Case Report

The Effect of Roxadustat on Transfusion-Dependent Myelodysplastic Syndrome Complicated by Chronic Kidney Disease

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Keywords

Myelodysplastic syndrome · Hypoxia-inducible factor-prolyl hydroxylase inhibitor · Roxadustat · Renal anaemia · Essential thrombocythemia

Abstract

Haematopoietic insufficiency is the treatment target of lower-risk myelodysplastic syndrome (MDS). Although erythropoiesis-stimulating agents (ESAs) are generally effective for treating anaemia, resistance can develop. Hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) improves renal anaemia by promoting endogenous erythropoietin production and normalizing iron metabolism. HIF-PH inhibitors could be used to treat MDS, but their efficacy and safety have not been studied. A 78-year-old female patient with essential thrombocythemia gradually developed anaemia and was diagnosed with therapy-related MDS 4 years later. The anaemia temporarily improved with ESAs, but the patient became transfusion dependent. At the same time, anaemia and chronic renal failure due to nephrosclerosis progressed, and the patient was diagnosed with MDS with renal anaemia. After switching from ESAs to roxadustat, an HIF-PH inhibitor, anaemia improved, and the patient was no longer transfusion dependent. No progression of the underlying disease or any adverse events was observed 4 months after initiating roxadustat.

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Introduction

The primary target in the treatment of lower-risk myelodysplastic syndrome (MDS) is haematopoietic insufficiency, where anaemia is the most common haematopoietic cytopaenia. After excluding the coexistence of other diseases, the administration of erythropoiesis-stimulating agents (ESAs) improves anaemia in 48–55% of cases if the blood erythropoietin (EPO) concentration is ≤ 500 IU/L [1]. However, there are many cases where ESAs are ineffective or the patient develops resistance. These have been shown to indicate a high incidence of cardio- and cerebrovascular events [2]. Furthermore, in such cases, patients become transfusion dependent, resulting in decreased quality of life, increased medical expenses, blood transfusion-related infectious diseases, and post-transfusion iron overload. Therefore, new therapeutic strategies are needed to improve erythropoiesis and eliminate transfusion dependence in lower-risk MDS patients.

Hypoxia-inducible factors (HIFs) are transcription factors that sense the hypoxic environment and promote erythropoiesis through interaction with EPO and its receptor, as well as iron metabolism [3]. HIF prolyl hydroxylase (HIF-PH) hydroxylates the proline residue of the HIF- α subunit and induces subsequent ubiquitination and proteasomal degradation [4]. HIF-PH inhibitors prevent this process, even in an environment of adequate oxygenation, which protects against HIF degradation. Therefore, HIF-PH inhibitors result in the accumulation of HIF- α , improving anaemia. One such example is roxadustat, an oral HIF-PH inhibitor that has been shown to improve renal anaemia in phase 3 trials of chronic renal failure patients [5].

HIF-PH inhibitors can be expected to improve anaemia in MDS patients, but their efficacy and safety have not yet been demonstrated. We report a case of MDS with anaemia due to chronic renal failure in which transfusion dependence was treated with roxadustat.

Case Report/Case Presentation

A 78-year-old female patient was referred to our hospital with a platelet count of 2.4 million/ μ L 4 years ago. JAK2V617F mutation was negative, and no other gene mutations characteristic of myeloproliferative neoplasms were examined. However, bone marrow examination revealed that the increased megakaryocytes were large and hyperlobulated and without characteristic features of other myeloproliferative neoplasms and MDS, such as erythroid/myeloid dysplasia, and there was no suspicion of reactive thrombocytosis. Therefore, a diagnosis of JAK2V617F-negative essential thrombocythemia (ET) was made. Hydroxycarbamide was initiated as a form of cell depletion therapy, and the platelet count was reduced to around 500,000/ μ L. During these 4 years, the patient progressively developed anaemia, and transition to myelofibrosis was suspected. The reticulocyte count of peripheral blood was not decreased (27.7%). Bone marrow examination was repeated, and no evidence of myelofibrosis was found. However, erythroblastopenia was found, and there were 3 strains of dysplasia (categories A and B), such as unusually large size and irregular hypersegmented granulocytes, micromegakaryocytes, non-lobulated and multiple widely separated nuclei megakaryocytes, megaloblastoid, and multinucleated erythrocytes. The bone marrow smear showed 2.4% myeloblasts, with a normal karyotype on chromosomal staining and <50 copies/ μ g RNA on the WT-1 mRNA quantitative test. Based on the above findings, the diagnosis of therapy-related MDS, MDS with multilineage dysplasia in the 2016 WHO classification, was made (low risk by the International Prognostic Scoring System [IPSS] and intermediate risk by the revised IPSS).

