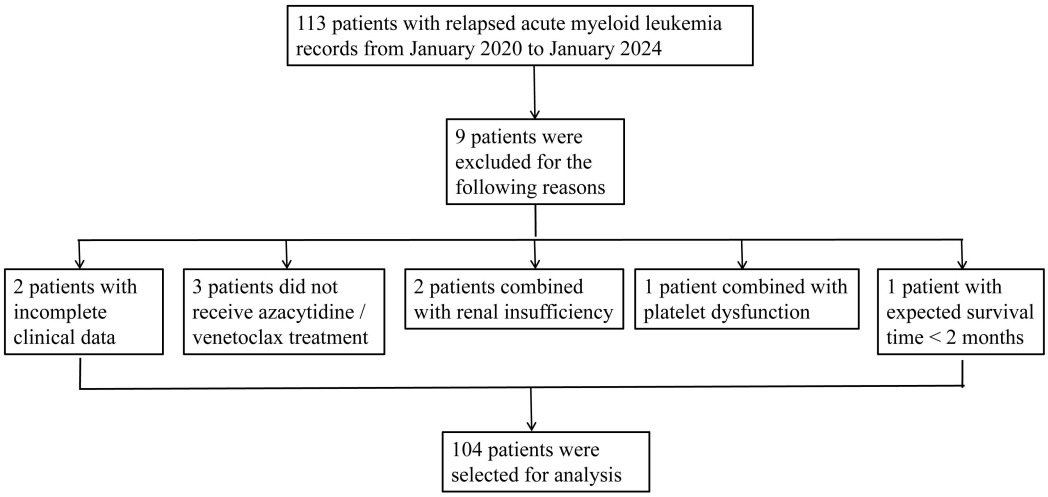

Fig. 1. The flowchart for patient selection.

Treatment

The azacitidine group was treated with azacitidine. Patients in this group received subcutaneous injections of azacitidine (Zhengda Tianqing Group, H20193278, Nanjing, China) at a dose of 75 mg/m^2. The treatment course lasted for 28 days, with azacitidine injections administered on days 1–7 and discontinued on days 8–28. Two treatment courses were given in total.

Patients in the combination group received a combination of venetoclax and azacitidine. In addition to azacitidine treatment, patients took a single daily oral dose of venetoclax (AbbVie Ireland NL B.V., HJ20200054, Sligo, Ireland). Each

treatment course lasted 28 days, with a total of 2 courses administered. During the first treatment course, the oral dose of venetoclax started at 100 mg on day 1, increased to 200 mg on day 2, and was further increased to 400 mg on day 3. The daily dose was maintained at 400 mg for the remainder of the course. In the second treatment course, the oral dose was consistently maintained at 400 mg, without a gradient increase. After each treatment course, bone marrow assessments were performed to guide subsequent dosing.

During treatment, patients received symptomatic care. Platelet transfusions were administered if the platelet count (PLT) fell below 20×10^9/L. If the hemoglobin (Hb) level dropped below 60 g/L, leukocyte-depleted red blood cell suspension was infused. Symptomatic treatment also addressed other reactions, such as infections and gastrointestinal side effects. Enhanced nutritional support and mental health interventions were provided to patients throughout the treatment period.

Efficacy Evaluation

The efficacy of treatment was assessed using remission rate criteria (Döhner et al, 2017). Complete remission (CR) was defined as having a PBMPC of $\leq$5% with the disappearance of clinical symptoms. Partial response (PR) was characterized by partial relief of clinical symptoms and a PBMPC of 5%–20%. No response (NR) was indicated by the persistence of clinical symptoms and a PBMPC of $>$20%. The remission rate was also calculated [remission rate = (CR + PR)/total cases].

Indicators of Detection

A range of indicators was collected from patients before and after treatment, including PBMPC, white blood cell count (WBC), PLT, neutrophil count (NEUT), Hb, immunoglobulins (IgG, IgA, and IgM), and inflammatory factors (interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]). The European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) scale was employed to assess patients' quality of life before and after treatment. Additionally, adverse reactions were monitored and recorded, including gastrointestinal symptoms (vomiting, nausea), lung infections, and hematologic effects.

