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Original Research Article

Venetoclax in combination with azacitidine or decitabine in relapsed/refractory acute myeloid leukemia

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Abstract

Purpose: *To investigate the clinical effects of venetoclax combined with azacitidine or decitabine in relapsed/refractory acute myeloid leukemia.*
Methods: *208 eligible first-line participants, who were diagnosed and treated for relapsed/refractory acute myeloid leukemia between January 2022 and December 2022, were recruited from the Department of Hematology of Loudi Central Hospital, China. The patients were randomly divided into study and control groups at the point of recruitment. Patients in the control group received venetoclax combined with decitabine, while those in the study group received venetoclax in combination with azacitidine. Clinical data for the two groups were recorded. The primary endpoints of this study included efficacy, routine blood indices, and adverse reactions.*
Results: *There was no statistically significant difference in baseline characteristics between the two groups ($p > 0.05$), indicating comparability. The total effectiveness of the treatment (i.e., efficacy) in the study group was higher than in the control group ($p < 0.05$), while the control group had a higher risk of platelet, red blood cell, and neutrophil absolute count reduction than the study group ($p < 0.05$). The platelet count and hemoglobin level were lower in the control group after treatment compared to the study group ($p < 0.05$).*
Conclusion: *The combination of venetoclax with azacitidine improves the efficacy and blood routine indices of patients with relapsed/refractory acute myeloid leukemia, while reducing adverse reactions.*

Keywords: *Venetoclax, Azacitidine, Decitabine, Relapsed/refractory acute myeloid leukemia*

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INTRODUCTION

Relapsed/refractory acute myeloid leukemia (AML) refers to a type of leukemia that relapses or is difficult to cure after a certain course of treatment. Typically, relapsed/refractory AML is defined as the presence of 20 % or more leukemia cells in the bone marrow after chemotherapy, or the reappearance of leukemia cells within weeks or months after treatment [1-3]. The clinical manifestations mainly include anemia, bleeding, infection, fever, weight loss,

and other symptoms. In the case of relapsed/refractory AML, the symptoms may be more severe, and relapse-related symptoms such as enlarged lymph nodes, bone marrow tumors, and hepatosplenomegaly may occur [4,5]. Venetoclax is an oral medication that targets B-cell lymphoma-2 (BCL-2) in cancer cells and promotes cancer cell apoptosis by inhibiting anti-apoptotic proteins. It is widely used to treat relapsed/refractory AML [6,7].

AML is a malignant disease that results from abnormal proliferation and differentiation of leukemia stem cells, leading to the appearance of abnormal leukemia cells in the blood. Venetoclax induces leukemia cell apoptosis by inhibiting the BCL-2 protein, thus reducing the number of leukemia cells. Therefore, venetoclax is considered an effective drug for treating AML. Azacitidine and decitabine are chemotherapy drugs commonly used to treat AML. Studies have shown that the combination of venetoclax with azacitidine or decitabine provides high treatment response rates and survival rates in patients with relapsed/refractory AML [8-10]. A prior study in 2018, reported a complete remission rate (CR) of 68 % for relapsed/refractory acute myeloid leukemia (AML) patients treated with the combination of venetoclax and azacitidine, along with a one-year overall survival rate of 75 % [11]. Another study in 2019, demonstrated a CR of 67 % for relapsed/refractory AML patients treated with the combination of venetoclax and decitabine, with a one-year overall survival rate of 47 % [12]. However, the combination of venetoclax with azacitidine or decitabine also has some side effects, such as thrombocytopenia, anemia, and infection.

Therefore, further research is needed to determine which approach is more suitable for the treatment of relapsed/refractory AML. This aims to investigate and examine the effects of venetoclax combined with azacitidine or decitabine in the management of the disease.

METHODS

Study subjects

In this study, a cohort of 200 patients diagnosed with AML and admitted to the Department of Hematology at Loudi Central Hospital between January 2022 and December 2022 was selected as the study population. Relevant demographic information, including gender, age, BMI, education level, and disease duration, was collected for each patient.

To ensure comparability between groups, the patients were randomly assigned to either a control group or a study group, with 100 patients in each group. It is worth noting that all patients included in the study exhibited no signs of immune dysfunction. The clinical data of the two groups showed comparability ($p < 0.05$).

Ethical approval

This study received ethical approval from the Institutional Review Board (IRB) of Loudi Central Hospital, with approval no. 2022-01-031, and followed international guidelines for human studies. The patients were fully informed about the study objectives, and their written consent were obtained prior to their participation.

Inclusion and exclusion criteria

Inclusion criteria

(1) Met the diagnostic criteria for MDS; (2) Age > 60 years; (3) Statisfied ECOG performance status < 2; (4) Patients who have received treatment for more than 4 cycles.

