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Observation on the Efficacy of Roxadustat in Treating Low-risk Myelodysplastic Syndrome

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Abstract: *Objective:* To observe the effect of different doses and frequencies of roxadustat on low-risk patients with myelodysplastic syndromes (MDS). *Methods:* This study was conducted using a comparative treatment observation approach. Low-risk MDS patients admitted to our hospital from February 2022 to February 2023 were selected, excluding patients with a history of severe drug allergies or known allergies to roxadustat. A total of 60 patients were included and randomly divided into observation group A (20 cases, 100 mg, twice weekly), observation group B (20 cases, 50 mg, once daily), and observation group C (20 cases, 150 mg, twice weekly). Patient recovery, adverse reaction rate, and hemoglobin recovery time were compared and statistically analyzed. *Results:* The recovery rate of group B in the observation group was significantly higher than that in the other two groups, and the incidence of adverse reactions and the time to Hb recovery were also better in group B than in the other two groups ($p < 0.05$). *Conclusion:* Low-dose, high-frequency (50 mg, once daily) administration can effectively improve the hemoglobin level of low-risk MDS patients and help improve their general survival.

Keywords: Low-risk MDS; Roxadustat; Anemia

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1. Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous myeloid clonal diseases originating from hematopoietic stem cells, characterized by ineffective hematopoiesis, varying degrees of cytopenia, hematopoietic failure, and high risk of progression to acute myeloid leukemia (AML). MDS is a chronic hematologic malignancy with high clinical heterogeneity [1]. Because MDS has high heterogeneity and complexity, the prognosis varies greatly, with median survival ranging from 6 months to 5 years [2]. Approximately 30% of MDS patients develop secondary acute leukemia within a few months to a few years [3]. MDS is the most common clinical disease type, which is common in the elderly. Patients with MDS may have a decrease in peripheral blood mono- or multi-lineage cells. Patients may have anemia, such as dizziness, fatigue, ecchymosis, hematochezia, hematuria,

infection and fever. Chemotherapy may also cause severe bone marrow suppression, gastrointestinal symptoms, accompanied by nausea, vomiting, loss of appetite, etc. Therefore, MDS has a great negative impact on the health of patients, is difficult to treat, and has the characteristics of progressive development. If the diagnosis is not timely or targeted treatment is not received in time, it is easy to endanger the patient's life [4].

According to the revised International Prognostic Score System (IRSS-R), MDS is divided into lower-risk and higher-risk groups. The lower-risk group includes IPSS-low-risk group, intermediate-1 group, IPSS-very-low-risk group, low-risk group and intermediate-risk group (≤ 3.5 points), WPSS-very-low-risk group, low-risk group and intermediate-risk group. The higher-risk group includes IPSS-intermediate-2 group and high-risk group, IPSS-R-intermediate group (> 3.5 points), high-risk group and very-high-risk group, WPSS-high-risk group and very-high-risk group [5]. Patients with higher-risk MDS have shorter survival time and are more likely to progress to acute myeloid leukemia (AML). The main feature of low-risk MDS is hematopoietic progenitor cell apoptosis, which is related to epigenetic changes and immune dysregulation [6]. Since the etiology and pathogenesis of MDS are not fully understood, there is no consensus on the treatment plan for MDS, but there are the same treatment principles.

(1) For patients in the lower risk group, blood transfusion dependence should be reduced as much as possible, the bone marrow hematopoietic microenvironment should be improved, and symptomatic or etiological treatment should be generally given

(2) For patients in the higher risk group, there are abnormal changes in cytogenetics and the prognosis is poor. Disease progression should be stopped as much as possible, survival time should be prolonged, and even clinical cure should be achieved [7]. At present, the main treatment methods for MDS include supportive treatment, immunosuppressants, immunomodulators, demethylation, hematopoietic stem cell transplantation, etc.

