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Efficacy and Prognosis of Venetoclax Combined with Hypomethylating Agents in the Treatment of Relapsed/Refractory Acute Myeloid Leukemia

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Abstract: *Objective:* To investigate the efficacy and prognosis of venetoclax combined with hypomethylating agents (HMAs) in the treatment of relapsed/refractory acute myeloid leukemia (AML). *Methods:* From June 2021 to February 2022, 14 patients with relapsed/refractory AML were treated with venetoclax combined with HMAs, among which nine patients were treated with venetoclax + azacytidine, while five patients were treated with venetoclax + decitabine. The efficacy of the treatments was observed, and the patients were followed up. *Results:* All patients received one to five courses of treatment, in which the median course of treatment was three; four cases achieved CR and another four achieved PR, with NR in six cases; there was no treatment-related death. There were seven deaths up to the end of the follow-up period, all of which were progressive deaths at the end of the disease, and the overall survival rate was 50.00%. All the patients experienced different degrees of nausea, vomiting, and myelosuppression (Grade II–IV), nine patients had Grade 3–4 hematological adverse reactions, and seven patients had infection. *Conclusion:* Venetoclax combined with hypomethylating agents is effective in the treatment of relapsed/refractory AML, with good prognosis, and some patients may even achieve CR. Although bone marrow suppression is serious with this combination, it is well tolerated.

Keywords: Recurrence/refractory acute myeloid leukemia; Venetoclax; Azacytidine; Dexitabine; Myelosuppression

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1. Introduction

Acute myelocytic leukemia (AML) is a common malignant tumor of the blood system, originating from the medullary system. Men are more likely to suffer from this condition than women, and its incidence rate increases with age [1]. Despite ongoing advancements in treatment methods, the clinical efficacy is still subpar. The cure rate of patients under 60 years old is about 35% to 40%, while that of patients over 60 years old is only 5% to 15% [2]. Refractory and relapse are significant contributors to the poor prognosis of AML as well as the primary cause of treatment failure. Clinically, AML that is resistant to standard induction regimen or relapses after a brief period of remission is known as relapsed/refractory AML. At present, there is no ideal regimen for it. The use of venetoclax, as the first small molecule inhibitor of Bcl-2, has been approved by the Food and Drug Administration (FDA) for the treatment of leukemia [3]. In 2018, it was approved for the treatment of AML in patients who are not suitable for strong induction chemotherapy. HMAs can reverse the DNA methylation process of cancer cells and induce their apoptosis [4]. It has been proven by clinical research models that the combination of Bcl-2 inhibitor and HMAs has synergistic anti-leukemic effect, which provides a basis for clinical treatment. In this study, the efficacy

and prognosis of 14 patients with relapsed/refractory AML who were treated with venetoclax + HMAs in the hospital were observed.

2. Methods

2.1. Study population

The 14 patients (June 2021 to February 2022) included in the study were patients with relapsed/refractory AML admitted to the hospital, all of whom received venetoclax + HMAs. Inclusion criteria: (1) patients who met the diagnostic criteria for AML based on the "Diagnostic and Therapeutic Criteria for Hematological Diseases (4th Edition) [5] and were diagnosed by immunology, cytomorphology, cytogenetics, molecular biology, and other investigations; (2) patients who met the definition of refractory AML or recurrent AML; (3) patients with estimated survival time of more than 6 months; (4) patients with complete clinical data. Exclusion criteria: (1) complicated with other malignant tumors, serious organ diseases, or other critical diseases; (2) contraindications to treatment related drugs; (3) serious mental disorders; (4) patients with a score of more than 3 based on the Eastern Cooperative Oncology Group (ECOG) Performance Status. Informed consent was taken from the patients and their family members.

2.2. Study design

The patients were treated with venetoclax + HAMs (azacytidine or decitabine): 100 mg of venetoclax (AbbVie Ireland NL B.V., 100 mg, GYZZ HJ20200055) was taken orally on the first day (D1), 200 mg on D2, and 400 mg on D3–D28; the drug was suspended following disease progression or unacceptable toxicity, and the dose was adjusted according to tolerance and bone marrow suppression; 75 mg/m^2 of azacytidine (Baxter Oncology GmbH, 100 mg, GYZZ H20170238) was injected subcutaneously once a day for seven consecutive days and was repeated following a 28-day cycle, whereas 20 mg/m^2 of dicitabine (Jiangsu Haosen Pharmaceutical Group Co., Ltd., 10 mg, GYZZ H20153045) was injected intravenously over one hour once a day for five days and was also repeated following a 28-day cycle. Before the first administration of azacytidine or decitabine, the patients' complete blood count, liver biochemical markers, and serum creatinine were detected.

