Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 6
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

The Effect of Venetoclax Combined with Azacitidine on the Clinical Efficacy, Immune Function, and Adverse Reactions in Elderly Patients with Acute Myeloid Leukemia

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Abstract: *Objective*: To evaluate the immune function and safety of Venetoclax combined with Azacitidine in the treatment of elderly patients with acute myeloid leukemia (AML). *Methods*: Sixty-eight elderly AML patients who visited the hospital from January 2021 to December 2024 were selected as samples and randomly divided into two groups. Group A was treated with Venetoclax and Azacitidine, while Group B was treated with Azacitidine alone. Immune indicators, inflammatory factors, tumor markers, and adverse reactions were compared between the two groups. *Results*: The levels of CD3+, CD4+, and CD8+ in Group A were higher than those in Group B ($P < 0.05$). The tumor necrosis factor-α (TNF-α) level in Group A was lower than that in Group B, while the interferon-γ (IFN-γ) level was higher ($P < 0.05$). The levels of cyclooxygenase-2 (COX-2), lactate dehydrogenase (LDH), and vascular endothelial growth factor (VEGF) in Group A were lower than those in Group B ($P < 0.05$). The adverse reaction rate in Group A was lower than that in Group B ($P < 0.05$). *Conclusion*: The combination of Venetoclax and Azacitidine in the treatment of elderly AML patients can improve immune function, inhibit inflammation, delay disease progression, and is safe and efficient.

Keywords: Acute myeloid leukemia; Venetoclax; Azacitidine; efficacy

Online publication: July 2, 2025

1. Introduction

AML is a malignant disease of the blood system that often occurs in the elderly population. It is related to factors such as organ degeneration, intolerance to chemotherapy, and comorbidities in the elderly population. Additionally, drug resistance of leukemic cells can affect the prognosis of AML [1]. Furthermore, many elderly AML patients have DNA methylation issues, so demethylating drugs such as Azacitidine should be selected, which can optimize patients' hematopoietic function and prolong their survival. However, the effect of monotherapy is limited. Bcl-

2 is a common analyte that regulates tumor cell apoptosis and is a target drug for modern diagnosis and treatment of leukemia. Venetoclax can inhibit Bcl-2, and its pharmacological components can activate T cells, block the formation of respiratory chain supercomplexes in the body, thereby increasing the amount of reactive oxygen species generated in the patient's body and enhancing T cell function [2]. Based on this, this study explores the efficacy of Venetoclax combined with Azacitidine using 68 elderly AML patients who visited the hospital from January 2021 to December 2024 as samples.

2. Materials and methods

2.1. Materials

Sixty-eight elderly AML patients who visited the hospital from January 2021 to December 2024 are selected as samples and randomly divided into two groups. The baseline data of elderly AML patients in Group A are compared with those in Group B ($P > 0.05$), as shown in **Table 1**.

Table 1. Baseline data analysis of elderly AML patients

Group	*n*	Gender (%)		Age (years)		Duration of illness (months)	
		Male	Female	Mean	Range	Mean	Range
Group A	34	20(58.82)	14(41.18)	66–87	77.28 ± 2.11	8–15	10.25 ± 1.43
Group B	34	21(61.76)	13(38.24)	66–88	77.31 ± 2.13	8–16	10.28 ± 1.45
X^2/t	-	0.0614		0.0583		0.0859	
P	-	0.8043		0.9536		0.9318	

2.2. Inclusion and exclusion criteria

The inclusion criteria are: (1) Meet the criteria for AML in the "Chinese Guidelines for the Diagnosis and Treatment of Adult Acute Myeloid Leukemia (Non-Acute Promyelocytic Leukemia)" [3]; (2) Signed informed consent; (3) Molecular, cytological, and blood routine tests suggest AML; (4) Newly diagnosed AML patients who are difficult to tolerate chemotherapy.