Exclusion criteria

(1) Recent use of the study drugs; (2) Patients with severe infections that cannot be controlled by anti-infective therapy; (3) Patients with other types of malignant tumors; (4) Patients with incomplete medical records.

Treatments

Control group

Patients in the control group were treated with venetoclax in combination with decitabine. Venetoclax was subjected to a brief dose escalation in cycle 1, starting from 20 mg (early cohorts of escalation stage) and reaching a daily target dose of 400 mg. All patients were hospitalized during venetoclax dose escalation in cycle 1 for a minimum of 3 to 5 days. Decitabine was administered intravenously at a dose of 20 mg/m^2 from days 1 - 5.

Study group

Patients in the study group were treated with venetoclax in combination with azacitidine. The administration of venetoclax was the same as that used in the control group. Azacitidine was administered subcutaneously at a dose of 75 mg/m^2 from days 1 - 7.

Evaluation of parameters/indices

Therapeutic effectiveness/efficacy

Detailed records of clinical efficacy for the two groups of patients were kept and evaluated based on the relevant criteria in the "Diagnosis and Therapeutic Efficacy Criteria for Hematological Diseases" [13]. Complete remission (CR) is defined as the complete disappearance of clinical symptoms and signs, and a bone marrow primitive cell ratio not exceeding 5 %; partial remission (PR) is defined as a significant improvement in symptoms and signs, with a bone marrow primitive cell ratio exceeding 5 % but decreased by half compared to the value before treatment; and no remission (NR) is defined as failure to meet the above criteria.

Adverse reactions

The adverse reactions experienced by patients were evaluated based on the World Health Organization's (WHO) grading criteria for acute and accelerated chemotherapy drugs, such as pulmonary infection, decreased red blood cells, decreased platelets, decreased absolute neutrophil count, and gastrointestinal reactions.
The determination of pulmonary infection involves several factors: (1) the presence of signs and symptoms consistent with pneumonia diagnosis, (2) a clinical setting that aligns with pneumonia acquisition, (3) host susceptibility factors that predispose individuals to pneumonia, and (4) exposure and risk factors associated with specific pathogens [14]. Decreased red blood cells were determined when a blood test shows a hemoglobin value of less than 13.5 gm/dl in a man or < 12.0 gm/dl in a woman [15].

Decreased platelets are determined when the platelet count falls below the lower limit of normal, i.e., 150000/microliter (for adults) [16].

Decreased absolute neutrophil count is determined when the absolute neutrophil count is less than 2,500 cells/mcL [17].

Common gastrointestinal symptoms include abdominal cramps, nausea, vomiting, and diarrhea.

Routine blood indicators

The routine blood indicators after treatment were compared between the two groups of patients, including platelet count and hemoglobin. Blood parameters, specifically platelet count and hemoglobin levels, were compared between the two patient groups following the treatment. Morning fasting blood (5 mL) was collected from the patients on the first day after treatment and centrifuged (1500 rpm/min) to collect the serum. The platelet count was measured using a hematology analyzer, while hemoglobin was determined by routine blood test.

Statistical analysis

Data organization and statistical analysis for this study were performed using SPSS 26.0 software. Measurement data were presented as mean (± standard deviation), and t-tests were utilized to evaluate statistically significant differences. Categorical data were expressed as percentages (%), and chi-square tests (χ^2) were employed to assess statistically significant differences. A *p*-value of <0.05 was considered indicative of statistical significance.

RESULTS

Baseline characteristics

There were no statistically significant differences between the two groups in baseline characteristics, including gender, age, and BMI, indicating comparability ($p > 0.05$), as shown in Table 1.

Efficacy

The study group exhibited a higher total treatment effectiveness rate in terms of clinical efficacy compared to the control group ($p < 0.05$), as shown in Table 2.

Adverse reactions

Table 3 illustrates that the control group had a higher incidence of decreased platelet, red blood cell, and neutrophil absolute values compared to the study group ($p < 0.05$).

Routine blood indices

Both the platelet count and hemoglobin index of patients in control group were lower after treatment compared to those in the study group ($p < 0.05$), as shown in Table 4.

DISCUSSION

With the population aging, the incidence of relapsed/refractory acute myeloid leukemia in the elderly population is also increasing year by year.