2.3. Outcomes

Complete remission (CR): platelet count $\geq 100 \times 10^9$/L, neutrophil count $\geq 1.5 \times 10^9$/L, primordial cells in bone marrow ≤ 0.05, and no leukemic infiltration outside the marrow; partial remission (PR): platelet count $\geq 100 \times 10^9$/L, neutrophil count $\geq 1.5 \times 10^9$/L, the proportion of primordial cells in bone marrow is 5–25% and decreased by more than 50%; no remission (NR): failure to meet PR standard or treatment failure, including drug resistance, death during myelosuppression, morphological recurrence, molecular or cytogenetic recurrence, and others. The outcomes were analyzed based on the best efficacy achieved by the patients during the treatment period.

2.4. Evaluation and treatment of toxic and side effects

The toxic and side effects were evaluated according to the World Health Organization (WHO) classification standard for common toxic and side effects of anticancer drugs. All patients were hospitalized in laminar flow beds with full environmental protection; routine administration of antiemetics, liver protection, stomach protection, and other drugs, in addition to fluid replacement, alkalization, and diuretic treatment were initiated to prevent uric acid nephropathy; platelets and red blood cell suspensions were transfused with low platelet levels and hemoglobin levels, respectively; anti-infectives were strengthened for infected patients, and relevant investigations, including chest computed tomography (CT), microbiological examination, and others were improved.

3. Results

3.1. Clinical features of the patients and therapeutic drugs used

Among the 14 patients, eight were male and six were female, age ranging from 53 to 77, with a median age of 65. There were two refractory cases, two relapsed cases, and 10 refractory and relapsed cases. Among the cases, nine were treated with azacytidine, whereas five were treated with decitabine. In terms of the ECOG score, seven cases scored 1 point, whereas the other seven cases scored 2 points. According to the French-American-British (FAB) classification of AML, there were three cases of M2 and M3, respectively, and 4 cases of M4 and M5, respectively. Prior to the study, the patients received different treatments, including methylated drugs alone, preexcitation therapy, demethylated drugs combined with preexcitation therapy, and other treatment regimens. **Table 1** shows the clinical features of all 14 patients and the therapeutic drugs used.

Table 1. Clinical features and therapeutic drugs of all 14 patients with relapsed/refractory AML

Patient	Gender	Age	FAB typing	ECOG score	Type	HAMs
1	Male	56	M5a	1	Refractory	Azacytidine
2	Male	67	M5b	1	Relapsed/Refractory	Azacytidine
3	Female	62	M4	2	Relapsed/Refractory	Dicitabine
4	Male	75	M4	2	Relapsed/Refractory	Dicitabine
5	Male	59	M3	1	Refractory	Azacytidine
6	Female	65	M2	1	Relapsed/Refractory	Azacytidine
7	Male	61	M4	1	Relapsed	Dicitabine
8	Male	72	M5a	2	Relapsed	Azacytidine
9	Female	53	M2	2	Relapsed/Refractory	Azacytidine
10	Male	77	M5b	2	Relapsed/Refractory	Azacytidine
11	Female	64	M3	2	Relapsed/Refractory	Dicitabine
12	Male	66	M4	2	Relapsed/Refractory	Azacytidine
13	Female	65	M3	1	Relapsed/Refractory	Dicitabine
14	Female	67	M2	1	Relapsed/Refractory	Azacytidine

3.2. Efficacy and follow-up results

All patients received one to five courses of treatment, with a median of three courses. There were four cases of CR, four cases of PR, and six cases of NR. Among the four patients with CR, three were treated with azacytidine regimen, while one of the patients was treated with dicitabine regimen; among the four PR patients, two were treated with azacytidine regimen, while the other two were treated with dicetabine regimen. There were no treatment-related deaths. There were seven deaths in total up to the follow-up period, all of which were progressive deaths at the end of the disease. **Table 2** shows the best curative effect and the follow-up results of the patients.

Table 2. Efficacy and follow-up results of 14 patients with relapsed/refractory AML

Patient	Best curative effect	Number of courses required to achieve the best curative effect	Follow-up
1	PR	1	
2	NR		Death
3	NR		Death

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Patient	Best curative effect	Number of courses required to achieve the best curative effect	Follow-up
4	NR		Death
5	CR	1	
6	PR	3	
7	CR	1	
8	NR		Death
9	CR	2	
10	NR		Death
11	PR	1	
12	NR		Death
13	PR	2	Death
14	CR	1	

3.3. Toxic and side effects

All 14 patients had varying degrees of nausea, vomiting, and myelosuppression (Grade II–IV). Nine patients had grade 3–4 hematological adverse reactions, five patients had pulmonary infection, two patients had blood infection, one patient had mild creatinine elevation, and one patient had bleeding from the digestive tract. No heart, liver, kidney, or other organ related toxic and side effects occurred. **Table 3** shows the major toxic and side effects experienced by the patients.