Meanwhile, the exclusion criteria includes: (1) History of demethylating agent treatment; (2) Cardiovascular and cerebrovascular diseases; (3) Central nervous system diseases.

2.3. Treatment methods

Group A is treated with Venetoclax tablets (produced by AbbVie Ireland NL B.V, National Medical Approval Number HJ20200054; 100mg) in combination. The doses for the first day, second day, and 3–28 days were 100mg, 200mg, and 400mg, respectively. Administration for 28 days is considered one treatment course. Regular monitoring of blood routine is performed during the treatment. Bone marrow puncture is repeated from day 21 to 28 of administration. In case of disease progression or severe side effects, the medication is stopped for monitoring. If Hb is less than 60g/L and PLT is less than 20X109/L, blood products are transfused.

Group B received Azacitidine (produced by Chia Tai Tianqing Pharmaceutical Group Co., Ltd., National Medical Approval Number H20193278, 100mg) via subcutaneous injection. The single dose is 75mg/m², administered for 7 days. Targeted hydration and alkalization adjuvant therapy are provided during the treatment. It is noted that after the initial administration, the white blood cell count of AML patients is monitored, and

appropriate amounts of hydroxyurea are given until the white blood cell count returns to normal.

2.4. Observation indicators

(1) Immune indicators: 5ml of venous blood was collected, and CD3+, CD4+, CD8+, and other detections were completed using a flow cytometer.

(2) Inflammatory factors: 5ml of venous blood was collected, and TNF-α, IFN-γ, and other detections were completed using enzyme-linked immunosorbent assay.

(3) Tumor markers: 5ml of venous blood was collected, and COX-2, LDH, VEGF, and other detections were completed using enzyme-linked immunosorbent assay.

(4) Adverse reactions: Abnormal liver function, gastrointestinal reactions, infections, and other morbidities in AML patients were recorded.

2.5. Statistical analysis

Data are processed using SPSS 21.0 software. Measurement data are recorded as $\bar{x} \pm s$ (t-test), and count data are recorded as percentages (X^2 test). Statistical significance is considered at $P < 0.05$.

3. Results

3.1. Immune indicators

After treatment, the levels of CD3+, CD4+, and CD8+ in elderly AML patients in Group A were higher than those in Group B ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of immune indicators in elderly AML patients ($\bar{x} \pm s$)

Group	CD3+(%)		CD4+(%)		CD8+(%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A (*n*=34)	51.28 ± 1.82	56.71 ± 2.46	36.28 ± 1.88	43.48 ± 2.48	21.38 ± 1.52	25.68 ± 1.88
Group B (*n*=34)	51.27 ± 1.79	54.36 ± 2.11	36.24 ± 1.91	39.53 ± 2.16	21.39 ± 1.53	23.22 ± 1.68
t	0.0228	4.2280	0.0870	7.0033	0.0270	5.6893
P	0.9818	0.0001	0.9309	0.0000	0.9785	0.0000

3.2. Inflammatory factor indicators

After treatment, the TNF-α level of elderly AML patients in Group A was lower than that in Group B, while the IFN-γ level was higher than that in Group B ($P < 0.05$), as shown in **Table 3**.

3.3. Tumor marker indicators

After treatment, the levels of COX-2, LDH, and VEGF in elderly AML patients in Group A were lower than those in Group B ($P < 0.05$), as shown in **Table 4**.