Table 1: Comparison of baseline data between the two groups (mean ± SD)

Variable		Control group	Study group	*t/x* ^{2}	*P*-value
No. of patients		100	100		
Gender	*Male*	66	68	0.412	1.058
	Female	34	32		
Age)	*Range*	60-75	60-77	0.231	1.323
	Mean	68.26±2.22	69.27±2.41		
BMI (kg/m ^{2})	*Range*	21.2-31.0	21.0-31.0	0.525	1.210
	Mean	25.09±1.13	25.28±1.09		
Education background	*College and below*	67	66	0.216	1.166
	Bachelor's degree or above	33	34		
Disease course (month)	*Mean±SD*	12-25 15.1±1.1	12-26 15.3±1.1	0.239	0.012

Table 2: Comparison of efficacy between the two groups (mean ± SD, n = 100)

Group	CR	PR	NR	Total effectiveness {N(%)}
Control	4	10	14	28 (28.00)
Study	8	18	24	50 (50.00)
t				2.635
P-value				< 0.05

CR: Compete remission; PR: Partial remission; NR: No remission

Table 3: Comparison of adverse reactions between the two groups [n (%)]

Group	No.	Thrombocytopenia	Decreased red blood cells	Lung infection	Digestive tract reaction
Control	100	16	11	6	4
Study	100	8	5	1	1
x2 –		1.689	1.116	1.232	1.857
p-value		<0.05	<0.05	<0.05	<0.05

Table 4: Comparison of routine blood indices between the two groups of patients (mean ± SD, n = 100)

Group	Platelet count (×10 ^{9} /L)	Hemoglobin (g/L)
Control	81.29±12.58	74.84±7.64
Study	89.95±15.34	88.35±5.96
t	2.649	1.166
P-value	< 0.01	< 0.01

Relapsed/Refractory Acute Myeloid Leukemia (RR-AML) refers to a type of acute myeloid leukemia that relapses or cannot be effectively controlled after chemotherapy or transplantation treatment [18]. RR-AML is attributed to genetic mutations in leukemia cells, the existence of leukemia stem cells, and resistance to treatment medications. These factors make patients refractory to traditional chemotherapy and radiotherapy, and it is difficult to completely cure [19]. Venclexta (Venclyxto) is an oral drug that inhibits the survival of leukemia cells by targeting the BCL-2 protein, thereby promoting the apoptosis of leukemia cells. Venclexta/Venclyxto was originally approved to treat chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

In recent years, Venclexta/Venclyxto has also made some progress in the treatment of relapsed/refractory acute myeloid leukemia (RR-AML). Clinical studies have shown that when Venclexta/Venclyxto is used in combination with chemotherapy drugs or other drugs, it improves the complete remission rate and survival rate of patients with RR-AML. Azacitidine and decitabine are commonly used chemotherapy drugs for the treatment of relapsed/refractory acute myeloid leukemia. Veneclaxa combined with azacitidine (Venclexta/Venclyxto and azacitidine, referred to as V+A scheme) is a new treatment scheme for RR-AML. Both venetoclax and azacitidine are oral or injectable drugs that inhibit the growth and proliferation of leukemia cells through different mechanisms [20].

Studies have shown that the complete remission rate (CR) of the V+A regimen in RR-AML patients is 71 %, and the safety and tolerability of this regimen are also well guaranteed. Venecla combined with decitabine (Venclexta/Venclyxto and Decitabine, referred to as V+D regimen) is a new type of regimen for the treatment of RR-AML. Studies have shown that the rate of

complete remission of V+D regimen in patients with RR-AML was as high as 64 %, and the safety and tolerability of the program were well guaranteed [21] . The results of the present study are similar. The total (overall) efficacy in the study group was higher than in the control group.

Azacitidine is a cytosine analogue that acts as a DNA methyltransferase (DN-MT) inhibitor. At low doses, it induces hypomethylation by depriving cells of DNMTs, leading to reactivation of tumor suppressor gene expression, and achieving the effect of killing tumor cells. After entering the human body, azacitidine is converted through the following two pathways: one is converted into azacitidine triphosphate and integrated into RNA, thereby inhibiting protein synthesis and producing cytotoxicity; the other is converted into diazepam triphosphate.

Tobine, acting on DNA, leads to DNA hypomethylation, manifested as inhibition of cell cycle arrest, differentiation and cytotoxicity 22]. Venecla improves the sensitivity of AML cells to azacitidine, and thus low doses of azacitidine can also exert a strong killing effect, thereby improving efficacy and reducing adverse reactions.

Limitations of the study

Limitations of the study include a single-center design, potentially limiting the generalizability of findings. The sample size, while substantial (200 patients), might benefit from expansion for increased statistical power. The relatively short follow-up period may not capture long-term outcomes adequately. Addressing these limitations in future research would enhance the study's comprehensiveness and applicability.

CONCLUSION

Venetoclax, when combined with azacitidine in the treatment of relapsed/refractory acute myeloid leukemia, enhances therapeutic efficacy, improves routine blood indices in patients, and lowers adverse reactions. However, due to factors such as the single-center nature of this study and the low sample size used, the research results will need to be validated in larger multicenter trials.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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