Routine Blood Tests

Fasting venous blood was collected from patients both before and after treatment. A blood cell analyzer (BC760CS, Myriad, Shenzhen, China) was used to analyze PBMPC, WBC, PLT, NEUT, and Hb.

Detection of Immunoglobulins and Inflammatory Factors

Immunoglobulin levels were measured using an immunoturbidimetric assay. Serum levels of IgA, IgG, and IgM were assessed according to the instructions provided with the kit (TW Reagent, Shanghai, China). Inflammatory factors, including IL-6 and TNF-α, were measured using an enzyme-linked immunosorbent assay (ELISA) (Beijing Xinbosheng Biotechnology, Beijing, China).

Quality of Life

The EORTC QLQ-C30 scale was used to evaluate patients' quality of life before and after treatment (Efficace et al, 2019). This scale comprises 15 components, including 5 functional scales (Physical, Emotional, Cognitive, Social, and Role Function), 9 symptom scales (Fatigue, Nausea, Dyspnea, Insomnia, Pain, Cough, Diarrhea, Constipation, and Financial Impact), and a General Health Condition scale. Each scale is scored from 0 to 100 points. For the General Health Condition scale and functional scales, a higher score indicates better functionality; for the symptom scales, a higher score reflects more severe symptoms. Patients completed the scale based on their experiences, and scores were calculated by researchers.

Statistical Analysis

All data were statistically analyzed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed using the Shapiro-Wilk test. Measurement data with a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), and statistical differences between groups were determined using the *t*-test. For data not following a normal distribution, results were presented as median values with interquartile ranges, and the Mann-Whitney U test was applied. Categorical data were expressed as percentages (%), and differences between groups were analyzed using the chi-square test. A p-value of <0.05 was considered indicative of statistical significance.

Results

Comparison of General Information between Two Groups

There were 51 patients in the azacitidine group, comprising 29 males and 22 females, with a mean age of 63.61 ± 13.96 years. The combination group included 53 patients, with 27 males and 26 females, and a mean age of 68.09 ± 13.99 years. There was no statistically significant difference between the two groups in terms of general information ($p > 0.05$, Table 1), indicating that the groups were comparable.

Comparison of Clinical Efficacy between the Two Groups

In the azacitidine group, 3 patients achieved CR and 20 patients achieved PR, resulting in a remission rate of 45.1%. In the combination group, 6 patients achieved CR and 29 patients achieved PR, leading to a remission rate of 66.0%. This remission rate was significantly higher than that observed in the azacitidine group ($p < 0.05$) (Table 2).

Comparison of Hematological Indexes between the Two Groups

Compared to before treatment, the PBMPC was significantly reduced in both groups after treatment ($p < 0.05$), and WBC, PLT, NEUT, and Hb were significantly increased ($p < 0.05$). There was no significant difference in PBMPC, WBC, PLT, NEUT, and Hb between the two groups before treatment ($p > 0.05$). After treatment, PBMPC was significantly lower in the combination group compared to the azacitidine group ($p < 0.05$), and WBC, PLT, NEUT, and Hb were significantly higher ($p < 0.05$) (Table 3).

Table 1. Comparison of general information of the two groups.

Clinical information	Azacytidine group (n = 51)	Combination group (n = 53)	t/χ^2	p
Age (Year)	63.61 ± 13.96	68.09 ± 13.99	–1.634	0.105
Gender			0.366	0.545
Female	22	26		
Male	29	27		
FAB classification			1.734	0.785
M1	13	10		
M2	26	25		
M4	5	8		
M5	5	7		
M6	2	3		
Receiving chemotherapy before relapse			0.123	0.726
Yes	32	35		
No	19	18		
Number of relapses			1.007	0.316
1	35	41		
2	16	12		
Prognostic stratification			0.131	0.988
High risk	17	16		
Moderate risk	22	24		
Low risk	9	10		
Unknown	3	3		

Note: FAB, French-American-British.