Considering the possibility of anaemia exacerbation caused by hydroxycarbamide, it was switched to anagrelide, and ESA therapy was initiated (darbepoetin alpha, 240 μ g per week). The anaemia temporarily improved; however, the patient gradually became transfusion dependent. Although the progression of anaemia was parallel to renal damage, a renal biopsy

Fig. 1. The patient's clinical course and laboratory test results. The patient's clinical course and laboratory test result changes are shown starting from the first visit. The upper row shows the course of treatment and blood transfusion frequency, the middle shows the platelet count and haemoglobin concentration, and the lower shows the creatinine. MDS, myelodysplastic syndrome.

could not be performed due to general condition and bleeding tendency due to antiplatelet drug prescribed for ET. She had a history of hypertension, had no proteinuria or urinary occult blood, and had no underlying illness such as diabetes; thus, she was diagnosed with hypertensive nephrosclerosis without performing a renal biopsy. The anaemia progressed with gradual renal damage, as shown in Figure 1. The patient was then diagnosed with MDS with renal anaemia, and the treatment was switched again from ESA to roxadustat (50 mg per day, 3 times a week) as a treatment for renal anaemia. The anaemia quickly resolved, and the patient was no longer transfusion dependent. The erythropoietin level before roxadustat administration was 101 mIU/mL but was 30–70 mIU/mL after roxadustat administration. Four months after this therapy was initiated, the patient's anaemia significantly improved, without progression of ET or MDS. Moreover, no adverse events, such as thromboembolic events and solid tumours, have been reported.

This case report was carried out following the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from the patient for its publication as well as any accompanying images.

Discussion/Conclusion

We encountered a case of MDS with renal anaemia, resistant to darbepoetin alpha, that was successfully treated with roxadustat and became transfusion independent. Along with pure red cell aplasia, MDS is a major cause of acquired erythroblastopenia [6]. MDS is a

heterogeneous disease, but anaemia is the most common form of cytopenia. In MDS, ineffective haematopoiesis, also called dyserythropoiesis, is due to an increased rate of progenitor cell apoptosis caused by the disruption of erythroid nuclear opening and histone release, as well as reduced levels of GATA-binding factor 1 (GATA-1) [7]. GATA-1 is a significant regulator of the erythroid progenitor lineage involvement, differentiation, and survival, and EPO allows the development of the GATA-1-induced erythroid differentiation program [8]. EPO is relatively low in MDS patients and renal anaemia; therefore, it allows GATA-1 cleavage in the erythroid progenitor cells [9]. Similar to ESAs, HIF-PH inhibitors are expected to improve anaemia in MDS. Recently, it was reported that ESA and roxadustat had been used in combination to treat anaemia in patients with ESA-resistant MDS [10]. Clinical trials of HIF-PH inhibitor treatment are currently underway in various countries (NCT03263091 and NCT03303066) [11], and at our institution, we are conducting studies to assess the efficacy and safety of HIF-PH inhibitors in patients with lower-risk MDS.

HIF-PH inhibitors have rather peculiar complications; therefore, caution is warranted. In the clinical trials of HIF-PH inhibitor use for renal anaemia, it has been reported that the incidence of thromboembolism is higher than that of the control group [12]. Since the patient in our case report had ET, which is already associated with an increased risk of thrombosis [13], platelet count control and low-dose aspirin therapy were initiated; thus, thrombosis did not occur. Furthermore, HIF-PH inhibitors increase vascular endothelial growth factor production, which may, in turn, increase the incidence of solid tumours. Moreover, ET is known to be associated with a higher incidence of solid tumours when compared to healthy individuals [14], and HIF-PH inhibitors may further increase this risk. Although the patient does not currently have any solid tumours, regular screening tests will be carried out for early detection. Furthermore, it is not yet known how HIF-PH inhibitors affect the pathology of MDS. HIF1A mRNA and protein expression have been reported to be enhanced in the bone marrow, while in cell line experiments, it has been shown that HIF1A protein expression was increased due to genetic abnormalities frequently observed in MDS [15]. The same study reported that inducing HIF-stabilizing mutations in mouse blood cells caused MDS and that HIF knockout and HIF inhibitors in MDS mice prolonged their survival. Therefore, the authors concluded that HIF1A is activated in MDS, and its inhibition may improve the outcome. It is important to note that when HIF-PH inhibitors are used, the expression of HIF1A is enhanced, and there is concern that MDS may progress to acute leukaemia. In our case report, the disease had not progressed. However, future prospective trials are needed to verify this association.

In this case report, roxadustat was significantly effective in improving anaemia in a patient with MDS. It is necessary to monitor thrombosis, solid tumours, and the progression of MDS. Prospective clinical trials are needed to verify the efficacy and safety of MDS.

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Statement of Ethics

This case report was carried out following the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. The study is exempt from ethics committee approval because it is a single case report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Ryujiro Hara. The first draft of the manuscript was written by Ryujiro Hara, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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