Table 3. Comparison of inflammatory factor indicators in elderly AML ($\bar{X}$ ±s)

Group	TNF-α(pg/ml)		IFN-γ(pg/ml)	
	Before treatment	After treatment	Before treatment	After treatment
Group A (*n*=34)	258.14 ± 3.87	86.49 ± 1.58	38.61 ± 1.82	74.29 ± 2.42
Group B (*n*=34)	258.19 ± 3.91	126.02 ± 2.09	38.59 ± 1.79	57.58 ± 2.03
t	0.0530	87.9755	0.0457	30.8467
P	0.9579	0.0000	0.9637	0.0000

Table 4. Comparison of tumor marker indicators in elderly AML ($\bar{X}$ ±s)

Group	COX-2(ng/L)		LDH(U/L)		VEGF(pg/ml)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A (*n*=34)	55.16 ± 2.17	35.17 ± 1.25	132.42 ± 3.29	105.43 ± 1.89	156.95 ± 5.26	76.14 ± 3.26
Group B (*n*=34)	55.19 ± 2.19	40.82 ± 1.68	132.39 ± 3.31	117.36 ± 2.43	156.99 ± 5.31	86.43 ± 4.29
t	0.0567	15.7329	0.0375	22.5967	0.0312	11.1357
P	0.9549	0.0000	0.9702	0.0000	0.9752	0.0000

3.4. Adverse reaction indicators

The adverse reaction rate of elderly AML patients in Group A was lower than that in Group B ($P < 0.05$), as shown in **Table 5**.

Table 5. Comparison of adverse reactions in elderly AML (n,%)

Group	Abnormal liver function	Gastrointestinal reaction	Infection	Incidence rate
Group A (*n*=34)	0(0.00)	1(2.94)	0(0.00)	1(2.94)
Group B (*n*=34)	1(2.94)	3(8.82)	2(5.88)	6(17.65)
X^2	-	-	-	3.9813
P	-	-	-	0.0460

4. Discussion

AML accounts for a relatively high proportion among the many pathological types of leukemia, and it predominantly affects the elderly population. Most patients have a poor prognosis. The main treatment option for AML is intensive chemotherapy. However, due to the weak physical functioning and poor tolerance to chemotherapy among elderly patients, issues such as poor prognosis and shortened lifespan may arise. Additionally, the immune function of elderly patients declines, leading to a reduction in T-cell production and higher treatment requirements. Elderly AML patients may experience problems such as increased adipose cells and decreased osteoblast count, which can affect the proliferation of leukemic cells. Coupled with the impact of chronic diseases, this can exacerbate inflammatory responses in the body. Therefore, it is crucial to explore effective management strategies for elderly AML patients [4].

Azacitidine is a commonly used drug for managing elderly AML. It exerts a demethylating effect, disrupting

the structure of deoxyribonucleic acid (DNA) in cancer lesions and inhibiting DNA repair and transcription processes. When used as prescribed, it can accelerate the differentiation of bone marrow cells and optimize the function of hematopoietic stem cells [5]. However, the efficacy of Azacitidine monotherapy in treating elderly AML is limited, and it is difficult to prolong patient survival. Venetoclax can inhibit Bcl-2, blocking the process of Bcl-2 binding to proteins. It can also activate cell signaling molecules, accelerate damage to the mitochondrial membrane, and induce tumor cell apoptosis [6]. Combining these drugs for the treatment of elderly AML can synergistically inhibit AML cell proliferation, enhance anti-tumor efficacy, and improve the prognosis of AML patients.

The active ingredient of Venetoclax can directly act on T-cells, enhancing the immune system's anti-leukemia efficacy. When combined with Azacitidine, it can increase the sensitivity of AML cells to T-cells. CD3+ represents an independent or endogenous immune response to malignant cells; CD4+ can reflect the peripheral homeostatic state and tolerance to self-antigens, while also suppressing harmful immune responses and even inhibiting tumor-specific T-cells; CD8+ provides feedback on the clearance of leukemia cells and stimulates the body to produce immune factors [7]. Data presented in this study shows that the levels of CD3+, CD4+, and CD8+ in Group A are higher than those in Group B, with $P < 0.05$. This indicates that Venetoclax combined with Azacitidine treatment can improve immune function in elderly AML patients. Another set of data shows that TNF-α is lower in Group A than in Group B, while IFN-γ is higher in Group A, with $P < 0.05$. TNF-α, which originates from the serum and bone marrow of elderly AML patients, reflects the level of inflammation. Excessively high levels of TNF-α in the body can activate the NF-κB signaling pathway, stimulate the activation of leukemia cells, inhibit hematopoietic stem cell proliferation, induce myelosuppression, damage the bone marrow microenvironment, and exacerbate AML.