Table 2. Comparison of remission rates between the two groups [n (%)].

Group	CR	PR	NR	Remission rate
Azacytidine group (n = 51)	3 (5.9%)	20 (39.2%)	28 (54.9%)	23 (45.1%)
Combination group (n = 53)	6 (11.3%)	29 (54.7%)	18 (34.0%)	35 (66.0%)
χ^2				4.620
p				0.032

Note: CR, complete remission; PR, partial response; NR, no response.

Comparison of Immune Function between Two Groups

There was no significant difference in the levels of serum immunoglobulins (IgG, IgA, and IgM) and inflammatory factors (IL-6 and TNF-α) between the two groups before treatment ($p > 0.05$). After treatment, the levels of IgG, IgA, IgM, IL-6, and TNF-α were significantly decreased in both groups compared to before treatment ($p < 0.05$). Additionally, the levels of IgG, IgA, IgM, IL-6, and TNF-α were significantly lower in the combination group compared to the azacitidine group ($p < 0.05$) (Table 4).

Table 3. Comparison of hematological indices between the two groups.

Group	PBMPC (%)[&]		WBC (10^9/L)		PLT (10^9/L)		NEUT (10^9/L)		Hb (g/L)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Azacytidine group (n = 51)	25.30 (24.20, 26.40)	20.10 (12.60, 21.70)*	2.74 ± 1.12	4.85 ± 1.36*	64.35 ± 7.12	170.23 ± 9.34*	1.91 ± 0.52	2.58 ± 0.95*	80.23 ± 7.98	90.25 ± 4.99*
Combination group (n = 53)	25.70 (24.15, 27.15)	8.70 (6.10, 20.65)*	2.89 ± 0.27	6.52 ± 1.02*	63.54 ± 7.45	218.36 ± 6.38*	1.84 ± 0.15	3.05 ± 1.02*	79.35 ± 5.56	95.22 ± 5.23*
t/Z	–1.002	–3.789	0.947	–7.102	0.566	–30.788	0.940	–2.429	0.655	–4.955
p	0.317	<0.001	0.346	<0.001	0.572	<0.001	0.349	0.017	0.514	<0.001

Note: *$p < 0.05$ compared with before treatment. [&]The data was represented in medium with interquartile ranges, and Mann-Whitney U test was utilized. PBMPC, proportion of bone marrow progenitor cells; WBC, white blood cell count; PLT, platelet count; NEUT, neutrophil count; Hb, hemoglobin.

Table 4. Comparison of immunoglobulin and inflammatory factor levels between the two groups ($\bar{x} \pm s$).

		Azacytidine group (n = 51)	Combination group (n = 53)	t	p
IgG (g/L)	Before	12.69 ± 0.93	12.65 ± 1.22	0.188	0.852
	After	9.12 ± 1.01*	8.26 ± 0.95*	4.474	<0.001
IgA (g/L)	Before	3.36 ± 0.38	3.29 ± 0.56	0.743	0.459
	After	1.68 ± 0.16*	1.52 ± 0.25*	3.871	<0.001
IgM (g/L)	Before	1.20 ± 0.30	1.19 ± 0.21	0.198	0.844
	After	0.89 ± 0.15*	0.78 ± 0.16*	3.614	<0.001
IL-6 (pg/mL)	Before	3.45 ± 0.68	3.58 ± 0.36	–1.225	0.223
	After	1.40 ± 0.22*	1.16 ± 0.51*	3.095	0.003
TNF-α (pg/mL)	Before	221.58 ± 8.78	220.43 ± 9.54	0.639	0.524
	After	138.25 ± 7.89*	95.56 ± 6.52*	30.126	<0.001

Note: *$p < 0.05$ compared with before treatment. Ig, immunoglobulin; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

Comparison of Quality of Life between the Two Groups

After treatment, the scores for physical function, emotional function, cognitive function, social function, role function, and general health condition in both groups were significantly higher than before treatment ($p < 0.05$). Additionally, scores for fatigue, nausea, dyspnea, insomnia, pain, appetite loss, diarrhea, constipation, and financial difficulties were significantly lower than before treatment ($p < 0.05$). The combination group showed significantly higher scores for physical function, emotional function, cognitive function, social function, and general health condition compared to the azacitidine group ($p < 0.05$). Furthermore, the combination group had significantly lower scores for nausea, dyspnea, insomnia, pain, and constipation compared to the azacitidine group ($p < 0.05$) (Table 5).