Table 3. Major toxic and side effects of the 14 patients with relapsed/refractory AML

Patient	Major toxic and side effects
1	Grade 3 hematological adverse reaction, Grade III myelosuppression, blood infection, nausea, and vomiting.
2	Grade 4 hematological adverse reaction, Grade IV myelosuppression, pulmonary infection, nausea, and vomiting.
3	Grade 3 hematological adverse reaction, Grade IV myelosuppression, nausea, and vomiting.
4	Grade 3 hematological adverse reaction, Grade IV myelosuppression, pulmonary infection, nausea, and vomiting.
5	Grade 3 hematological adverse reaction, Grade II myelosuppression, nausea, and vomiting.
6	Grade 3 hematological adverse reaction, Grade II myelosuppression, nausea, and vomiting.
7	Elevated creatinine, Grade II myelosuppression, nausea, and vomiting.
8	Grade 4 hematological adverse reaction, Grade IV myelosuppression, pulmonary infection, nausea, and vomiting.
9	Grade III myelosuppression, blood infection, nausea, and vomiting.
10	Grade 3 hematological adverse reaction, nausea, and vomiting.
11	Grade IV myelosuppression, pulmonary infection, nausea, and vomiting.
12	Grade IV myelosuppression, gastrointestinal bleeding, nausea, and vomiting.
13	Grade 4 hematological adverse reaction, Grade IV myelosuppression, pulmonary infection, nausea, and vomiting.
14	Grade 3 hematological adverse reaction, Grade III myelosuppression, nausea, and vomiting.

4. Discussion

Relapsed AML is defined as more than 5% of leukemic cells in bone marrow or their reappearance in peripheral blood after CR [6]. However, the definition of refractory AML is quite complex. At present, most guidelines define it as the failure of one course of sufficient induction chemotherapy to achieve CR, thus requiring a change in the treatment regimen. The prognosis of relapsed/refractory AML is very poor, and the 3-year survival rate is only 10% [7].

Studies have shown that the remission rate of recurrent/refractory AML can reach up to 30% to 50% with venetoclax-based regimen [8]. In a study [9], Pan showed that the 1-year expected cumulative overall survival rate of patients receiving venetoclax combined with HMAs in the treatment of relapsed/refractory AML was 36.6% ± 11.8%. Another study found that after one course of treatment, the ORR rate was as high as 83.3% and the CR/CR with incomplete hematological recovery (CRi) rate was 58.3% [10]. A study on the relationship between the efficacy and exposure safety of venetoclax showed that when combined with HMA, the concentration of venetoclax increased to a QD (four times a day) dose of less than or equal to 400 mg, and the efficacy was positively correlated with the dose, in which the greater the dose, the stronger the efficacy; when the once daily dose was more than 400 mg, the response probability tended to decrease or stabilize, and the efficacy did not increase significantly with the dose; issues with tolerance were observed at doses greater than or equal to 800 mg QD [11]. Therefore, following venetoclax listing in China, the relevant treatment regimens should ensure that the prescription of venetoclax is in sufficient doses and its course is long enough as tolerated by the patient. This study found that the toxic and side effects of venetoclax mainly include hematological adverse reaction, bone marrow suppression, infection, nausea, and vomiting.

Malignant tumors can escape apoptosis through various mechanisms, one of which is the disruption of Bcl-2 family protein balance. The overexpression of Bcl-2 protein is associated with various hematological tumors [12]. The high expression in AML suggests that chemotherapy is not effective. As a powerful oral selective inhibitor of Bcl-2, venetoclax is a small-molecule drug that is significant the field of protein-protein interaction. It selectively combines with Bcl-2, replaces Bcl-2-like protein 11 (BIM), changes the outer membrane permeability of mitochondria, activates caspase, repairs tumor cell apoptosis pathway, and initiates tumor cell apoptosis [13]. It also regulates related genes to promote the release of inflammatory factors, thus playing an anti-tumor role.

The use of HMA on its own has limitations, including low response rate and short remission duration; in addition, it is not suitable for elderly patients with AML requiring intensive therapy. The synergistic effect of venetoclax combined with HMAs include the following mechanisms: (1) MCL-1 is related to AML cell survival and venetoclax resistance, in which its level is downregulated by azacytidine; (2) venetoclax can induce apoptosis in AML cells and increase the sensitivity of AML cells to HMAs [14]; (3) reactive oxygen species (ROS) are an important part of AML treatment, and many chemotherapy drugs such as HMAs can activate Nrf2–antioxidant response pathway, induce the production of antioxidant enzymes, and neutralize reactive oxygen species (ROS) while inducing ROS production; venetoclax combined with HMAs can inhibit Nrf2 production [15].

In conclusion, venetoclax combined with HMAs has a definite effect on relapsed/refractory AML, with a good prognosis, and some patients can even achieve CR. Although bone marrow suppression is serious, it is well tolerated. As guidelines have changed in recent years, the targeted treatment of specific gene mutations and certain pan-cancer genes has garnered widespread attention. Venetoclax is an effective drug compared to many targeted drugs in the treatment of AML. This study did not analyze the chromosomal karyotype and gene mutation in patients, which should be taken as the research direction for future research.

Disclosure statement

The authors declare no conflict of interest.

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