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Observation on the Clinical Effect of Applying Venetoclax Combined with Demethylation Drug Therapy in Patients with Acute Myeloid Leukemia

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Abstract: *Objective:* To investigate the therapeutic effect of applying venetoclax combined with demethylating drugs in treating patients with acute myeloid leukemia (AML). *Methods:* Eighty cases of AML patients treated with venetoclax combined with demethylating drugs in our hospital were selected from March 2021 to March 2024, including 40 cases of primary treatment patients and 40 cases of relapsed and refractory patients. The efficacy and safety of the combined drug therapy was analyzed. *Results:* The primary treatment group was presented with a complete remission (CR) rate of 40.5%, partial remission (PR) rate of 47.50%, no response (NR) rate of 12.50%, and a remission rate of 87.50%. The relapsed-refractory group was presented with a CR rate of 37.50%, PR rate of 42.50%, NR rate of 17.50%, and a remission rate of 87.50%. There was no statistical significance between the groups ($P > 0.05$). The hematological adverse reactions of the combined treatment for AML were leukopenia and the non-hematological adverse reactions were mainly infections, with an incidence rate of 87.50%. *Conclusion:* The efficacy of venetoclax combined with demethylating drugs in AML was remarkable and the treatment regimen can be adjusted according to the treatment-resistant response.

Keywords: Acute myeloid leukemia; Venetoclax; Demethylating drugs; Combination therapy; Efficacy

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1. Introduction

Acute myeloid leukemia (AML) is the abnormal differentiation, proliferation, and apoptosis of myeloid stem cells as a specific manifestation of hematologic malignant diseases, mainly affecting elderly patients. The desired efficacy cannot be achieved via conventional treatment, thus limiting its clinical application value. Hence, developing safe and efficient therapeutic drugs is crucial [1]. Acute myeloid leukemia research in China was carried out late, with a complex etiology and a low tolerance towards standard intensive induction chemotherapy tolerance, easily leading to chemotherapy comorbidities and other organ function damage. The combination of venetoclax and demethylation drugs was controversial, as this combination showed a high

response rate and safety. Furthermore, it can meet the treatment needs of elderly AML patients and improve the resistance to treatment [2]. Given this, 80 cases of AML patients were selected as study subjects to conduct a prospective analysis and observe the therapeutic effect of venetoclax combined with demethylating drugs.

2. Information and methods

2.1. General information

Eighty patients with AML treated with Venetoclax combined with demethylating drugs were selected from March 2021 to March 2024, of which 40 were primary patients and 40 were relapsed-refractory patients. The primary group consisted of 18 males and 22 females aged 29–79 years old, with an average of 65.77 ± 3.18 years. There were 36 patients with primary AML and 4 patients with secondary AML. The body mass index (BMI) was 19.5–35 kg/m^2, with an average of 22.85 ± 1.05 kg/m^2. The relapsed refractory group consisted of 20 males and 20 females aged 33–81 years old, with an average of 65.12 ± 3.04 years. There were 35 patients with primary AML and 5 patients with secondary AML. The BMI was 19–34.5 kg/m^2, with an average of 23.01 ± 1.12 kg/m^2. There was no difference in the general data of both groups ($P > 0.05$).

2.2. Methods

The selected patients were treated with venetoclax combined with demethylating drugs. The first combination was venetoclax and decitabine. Venetoclax was administered in a gradient, with an initial dose of 100 mg/d on the first day, 200 mg/d on the second day, and 400 mg/d on the third day. The maintenance dose of the drug was continued for 28 days. Decitabine was administered intravenously with an initial dose of 20 mg/(m^2/d), and platelet and hemoglobin indexes were observed during the period of medication. If the platelet (PLT) count is < 30 x 109/L and hemoglobin < 60 g/L, blood product infusion is performed. In cases of neutropenia, antimicrobial drug treatment was administered, whereas in cases of severe infection, the treatment was stopped entirely. The second combination was venetoclax with azacitidine. Venetoclax dosage was the same as above, and a drug dose of azacitidine 75 mg/(m^2/d) was injected intramuscularly, which was used continuously for 7 days. The selected patients were checked regularly for liver function, blood routine, uric acid, electrolytes, and other indexes during the medication period. If the results were abnormal, appropriate symptomatic treatment was performed.

2.3. Evaluation criteria

To assess the efficacy of 28-day AML medication in the two groups, the Diagnostic Guidelines for Adult Acute Myeloid Leukemia (2023 edition) was referred to [3]. CR was considered if PLT > 100 × 10^9/L, bone marrow primitive cell percentage < 5%, peripheral blood absolute neutrophil count (ANC) > 1.0 × 10^9/L, no Auer vesicles in the primitive cells, and no extramedullary leukemia. PR was considered if there was no abnormality of the peripheral blood cells and the bone marrow primitive cells were reduced by more than 50%. NR was considered if the above indications were not met. Remission rate = (CR + PR)/n × 100%. The observation of adverse drug reactions was conducted for 28 days of drug administration and medical follow-up.

