Clinical Effects of Venetoclax in the Treatment of Acute Myeloid Leukemia in the Elderly

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Abstract: Objective: To investigate the clinical efficacy of venetoclax in the treatment of elderly acute myeloid leukemia (AML). Methods: 50 cases of elderly AML patients receiving venetoclax for treatment in the hospital from January 2022 to January 2024 were selected, including 38 cases of patients whose primary treatment was not suitable for intensive chemotherapy and 12 cases of relapsed/refractory AML patients, to observe the therapeutic efficacy and safety of venetoclax. Results: Among the 38 patients whose primary treatment was not suitable for intensive chemotherapy, 5 cases were treated with venetoclax monotherapy, 33 cases were treated with venetoclax + azacitidine, and 25 patients (65.79%) achieved complete remission (CR) with incomplete hematologic recovery (CRi) after 28 days of treatment; 10 patients with relapsed/refractory AML were treated with venetoclax + azacitidine, and 2 patients were treated with venetoclax + azacitidine + chemotherapy, and 2 patients achieved optimal therapeutic response after 28 days of treatment and CR/CRi was achieved in 7 patients (58.33%). There were 47 (94.0%) patients with grade 3 or higher granulocytopenia, 46 (92.0%) patients with hemoglobin reduction, and 43 (86.0%) patients with thrombocytopenia, developed after 28 days of treatment. 11 patients developed infections after treatment and there was one case of tumor lysis syndrome. Conclusion: The response rate of venetoclax monotherapy and combination in elderly AML induction therapy is high, and the overall tolerability of elderly patients is good, so it can be popularized and applied.

Keywords: Venetoclax; Elderly; Acute myeloid leukemia; Efficacy

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1. Introduction

Acute myeloid leukemia (AML) is a common malignant blood disease that is more likely seen in the elderly. There is a high number of elderly AML patients over 65 years of age in clinical treatment, with a high risk of poor prognosis, inducing multi-organ failure, and a high mortality rate [1]. Currently, AML treatment in the elderly includes the oral B-cell lymphoma/leukemia 2 (Bcl-2) selective inhibitor venetoclax, as the first-line drug. Due to the low drug resistance of drug therapy in the elderly, there are more adverse reactions in the standard intensive induction therapy, which can easily lead to relapsed/refractory AMLs, and increase the difficulty of clinical treatment [2]. In view of China’s less research on elderly AML drugs, we discuss the
efficacy and safety of venetoclax monotherapy and a combination of drugs in elderly AML cases, aiming to provide references for the clinical use of drugs.

2. General information and methods

2.1. General information

50 cases of elderly AML patients who received venetoclax for treatment in the hospital from January 2022 to January 2024 were selected, including 38 cases of patients whose primary treatment was not suitable for intensive chemotherapy and 12 cases of relapsed/refractory AML patients. Among the 38 patients, there were 17 males and 21 females, aged 60–78 (68.72 ± 3.19) years old, were not suitable for intensive chemotherapy at the initial treatment, 19 cases of a non-specific type of primary AML, 17 cases of primary AML with a reproducible genetic abnormality, and two cases of myelodysplastic syndromes (MDS)-transformed AML. Among the 12 patients with refractory/relapsed AML, there were 5 males and 7 females, aged 60–82 (69.01 ± 3.14) years, nine cases of a non-specific type of primary AML, two cases of primary AML with a reproducible genetic abnormality, and one case of MDS-transformed AML; the baseline data of AML patients in the two groups were comparable (P > 0.05).

2.2. Methods

Elderly AML patients were given venetoclax in an incremental dosing regimen with a dose of 100 mg/d on day 1, 200 mg/d on day 2, and 400 mg/d on days 3–28, with the maintenance drug dose adjusted according to the resistance response. Patients who received a combination of drugs were administered azacitidine by subcutaneous injection at a dose of 75 mg/(m²/d) for 1–7 days. If posaconazole was co-administered to control fungal infections, venetoclax was reduced to 100 mg/d.