Comparison of Adverse Reactions between Two Groups

In the azacitidine group, 2 patients developed lung infections, 10 patients experienced nausea and vomiting, 10 patients had constipation, 7 patients had diarrhea, 2 patients developed thrombocytopenia, and 4 patients developed anemia, resulting in a total incidence rate of 68.6%. In the combination group, 1 patient developed a lung infection, 13 patients experienced nausea and vomiting, 9 patients had constipation, 8 patients had diarrhea, 1 patient developed thrombocytopenia, and 3 patients developed anemia, with a total incidence rate of 66.0%. There was no statistically significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$) (Table 6).

Discussion

Relapse is a major obstacle for AML patients following initial treatment. Relapsed AML patients generally experience poor outcomes and lack standard treatment options (Thol and Ganser, 2020). Currently, demethylating drugs such as azacitidine and decitabine are primarily used for treating relapsed AML, but their efficacy remains unsatisfactory (Petit et al, 2024). A retrospective study reported

Table 5. Comparison of EORTC QLQ-C30 scores between the two groups ($\bar{x} \pm s$).

		Azacytidine group (n = 51)	Combination group (n = 53)	*t*	*p*
Physical function	Before	52.94 ± 8.38	53.08 ± 8.71	–0.083	0.934
	After	56.14 ± 7.69*	61.04 ± 7.12*	–3.353	0.001
Emotional function	Before	53.10 ± 8.15	54.34 ± 7.62	–0.802	0.425
	After	57.00 ± 8.25*	63.38 ± 8.05*	–3.992	<0.001
Cognitive function	Before	64.20 ± 6.79	65.23 ± 8.10	–0.701	0.485
	After	70.25 ± 7.52*	77.72 ± 7.79*	–4.972	<0.001
Social function	Before	50.00 ± 9.44	50.66 ± 8.15	–0.382	0.703
	After	55.24 ± 8.88*	62.91 ± 7.66*	–4.722	<0.001
Role function	Before	41.12 ± 8.83	40.08 ± 7.58	0.645	0.520
	After	45.88 ± 7.67*	48.94 ± 9.03*	–1.859	0.066
General healthy condition	Before	61.06 ± 7.65	60.13 ± 7.44	0.629	0.531
	After	65.33 ± 8.69*	72.53 ± 8.19*	–4.350	<0.001
Fatigue	Before	52.14 ± 7.90	52.30 ± 7.59	–0.105	0.916
	After	48.84 ± 8.34*	46.38 ± 8.78*	1.464	0.146
Nausea	Before	33.02 ± 6.89	32.94 ± 6.24	0.062	0.951
	After	28.10 ± 5.35*	22.79 ± 6.48*	4.547	<0.001
Dyspnea	Before	39.14 ± 3.19	38.17 ± 4.38	1.287	0.201
	After	34.29 ± 2.38*	30.25 ± 5.05*	5.185	<0.001
Insomnia	Before	38.25 ± 5.21	37.53 ± 6.02	0.651	0.516
	After	33.04 ± 6.91*	28.64 ± 6.09*	3.448	0.001
Pain	Before	31.92 ± 7.02	32.34 ± 6.89	–0.308	0.759
	After	25.08 ± 7.76*	22.04 ± 6.66*	2.147	0.034
Appetite loss	Before	35.29 ± 6.95	35.64 ± 6.22	–0.271	0.787
	After	30.14 ± 7.89*	27.85 ± 6.79*	1.588	0.115
Diarrhea	Before	19.96 ± 6.14	21.04 ± 5.90	–0.915	0.362
	After	17.41 ± 3.69*	15.45 ± 6.05*	1.985	0.050
Constipation	Before	24.57 ± 6.00	24.51 ± 4.62	0.057	0.954
	After	20.96 ± 6.60*	16.77 ± 2.38*	4.339	<0.001
Financial difficulties	Before	60.76 ± 8.76	62.00 ± 9.95	–0.674	0.502
	After	55.00 ± 8.92*	52.28 ± 8.87*	1.559	0.122