Impaired immune function in elderly AML patients can reduce IFN-γ levels. IFN-γ has anti-tumor and anti-leukemia cell proliferation effects, and it can also enhance the activity of immune cells, delaying the progression of AML [8]. In this study, Azacitidine treatment is chosen based on its pharmacological mechanism, which can inhibit the production of proteins in lesions and bind to the DNA of lesion cells, generating 5-Aza-2'-deoxycytidine. This blocks the demethylation process in patients' bodies and inhibits tumor proliferation. However, the efficacy of Azacitidine alone may be weakened by tumor cell heterogeneity, especially in a few subtypes with gene mutations that can block Azacitidine's DNA generation and even methylation processes. Therefore, combination therapy with Venetoclax is necessary. The active ingredients of Venetoclax can accelerate tumor cell apoptosis, enhance the activity of cell apoptosis signals, damage tumor cell membranes, increase cell membrane permeability, activate caspases, and inhibit the body's release of inflammatory factors [9]. Additionally, the combination of Azacitidine and Venetoclax can inhibit oxidative damage to tumor cells and enhance anti-inflammatory effects.

C0X-2 belongs to the category of proteolytic enzymes, which are inducible and can participate in the regulation of tumor cell proliferation. VEGF, a growth factor with specificity, can accelerate the formation of blood vessels in tumor cells and promote their spread. LDH can block immune response, and abnormally elevated LDH levels suggest the spread and proliferation of cancer cells in elderly patients with AML. Based on the data analysis in this study, the levels of COX-2, LDH, and VEGF in Group A were lower than those in Group B ($P < 0.05$). This suggests that the combination therapy of Azacitidine and Venetoclax can inhibit tumor progression and delay the increase in tumor marker levels. In addition, Azacitidine exerts its effects on tumor cell DNA in elderly AML patients, inhibiting tumor proliferation through demethylation, thereby reducing COX-2 levels. The active ingredients of Venetoclax can bind to Bcl-2, specifically inhibiting the anti-tumor apoptosis pathway, damaging

and destroying tumor cell blood vessels, and accelerating vascular dissociation, thus reducing LDH and VEGF levels in elderly AML patients [10].

Furthermore, the synergistic effect of Azacitidine and Venetoclax allows for rapid and efficient regulation of tumor marker levels. The final set of data shows that the adverse reaction rate in Group A was lower than that in Group B ($P < 0.05$). The analysis suggests that the combined use of Azacitidine and Venetoclax, with complementary mechanisms of action, can inhibit the toxic effects of single high-dose drug administration, reduce toxicity to healthy cell tissues while enhancing tumor cell killing, and generate synergistic effects through Azacitidine's sensitization of tumor cells to apoptosis and Venetoclax's induction of apoptosis in tumor cells. Combined drug use can also improve the targeting of active ingredients, inhibit damage to the hematopoietic system caused by drug toxicity, and reduce the risk of bone marrow suppression. Additionally, different mechanisms of action can avoid the risk of drug resistance associated with single-drug administration, ensuring the safety of medication for elderly AML patients. However, this study included a limited number of elderly AML patients and did not explore the long-term efficacy of Azacitidine plus Venetoclax treatment across multiple centers. Future research should increase the number of elderly AML patients to ensure data reliability.

5. Conclusion

In summary, the combination therapy of Azacitidine and Venetoclax for elderly AML patients can improve immune function, inhibit inflammatory responses, and reduce tumor marker levels without increasing drug toxicity, making it a safe and effective treatment option.

Disclosure statement

The author declares no conflict of interest.

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