2.3. Evaluation criteria

The drug responsiveness of venetoclax was observed, if after 28 days of treatment, platelet > 100×10⁹/L, bone marrow primitive cell proportion < 5%, peripheral blood ANC > 1.0×10⁹/L, no Auer bodies in primitive cells, no extramedullary leukemia, it was considered as complete remission (CR) with incomplete hematologic recovery (CRi); if there was no abnormality of the peripheral blood cells, bone marrow primitive cells decreased by more than 50%, it is considered as partial remission (PR) [3]. Adverse effects of venetoclax alone and in combination were observed.

3. Results

3.1. Analysis of venetoclax drug efficacy

38 patients who were initially unsuitable for intensive chemotherapy were treated with venetoclax monotherapy in 5 cases and venetoclax + azacitidine in 33 cases, 25 patients (65.79%) achieved CR/CRi after 28 days of treatment, and 9 patients (23.68%) achieved PR.

All 12 patients with relapsed/refractory AML were treated with venetoclax drug combination, 10 patients were treated with venetoclax + azacitidine while two patients were treated with venetoclax + azacitidine + chemotherapy, of which three patients had their dosage adjusted downward due to the combination of azoles. Two patients achieved the optimal therapeutic response after 28 days, seven patients (58.33%) reached CR/CRi, and two patients (16.67%) reached PR.
3.2. Analysis of venetoclax drug safety
There were 47 (94.0%) patients with grade 3 or higher granulocytopenia after 28 days of treatment, 46 (92.0%) patients with hemoglobin reduction, and 43 (86.0%) patients with thrombocytopenia. There were 11 (22.0%) patients with infections after treatment, 9 (18.0%) cases of exacerbation of infections, 41 (82.0%) cases of gastrointestinal discomfort, one (2.0%) case of elevation of hepatic aminotransferases, and one (2.0%) case of tumor lysis syndrome.

4. Discussion
Elderly AML patients have high recurrence and mortality rates due to functional decline, more underlying comorbidities, and poorer ability to tolerate treatment, and have specific requirements for drug efficacy and safety. Venetoclax mainly acts on Bcl-2, which is a small molecule inhibitor. The drug is absorbed orally and can be rapidly combined with Bcl-2, increase the release of pro-apoptotic proteins, activate cysteine asparagine to destroy the outer membrane of mitochondria, and promote apoptosis of tumor cells, which has been highly concerned by scholars at home and abroad, and has achieved good efficacy in the treatment of AML [4]. The clinical acceptance of elderly AML patients is mainly patients whose initial treatment is not suitable for intensive chemotherapy, and most of them are relapsed/refractory AML. Observation of the venetoclax monotherapy and combination of drugs showed that among the 38 cases that were not suitable for intensive chemotherapy, 25 cases (65.79%) achieved CR/CRi after treatment for 28 days; among the 12 cases with relapsed/refractory AML, seven patients (58.33%) reached CR/CRi, two (16.67%) patients reached PR, and two patients reached the best therapeutic response. The data show that the clinic uses mainly venetoclax combination therapy, such as demethylation drugs, and the combination of the two drugs can reduce the oxidative phosphorylation of leukemia stem cells by inhibiting amino acid uptake, which in turn prompts apoptosis of leukemia stem cells. Drug combination therapy has a synergistic mechanism, effectively activates mitochondrial apoptosis in AML patients, plays a role in killing cancer cells in vitro, has a synergistic anti-tumor activity, and thus prolongs the expected survival time of elderly AML [5-7].

Elderly AML patients have a lower treatment tolerance, and combined venetoclax monotherapy can lead to hematologic toxicity reactions, with varying degrees of blood cell count abnormalities, and all of them are grade 3 or higher. Clinical reports found that in elderly AML patients with symptomatic treatment, or after stopping the drug, blood cell count abnormalities can be restored; for infected patients, dynamic monitoring of blood routine indexes, timely combination therapy, adjusting the dose of venetoclax, close monitoring of tumor lysis syndrome and other critical events, can effectively prevent negative prognosis [8-10].

5. Conclusion
In conclusion, the response rate of venetoclax monotherapy and combination therapy in elderly acute myeloid leukemia induction therapy is high, and the overall tolerability of elderly patients is good, so it can be popularized and applied.

Disclosure statement
The authors declare no conflict of interest.
References


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