Note: $^*p < 0.05$ compared with before treatment. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life.

that the remission rate for demethylating drugs in relapsed/refractory AML patients was only 11%, with an overall survival of just 7 months (Stahl et al, 2018). Thus, there is a pressing need to explore more effective therapeutic strategies for relapsed AML.

In this study, we explored the efficacy of the combination of venetoclax and azacitidine for relapsed AML patients. Our results showed that 6 patients in the combination group achieved CR, and 29 cases reached PR, with a remission rate of 66%. This was more efficacious than treatment with azacitidine alone. Changes in hematological indices showed the positive effect of combination therapy in re-

Table 6. Comparison of the adverse reactions between the two groups [n (%)].

Group	Lung infection	Nausea and vomiting	Constipation	Diarrhoea	Thrombocy-topenia	Anemia	Total
Azacytidine group (n = 51)	2 (3.9%)	10 (19.6%)	10 (19.6%)	7 (13.7%)	2 (3.9%)	4 (7.8%)	35 (68.6%)
Combination group (n = 53)	1 (1.9%)	13 (24.5%)	9 (17.0%)	8 (15.1%)	1 (1.9%)	3 (5.7%)	35 (66.0%)
χ^2							0.079
p							0.778

lapsed AML patients. A previous study reported that after azacitidine and vinpocetine combination therapy, approximately 30% of patients with refractory/relapsed AML achieved CR, and 20% achieved PR (Aldoss et al, 2018). In contrast, another retrospective study reported an efficacy rate of approximately 37% for the combination of venetoclax and azacitidine in refractory/recurrent AML patients (Garciaz et al, 2022). The differences in treatment efficacy between our study and previous reports may be attributed to variations in patient populations. Our study focused exclusively on recurrent AML patients and did not include refractory AML cases. Due to the lack of large prospective clinical trials to support the combined use of venetoclax and azacitidine for relapsed AML patients, our findings suggest that this combination therapy shows promise.

In our study, some patients reported adverse events, including pulmonary infections, hematologic side effects (such as thrombocytopenia and anemia), nausea, vomiting, and gastrointestinal reactions (such as diarrhea and constipation). Nausea, vomiting, and gastrointestinal issues were the most common adverse events. There was no significant difference in the frequency of adverse effects between the two groups, suggesting that combination therapy does not increase the risk of adverse events in relapsed AML patients. Furthermore, symptomatic treatment was promptly administered to patients who experienced adverse reactions, and all symptoms resolved.

A previous report documented adverse events in various systems following treatment with venetoclax plus azacitidine and donor lymphocyte infusion in relapsed AML patients (Zhao et al, 2022). Common adverse events in the hematologic system include anemia, agranulocytosis, and thrombocytopenia (Zhao et al, 2022). These adverse reactions are consistent with those observed in our study. The combination of azacitidine and venetoclax often leads to hematological toxicity, as noted in previous studies (Garciaz et al, 2022; Pollyea et al, 2021). It is crucial to monitor for adverse reactions during treatment and provide symptomatic management in a timely manner.

AML cells evade and inhibit the immune system through various immune evasion mechanisms, leading to an imbalance in the immune system of affected patients (Bindea et al, 2014; Vago and Gojo, 2020). Relapse in AML patients is also strongly associated with changes in the immune system (Tang et al, 2020). Immunoglobulins play a role in the proliferation, migration, and apoptosis of AML

cells (Wu et al, 2020). High levels of immunoglobulins are associated with shorter overall survival in AML patients (Wu et al, 2020). Our study demonstrated that immunoglobulin levels in relapsed AML patients decreased following treatment, with the combination of venetoclax and azacitidine showing superior efficacy compared to azacitidine alone.