2.4. Statistical analysis

Data were analyzed using the SPSS 26.0 software. The recent efficacy, adverse reactions, and other count data were expressed as *n* (%) and analyzed using a chi-squared (χ^2) test. Results were considered statistically significant at $P < 0.05$.

3. Results

3.1. Comparison of recent efficacy of AML treatment between the two groups for 28 days

As shown in **Table 1** there was no statistical significance in the CR, PR, NR, and remission rates between the two groups ($P > 0.05$).

Table 1. Comparison of recent efficacy of AML treatment between the two groups for 28 days [*n* (%)]

Group	Cases, *n*	CR	PR	NR	Remission rate
Primary treatment group	40	16 (40.0%)	19 (47.50%)	5 (12.50%)	87.50%
Relapsed and refractory group	40	16 (40.0%)	17 (42.50%)	7 (17.50%)	82.50%
χ^2					0.392
P					0.531

3.2. Statistics of adverse reactions of AML combination therapy between the two groups

The hematological adverse reactions of AML combined treatment were manifested as leukopenia and non-hematological adverse reactions were dominated by infections, with an incidence rate of 87.50%. There was 1 case in the primary treatment group with tumor lysis syndrome, combined with hepatic and renal function injury, 1 case in the relapse refractory group with tumor lysis syndrome, and 4 patients with hepatic and renal function injury. As shown in Table 2, the incidence rate of adverse reactions between the two groups was not significant ($P > 0.05$).

Table 2. Statistics of adverse reactions of AML combination therapy between the two groups [*n* (%)].

Reactions	Cases, *n*	Primary treatment group	Relapsed and refractory group	P
Hematologic adverse reactions	Leukopenia	40 (100%)	40 (100%)	> 0.05
	Anemia	36 (90.0%)	38 (95.0%)	> 0.05
	Thrombocytopenia	35 (87.50%)	36 (90.0%)	> 0.05
Non-hematologic adverse reactions	Granulocytopenia	19 (47.50%)	22 (55.0%)	> 0.05
	Infections	35 (87.50%)	35 (87.50%)	> 0.05
	Gastrointestinal complaints	19 (47.50%)	20 (50.0%)	> 0.05
	Cardiac arrhythmias	6 (15.0%)	5 (12.50%)	> 0.05
	Tumor lysis syndrome	1 (2.50%)	1 (2.50%)	> 0.05
	Hepatic and renal impairment	2 (5.0%)	4 (10.0%)	> 0.05
	Other	5 (12.50%)	6 (15.0%)	> 0.05

4. Discussion

Clinical reports have shown that Bcl-2 is closely associated with a variety of hematologic malignancies and its expression level correlates with AML cell survival and chemotherapy resistance. Venetoclax is a clinically used Bcl-2 inhibitor with high selectivity, which can mimic BH3-only pro-apoptotic proteins combined with BH3, an anti-apoptotic protein in the Bcl-2 family, to improve the permeability of the outer mitochondrial membrane to accelerate the apoptosis of tumor cells, and then exert the anti-disease mechanism [4,5]. Based on the clinical feedback of venetoclax resistance and AML cell sensitivity, *in vitro* experiments have shown that demethylation drugs can effectively reduce the level of anti-apoptotic protein MCL-1, which in turn reduces the resistance

of venetoclax. The combination of both drugs can improve the therapeutic effect and alleviate the toxicity of venetoclax drug reactions [6–8]. Demethylation drugs are commonly used in the clinic, such as azacitidine and decitabine, which can achieve ideal efficacy. However, there is no difference in the efficacy of the two drugs, and the route of administration of a reasonable choice of demethylation drugs must be performed according to the patient's drug-resistance reaction.

AML adverse drug reactions are mainly hematological adverse reactions. Venetoclax combined with demethylating drugs can lead to different degrees of blood cell count abnormalities. Some patients experience blood cell abnormalities before treatment and the abnormality is aggravated after drug treatment, which can be effectively improved by symptomatic treatment. Non-hematological adverse reactions are mainly gastrointestinal discomfort and arrhythmia symptoms. Some patients are presented with liver function abnormalities, hyperkalemia and epilepsy, and even secondary tumor lysis syndrome. Hence, it is crucial to closely monitor the patient's drug response and regularly review the patient's blood routine, electrolytes, liver and kidney function, and other indexes during treatment. It is also necessary to conduct timely screening of high-risk patients and regulate the therapeutic regimen [9,10].

5. Conclusion

The efficacy of venetoclax combined with demethylating drugs in the treatment of AML application was remarkable and the treatment plan can be adjusted according to the patient's condition.

Disclosure statement

The authors declare no conflict of interest.

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