Roxadustat is a small molecule hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor. It is the world's first HIF-PHI drug. As a new generation of renal anemia treatment drug with a brand-new mechanism, my country took the lead in completing the Phase III clinical trial in 2018 and was officially approved for marketing [8]. Chen N proved in a Phase III trial of chronic renal failure patients that roxadustat can improve renal anemia [9]. In the clinical study, 24 patients were treated with roxadustat at doses of 1.5, 2.0 and 2.5 mg/kg, respectively. Nine patients (37.5%) were weaned off transfusion at 28 and 52 weeks, of which 7 were treated with 2.5 mg/kg. None of the patients died or progressed to AML, indicating that roxadustat can effectively improve nephropathy-related anemia [10].

Roxadustat is a new drug for the treatment of renal anemia, so there is a lack of clinical experience in its use, and the clinical effect of some patients is not good. There is still a lack of large-sample analysis of the clinical factors affecting its efficacy. Chen Yanlin referred to the dosage adjustment principles of the 2018 Chinese Expert Consensus on the Diagnosis and Treatment of Renal Anemia and treated roxadustat orally for 4 weeks [11,12]. Finally, it was found that baseline serum ferritin was the influencing factor of the short-term efficacy of roxadustat in the treatment of renal anemia. Ideal mean serum albumin helps to improve the long-term efficacy of roxadustat. Improving iron metabolism and improving nutritional status can improve the clinical efficacy of roxadustat in the treatment of renal anemia. However, no reliable evidence was provided regarding the specific use of roxadustat. Patients with low-risk MDS have limited clonal hematopoiesis and minimal blast cell infiltration. Therefore, we found that adding roxadustat to the treatment of these patients may alleviate anemia and transfusion dependence to some extent, thereby improving their quality of life. Therefore, this study used roxadustat to treat low-risk

MDS. By observing different administration methods of roxadustat, we statistically analyzed the recovery status, incidence of adverse reactions, and hemoglobin recovery time of low-risk MDS patients to explore the specific value of roxadustat in treating low-risk MDS.

2. Materials and methods

2.1. General information

This study was conducted in the form of a comparative treatment observation, selecting 60 low-risk MDS patients admitted to our hospital from February 2022 to February 2023, who were randomly divided into 3 groups. This study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from the patients and their families.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

(1) Age ≥ 18 years, gender not limited.
(2) MDS patients who meet the WHO revised classification and the International Prognostic Score IPSS-R < 3.
(3) Relevant laboratory values
Serum albumin > 30 g/L; ALT and AST ≤ 80 U/L; creatinine ≤ 198 μmol/L; total bilirubin ≤ 33 μmol/L.

2.2.2. Exclusion criteria

(1) Patients with a clear history of bleeding, such as gastrointestinal bleeding, chronic active bleeding, etc [11].
(2) Patients with a history of severe drug allergy or known allergy to Roxadustat [11].
(3) Serum ferritin (SF) ≥ 500 ng/mL or parathyroid hormone (PTH) ≥ 800 pg/mL [11].
(4) Mental illness and poor compliance, refusal to cooperate [11].

2.3. Methods

All three groups of patients received routine treatment, including gastric protection, liver protection and anti-infection treatment, and blood transfusion treatment was assessed based on the specific condition of the patients. On the basis of routine treatment, all three groups of patients were treated with roxadustat (manufacturer: FibroGen (China) Pharmaceutical Technology Development Co., Ltd., National Drug Approval Number: H20180023).

Dosage and administration

(1) Observation group A
11 males and 9 females, aged 54–79 years, mean (62.12 ± 1.23), administration method: 100 mg, twice a week
(2) Observation group B
10 males and 10 females, aged 53–78 years, mean (61.02 ± 1.56), administration method: 50 mg, once a day
(3) Observation group C
12 males and 8 females, aged 54–79 years, mean (61.88 ± 1.92), administration method: 150 mg, twice a week.
Continue to take for 13 weeks, and follow up by telephone or visit the hospital for examination every week.

During the treatment, patients should be instructed to strictly follow the doctor's orders for medication.

