Clinical Study of Bcl-2 Inhibitor, Demethylation Agent and Low-dose Cytarabine Combined Therapy in Elderly Patients with High-risk MDS

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Abstract: Objective: To investigate the clinical efficacy of combined therapy with Bcl-2 inhibitor (venetoclax), demethylating drug (azacitidine) and low-dose cytarabine in elderly patients with intermediate- or high-risk myelodysplastic syndromes (MDS). Methods: A total of 90 elderly patients with intermediate- or high-risk MDS admitted to our hospital from January 2023 to December 2025 were randomly divided into three groups: Control Group 1 (30 cases, azacitidine alone), Control Group 2 (30 cases, azacitidine plus low-dose cytarabine), and Observation Group (30 cases, venetoclax combined with azacitidine and low-dose cytarabine). The clinical efficacy was compared among the three groups. Results: The Observation Group showed a significantly higher overall response rate (ORR) and significantly higher overall survival (OS) than the two control groups ($p<0.05$). There was no significant difference in the incidence of adverse reactions among the three groups ($p>0.05$). Conclusion: The triple regimen of venetoclax plus demethylating agent and low-dose cytarabine is significantly superior to monotherapy or dual therapy in elderly patients with intermediate- or high-risk MDS. It can markedly improve the response rate and survival rate without increasing adverse reactions, indicating acceptable and controllable safety.

***Keywords*:** myelodysplastic syndromes; elderly; intermediate-high risk; Bcl-2 inhibitor; demethylating drug; low-dose cytarabine

1. Introduction

Myelodysplastic syndromes (MDS) are myeloid clonal diseases derived from hematopoietic stem cells with high heterogeneity. Patients with intermediate- or high-risk MDS have a high risk of transformation to acute myeloid leukemia and poor prognosis. MDS predominantly occurs in the elderly. Elderly patients often present with declined organ function, multiple comorbidities, and significantly reduced tolerance, leading to increased difficulty in treatment.

At present, conventional treatment for elderly intermediate- or high-risk MDS mainly consists of demethylating agents alone or in combination with low-dose cytarabine. Although such regimens can control the disease to a certain extent, the treatment response rate is relatively low and long-term survival is unsatisfactory, which can hardly meet clinical needs [1]. Bcl-2 inhibitors are a class of drugs targeting apoptosis regulation. They can promote tumor cell apoptosis by inhibiting the activity of the anti-apoptotic protein Bcl-2. Venetoclax is a commonly used Bcl-2 inhibitor in clinical practice and has shown favorable efficacy in the treatment of hematological malignancies.

This study aimed to explore the clinical efficacy of venetoclax combined with azacitidine and low-dose cytarabine in elderly patients with intermediate- or high-risk MDS, and the results are reported as follows.

2. Materials and Methods

2.1 General Data

Ninety elderly patients with intermediate- or high-risk MDS were divided into three groups:(1) Control Group 1: 30 cases, including 17 males and 13 females, aged 60–78 (mean 68.54±3.21) years.(2) Control Group 2: 30 cases, including 16 males and 14 females, aged 60–78 (mean 68.59±3.16) years.(3) Observation Group: 30 cases, including 17 males and 13 females, aged 60–78 (mean 68.62±3.20) years.

There were no significant differences in general data among the three groups ($p>0.05$).

2.2 Treatment Methods

Control Group 1: Azacitidine 75 mg/m² on days 1–7 for induction therapy.

Control Group 2: Azacitidine 75 mg/m² on days 1–7 plus low-dose cytarabine 20 mg/m² q12h on days 1–7 for induction therapy.

Observation Group: Venetoclax 200 mg twice daily orally for 28 consecutive days, plus azacitidine 75 mg/m² on days 1–7 and low-dose cytarabine 20 mg/m² q12h on days 1–7 for induction therapy.

2.3 Observation Indicators

(1) Overall Response Rate (ORR)Efficacy evaluation criteria:

Complete remission (CR): bone marrow blasts ≤5%, normal maturation of all cell lines, maintained for ≥4 weeks;

Marrow complete remission (mCR): bone marrow blasts ≤5% and reduced by ≥50%;

Partial remission (PR): bone marrow blasts reduced by ≥50% but still ≥5%, maintained for ≥4 weeks;

Hematologic improvement (HI): hematologic improvement without meeting PR criteria;

Stable disease (SD): no evidence of disease progression for at least 8 weeks without meeting PR;

Progressive disease (PD): transformation to AML.