Inflammatory factors can bind to specific receptors and regulate cell growth, differentiation, and immune responses. TNF-α, a key pro-inflammatory cytokine, is secreted by immune cells such as macrophages, T lymphocytes, and monocytes. The production of pro-inflammatory cytokines like TNF-α and IL-6 can stimulate the differentiation and proliferation of AML cells (Karimdadi Sariani et al, 2021). In our study, combination treatment reduced serum levels of IL-6 and TNF-α in relapsed AML patients. This suggests that the combination of azacitidine and venetoclax can improve immune function imbalance in relapsed AML patients, with a greater effect than azacitidine alone.

Previous study also reported the impact of azacitidine and venetoclax on the immune system of AML patients. For example, increased lymphocyte percentages were observed in AML patients following treatment with azacitidine and venetoclax, with natural killer (NK) cell frequency peaking after the second cycle, indicating an influence on the immune system (Giudice et al, 2021). Lee et al (2021) found that azacitidine and venetoclax enhance T-cell effector function, increasing their cytotoxicity against AML. While our study did not specifically explore the effects of combination therapy on immune cells, changes in immune factors and immunoglobulins suggest that the combination therapy has a regulatory effect on the immune system.

Improving quality of life is a crucial goal in the treatment of relapsed AML. AML patients often experience a reduced quality of life, characterized by diminished physical function, increased fatigue, and a decreased ability to perform daily activities (Granroth et al, 2022; Mamolo et al, 2019). Previous study has indicated that the combination of venetoclax and azacitidine positively impacts the quality of life in elderly and unfit AML patients undergoing intensive chemotherapy; the combination has been shown to improve general health condition scores in a higher proportion of patients compared to azacitidine alone (Pratz et al, 2022).

In our study, the combination of venetoclax and azacitidine also enhanced the quality of life in relapsed AML patients. This was evidenced by a significant increase in EORTC QLQ-C30 functional scale scores and a significant decrease in symptom scale scores, aligning with findings from previous research. Moreover, the combination therapy proved more effective than azacitidine alone in improving the quality of life for relapsed AML patients.

However, this study has limitations, including its retrospective design and small sample size. Our conclusions need to be validated through larger sample sizes and randomized controlled trials. Additionally, the study was constrained by a short follow-up period, and future research should focus on long-term outcomes for AML patients.

Conclusion

In conclusion, the combination therapy of venetoclax and azacitidine effectively regulates immune function, improves hematological indicators, and enhances the quality of life in relapsed AML patients. Furthermore, this combination therapy does not increase adverse reactions compared to treatment with azacitidine alone. Our research suggests that this combination therapy is a promising and effective treatment for relapsed AML, potentially supporting its broader clinical application.

Key Points

- Relapsed AML patients often face a lack of effective treatment options and a poor prognosis. The combination therapy of venetoclax and azacitidine demonstrated significant efficacy in these patients, achieving a remission rate of 66%.
- The relapse of AML is associated with an imbalance in immune function. The combination therapy effectively alleviates inflammatory responses in relapsed AML patients.
- The combination therapy of venetoclax and azacitidine improves the quality of life for patients with relapsed AML.
- The combination therapy of venetoclax and azacitidine does not increase the incidence of adverse reactions in relapsed AML patients.

Availability of Data and Materials

The data of this study are available from the corresponding author upon reasonable request.

Author Contributions

YFW, WZS and HYH designed the research. HYH and AWW performed the experiments. YFW and WZS analyzed the data. YFW made the first draft. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study has been approved by the Ethics Committee of the First People's Hospital of Fuyang (No.2024-LW-075), all programs complied with the Declaration of Helsinki, all patients gave informed consent for this study.

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Conflict of Interest

The authors declare no conflict of interest.

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