2.4. Observation indicators

2.4.1. Recovery status

Based on the revised criteria for the efficacy of osteodystrophy syndrome by the International Working Group, the recovery status of patients was divided into three levels: complete remission (CR), partial remission (PR), and no remission (NR) [13].

Efficacy assessment

(1) CR

Anemia and bleeding symptoms improved, blood transfusion dependence was eliminated, hemoglobin increased by 30 g/L compared with one month before treatment, and blast cells < 5%

(2) PR

Anemia and bleeding symptoms disappeared, hemoglobin ≥ 90 g/L, platelets ≥ 80 × 109 L, bone marrow dysplasia was significantly reduced, and blast cells < 5%

(3) NR

Anemia and bleeding symptoms did not completely disappear, bone marrow dysplasia was not reduced, and hemoglobin < 60g/L.

Overall response rate (ORR) = (CR + PR + NR) / (number of cases / total number of cases) × 100%.

2.4.2. Incidence of adverse reactions

This study observed and recorded whether the three groups of patients experienced adverse reactions such as anemia, neutropenia, thrombocytopenia, nausea and vomiting, fever, and infection during the treatment period [14].

2.4.3. Hemoglobin (Hb) recovery time

Time for Hb to recover to ≥ 30 g/L, 60 g/L and 90 g/L.

2.5. Statistical methods

Data were processed using SPSS 20.0 statistical software. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and *t*-tests were used for comparisons between groups. Count data were expressed as [n(%)], and chi-square tests were used for comparisons between groups. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient enrollment

According to the MDS prognostic system score (≤ 3 points) and the inclusion criteria, a total of 60 low-risk MDS patients were included, as shown in **Table 1**.

Table 1. Patient enrollment

Prognostic parameters	Male	Female	Total
Primitive cells > 10%	10	5	15
Platelets ≤ 80g/L	13	7	20
Hemoglobin < 30×10^9 L	8	8	16
Neutrophils ≤ 0.8×10^9 L	2	7	9
Total	33	27	60

3.2. Comparison of recovery in the three groups

In terms of overall recovery, observation group B (ORR = 95%) was higher than observation group A (ORR = 75%) and observation group C (ORR = 85%). The comparison shows that observation group B had the best recovery ($\chi^2 = 10.883$, $p = 0.001 < 0.05$), see **Table 2**.

Table 2. Comparison of recovery status among the three groups [n(%)]

Group	n	Complete remission	Partial remission	No remission	Overall response rate
Observation group A	20	10 (0.50)	5 (0.25)	5 (0.25)	15 (0.75)
Observation group B	20	14 (0.70)	5 (0.25)	1 (0.05)	19 (0.95)
Observation group C	20	12 (0.60)	5 (0.25)	3 (0.15)	17 (0.85)
χ^2					10.883
p					0.001

3.3. Comparison of adverse reactions in the three groups

During treatment, the incidence of adverse reactions in observation group B (10%) was lower than that in observation group A (20%) and observation group C (25%), indicating that the treatment effect of observation group B was superior to the other two groups ($\chi^2 = 6.883$, $p = 0.001 < 0.05$), see **Table 3**.

Table 3. Comparison of adverse reactions among the three groups [n(%)]

Group	n	Anemia	Neutropenia	Thrombocytopenia	Nausea and vomiting	Fever	Infection	Total
Observation group A	20	0 (0.00)	2 (0.10)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.10)	4 (0.20)
Observation group B	20	1 (0.05)	0 (0.00)	0 (0.00)	1 (0.05)	0 (0.00)	0 (0.00)	2 (0.10)
Observation group C	20	2 (0.10)	0 (0.00)	12 (0.60)	1 (0.05)	1 (0.05)	1 (0.05)	5 (0.25)
χ^2								6.883
p								0.001

3.4. Comparison of Hb recovery time among the three groups

Regarding Hb recovery time, the recovery time required in observation group B (67.45 ± 2.91) was shorter than that in observation group A (83.23 ± 2.12) and observation group C (72.03 ± 1.99), indicating that Hb recovery time is shorter under low-dose, high-frequency treatment ($\chi^2 = 11.772$, $p = 0.001 < 0.05$), see **Table 4**.

