Azacitidine With or Without All-trans Retinoic Acid for Newly Diagnosed Acute Myeloid Leukemia or Intermediate,High or Very High Risk Myelodysplastic Syndromes Unfit for Intensive Chemotherapy

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Background

Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are common clonal malignant diseases that originate from hematopoietic stem cells. A part of AML and intermediate, high or very high risk MDS patients cannot tolerate intensive chemotherapy due to the age and poor physical condition, resulting in limited overall survival.

Nowadays, hypomethylating agents (HMA) such as azacytidine(AZA) are recommended as first-line therapy for acute myeloid leukemia or myelodysplastic syndromes patients unfit for intensive chemotherapy[1,2]. Previous studies have shown that the CR rate and ORR of AZA in the treatment of adverse-risk MDS patients are 9 %~13 % and 30 %~34 % respectively [3-6]. HMA combined with all-trans retinoic acid (ATRA) can up-regulate tumor suppressor gene P16 and RARβ, down-regulate oncogene WT1, and cooperatively inhibit leukemia cell proliferation , induce apoptosis and differentiation [7-9] .

Thirty-one elderly patients with myeloid tumor who could not tolerate the intense chemotherapy were treated with low-dose DAC combined with ATRA to achieve a Good curative effect. The CR rate was 22.6 %, mCR was achieved in 7 cases (22.6 %), PR was achieved in 4 cases (12.9 %), ORR was 58.1 % and the median OS was 11 months [10]. A multicenter clinical trial on the treatment of elderly patients with newly diagnosed AML showed that the median ORR of 35 patients treated with decitabine plus ATRA was 26.1% and a median OS of 8.4 months [11]. These results suggest that HMA combined with ATRA may achieve better efficacy in patients who are not suitable for intensive chemotherapy.

In order to improve the prognosis and survival of newly diagnosed AML and MDS patients who are not eligible for intensive induction chemotherapy, we intend to conduct a prospective study to investigate the efficacy and safety of HMA combined with ATRA in newly diagnosed AML and intermediate/adverse risk MDS patients who are not eligible for intensive chemotherapy, and to explore the related mechanism of action.

Research purpose

This is a randomized, open-label, multi-center clinical trial. This study aims to to compare the efficacy and safety of AZA with or without ATRA in newly diagnosed unfit AML or Intermediate, High or Very High Risk MDS patients who can not tolerate intensive chemotherapy.

Study design

1. Patients meeting the criteria were enrolled according to inclusion and exclusion criteria.
2. The patients who meet the criteria for enrollment are randomly assigned 1:1.
3. Estimated Enrollment: 180 participants.

Inclusion Criteria:

1. Chinese guidelines for the diagnosis and treatment of acute myeloid leukemia (2021 edition), excludes acute promyelocytic leukemia (M3、APL) and Intermediate, High or Very High Risk myelodysplastic syndromes(2019 edition)

2. Be at least 18 years of age on day of signing informed consent.

3. Not suitable for newly diagnosed patients with intensive chemotherapy.

4. Not suitable for newly diagnosed patients with receiving hematopoietic stem cell transplantation

5. The proportion of blast cells was below 50% in bone marrow

6. Total white blood cell (WBC) count ⩽10,000/μL;

Exclusion Criteria:

1.Malignant neoplasms with other progression

2.Serious mental illness uncooperative

3.Refusal to join the study

Research scheme and Experimental diagram

Experimental Group A:
Azacytidine 75mg/m2/d by IV on days 1-7 of every cycle ATRA 20mg tid by po 1-21 day of every cycle 28 days

Experimental Group B:

Azacytidine 75mg/m2/d by IV on days 1-7 of every cycle 28 days

Assess disease status: In the course of treatment, if the proportion of blast cells in the patient increased compared with the initial diagnosis, indicating the disease progression. Patients with disease progression were dropped out of the study, and other patients continued with the original regimen. After 6 courses of treatment, experimental group A maintenance therapy: ATRA 20mg tid by po 1-21 day of every cycle for 1 year, azacytidine 75mg/m2/d by IV on days 1-7 every 3 months for 1 year. The disease should be assessed again after 3 cycles. If the disease progressed, the patient should be withdrawn from the study. experimental group B maintenance therapy: azacytidine 75mg/m2/d by IV on days 1-7 every 3 months for 1 year.

Study process

Screening phase

- Demographic data: age, sex, nationality, address, spouse's characteristics, contact information. Physical examination: height, body weight, blood pressure, body temperature, heart rate, body surface area, respiratory and cardiovascular system

examination, nervous system examination, hepatosplenomegaly, Eastern Cooperative Oncology Group (ECOG) score, etc.

- Laboratory examination: Blood analysis: blood routine test, blood biochemistry, coagulation function and cardiac biomarker. BM examination: marrow morphology examination, flow cytology, chromosome, gene mutation; Immune function test: humoral immunity, T lymphocyte subsets, NK cells, cytokines;

Treatment period (28 days for a cycle)

- Drugs will be given based on the protocol;
- Blood routine test once a day, coagulation function test and blood biochemistry are performed twice a week, respectively;
- T Cellular Subjects and NK cells, cytokines are performed after treatment.
- Bone marrow examination: Bone puncture was reviewed after every course of treatment for AML and three course for MDS, and the treatment response was evaluated according to the 2020 NCCN guidelines and the Chinese Guidelines for diagnosis and Treatment of Myelodysplastic syndrome (2019 edition) and Chinese guidelines for the diagnosis and treatment of myelodysplastic syndromes(2017 edition) ;
- Important vital signs are recorded.
- Adverse events will be recorded and managed according to this protocol.

Primary Outcome Measure

1.Overall Response Rate (ORR)[Time Frame: Up To 6 Months]
Number of participants (responders) achieving ORR (CR+PR+HI) after the 6 cycle treatments

2.Overall survival (OS) [Time Frame: Up To 24 Months]
OS is defined as the number of days from the date of randomization to the date of death of any cause, or last known date to be alive.

3.Progression-free survival (PFS) [Time Frame: Up To 24 Months]
Progression-free survival (PFS) will be measured from time of enrolling in the clinical trial to the date on which disease progresses or the date on which the patient dies, whichever comes first.

Secondary Outcome Measures:

1. Percentage of Participants Achieving Transfusion Independence (TI) Who are Transfusion Dependent at Baseline [Time Frame: Up To 6 months]TI is when the participants who were transfusion dependent on RBC and/or Platelet at baseline achieve transfusion independence post baseline. TI is a period of at least 56 days with no transfusion after the date of the first dose of study drug to the last dose of study drug + 30 days, the initiation of post-treatment therapy, or death, whichever is earliest.
2. Incidence of systemic infections [Time Frame: Up to 6 months]

Follow-up phase

All study patients should be followed up until the end of the study to obtain the data of survival.Follow-up time: Patients who completed treatment should be monitored 24 months after the start of the study and 6 months after the completion of treatment. During the follow-up period after treatment, blood routine, peripheral blood morphology and biochemistry were monitored every 12 weeks until the study end point. Follow up the treatment and prognosis of the patients who withdrawal from clinical trials until the end point of study.

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