ORR = (CR + mCR + PR + HI) / total cases × 100%.

(2) Overall Survival (OS)Survival was calculated from the date of diagnosis to death from any cause or the last follow-up (12-month follow-up).

2.4 Statistical Analysis

SPSS 28.0 was used for statistical analysis. Measurement data were expressed as mean ± sta(3) Incidence of adverse reactions.

ndard deviation and compared by t-test. Enumeration data were expressed as n (%) and compared by χ^2 test. $p<0.05$ was considered statistically significant.

3. Results

3.1 Overall Response Rate

In the three-group comparison, the observation group demonstrated a significantly higher total response rate ($p<0.05$), as shown in Table 1.

Table 1. Overall response rate to treatment [n (%)]

Group	n	CR	mCR	PR	HI	SD	PD	ORR
Control Group 1	30	5	4	3	3	8	7	15 (50.00)
Control Group 2	30	6	5	4	3	9	3	18 (60.00)
Observation group	30	11	7	5	2	3	2	25 (83.33)ab

Note: Compared with control group 1, ap<0.05; compared with control group 1, bp<0.05

3.2 Overall Survival

The overall survival rate in the observation group was 86.67% (26/30), which was significantly higher than 56.67% (17/30) in control group 1 ($p<0.05$) and 66.67% (20/30) in control group 2 ($p<0.05$).

3.3 Incidence of Adverse Reactions

There was no significant difference in the incidence of adverse reactions among the three groups ($p>0.05$). See Table 2.

Table 2. Incidence of adverse reactions [n (%)]

Group	n	Neutropenia	Thrombocytopenia	Gastrointestinal reactions
Control Group 1	30	13(43.33)	11(36.67)	7(23.33)
Control Group 2	30	16(53.33)	13(43.33)	9(30.00)
Observation group	30	18(60.00)	16(53.33)	11(36.67)

Note: The incidence rates of the three adverse reactions among the three groups were compared, with p values all>0.05.

4. Discussion

Bcl-2 inhibitors are a class of small-molecule drugs that target and regulate apoptosis. By specifically binding to the anti-apoptotic protein Bcl-2, they relieve its inhibitory effect on pro-apoptotic proteins, break the apoptotic balance of tumor cells, and induce programmed cell death, providing a new direction for targeted therapy of hematological malignancies.

Venetoclax is a commonly used Bcl-2 inhibitor in clinical practice. Its mechanism of action is to bind with high affinity to the BH3 domain of the Bcl-2 protein, competitively block the interaction between Bcl-2 and pro-apoptotic proteins, and

release pro-apoptotic proteins to initiate the apoptotic pathway. Related studies have shown that venetoclax is suitable for the treatment of elderly patients with intermediate- or high-risk MDS. Elderly patients often have declined organ function and poor tolerance, while venetoclax has high targeting ability and relatively mild toxic and side effects. It can exert anti-tumor effects without increasing the burden on the body, which meets the treatment needs of elderly patients [2]. Other studies have pointed out that hematopoietic stem cell clones in patients with intermediate- or high-risk MDS are abnormal with hyperactive anti-apoptotic signals, and venetoclax can specifically reverse this abnormality and provide a therapeutic target [3].The results of this study showed that compared with the two control groups, the observation group had a higher overall response rate and higher survival rate ($p<0.05$), while there was no significant difference in the incidence of adverse reactions ($p>0.05$). This indicates that the triple regimen of venetoclax combined with a demethylating agent and low-dose cytarabine is superior to monotherapy and dual therapy. The reasons are as follows: azacitidine reverses abnormal methylation of tumor cells by inhibiting DNA methyltransferase, restores the function of tumor suppressor genes, and inhibits tumor cell proliferation; low-dose cytarabine can mildly inhibit abnormal hematopoietic cells in the bone marrow with low toxicity, making it suitable for elderly patients; venetoclax eliminates tumor cells by targeting the apoptotic pathway. The synergistic effect of the three drugs inhibits tumor progression from multiple aspects including proliferation and apoptosis, thereby improving the therapeutic effect [4]. At the same time, the high targeting of venetoclax and the low toxicity of low-dose cytarabine avoid the superposition of toxic and side effects caused by multi-drug combination, ensuring the safety and controllability of the regimen in elderly patients.

In conclusion, venetoclax combined with a demethylating agent and low-dose cytarabine shows favorable efficacy in the treatment of elderly patients with intermediate- or high-risk MDS and has certain application value.

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