Table 4. Comparison of time for Hb recovery ≥ 90g/L

Group	Recovery ≥ 30 g/L, days	Recovery ≥ 60 g/L, days	Recovery ≥ 90 g/L, days
Observation group A	51.85 ± 3.29	62.95 ± 2.91	83.23 ± 2.12
Observation group B	39.05 ± 5.16	48.60 ± 4.70	67.45 ± 2.91
Observation group C	45.50 ± 5.92	54.95 ± 5.41	72.03 ± 1.99
χ^2	9.231	0.400	11.772
p	0.010	0.819	0.001

4. Discussion

MDS is a heterogeneous myeloid clonal disease, often manifested as chronic progressive anemia. As the disease

progresses, once thrombocytopenia or severe neutropenia occurs, it may lead to symptoms such as recurrent fever, infection, and bleeding, and progress to AML [15]. Among them, low-risk MDS has always maintained a high incidence rate in clinical practice. The inducing factors of the disease are more complex, and the negative impact on the health of patients is more serious. There are many treatment methods for this disease in clinical practice, and blood transfusion and platelet therapy have a high implementation rate. However, in order to promote the rapid improvement of the patient's symptoms, it is necessary to adopt the best treatment plan.

Roxadustat is a novel hypoxia-inducible factor and a prolyl inhibitor. When applied to patients, it can stabilize hypoxia-inducible factors, reduce their degradation rate, accelerate the production of erythrocytes in patients, and improve iron regulation by regulating hepcidin levels [16]. This can lead to a rapid improvement in various symptoms of patients. At the same time, it can regulate the non-specific cellular immune level of patients, which helps to improve the symptoms of myeloproliferative disorders [17,18]. A phase III study of roxadustat (NCT03263091) showed initial efficacy in the treatment of low-risk MDS patients [10]. Ikenoue reported a case of LR-MDS patient who failed to respond to EPO receptor activator treatment but recovered from anemia again after treatment with roxadustat and had a prolonged transfusion-free period [19]. This confirms the effectiveness of roxadustat in the treatment of MDS, but there is no clear report on the administration method and dosage of roxadustat.

In this study, the low-dose, high-frequency drug treatment method was more effective in treating low-risk MDS patients. The recovery effect in observation group B (ORR = 95%) was higher than that in observation group A (ORR = 75%) and observation group C (ORR = 85%) ($\chi^2 = 10.883$, $p = 0.001 < 0.05$), indicating that roxadustat treatment can improve the overall response rate and facilitate patient recovery; the adverse reaction rate in observation group B (10%) was lower than that in observation group A (20%) and observation group C (25%) ($\chi^2 = 6.883$, $p = 0.001 < 0.05$), indicating that during medication, Low-dose, high-frequency dosing can effectively alleviate adverse reactions in patients, indicating that roxadustat has a high safety profile in treating low-risk MDS. Simultaneously, the time required for Hb recovery in observation group B (67.45 ± 2.91) was shorter than that in observation groups A (83.23 ± 2.12) and C (72.03 ± 1.99) ($\chi^2 = 11.772$, $p = 0.001 < 0.05$), suggesting that roxadustat has a positive effect on Hb survival time and can improve patients' immune function. These results indicate that low-dose, high-frequency dosing can effectively improve the treatment effect in low-risk MDS patients, with fewer adverse reactions, relatively high safety, and a positive effect on patient survival time. However, this study has limitations due to its small sample size and incomplete observation indicators. Further research should expand the sample size and add more observation indicators to obtain more complete and accurate results.

5. Conclusion

In summary, when using roxadustat to treat low-risk MDS, it is possible to use a low-dose, high-frequency administration method to improve the treatment effect on low-risk MDS patients.

Disclosure statement

The authors declare no conflict of interest.

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