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Case Report

CASE REPORT

Transfusion-dependent anaemia treatment using continuous erythropoietin receptor activator (epoetin β pegol) and roxadustat after darbepoetin treatment failure in low-risk myelodysplastic syndrome: a case report

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Abstract

Treatment of anaemia and reduction of transfusion are major therapeutic goals in patients with low-risk myelodysplastic syndrome (MDS). Although erythropoiesis-stimulating agents (ESAs) are widely used to reduce transfusion requirement, ESAs lose effectiveness within 12 months. We report a 65-year-old Japanese woman diagnosed with low-risk MDS who underwent long-term use of continuous epoetin β pegol, an erythropoietin receptor activator (CERA), and her treatment after CERA failure. She received darbepoetin alpha (DPO) for transfusion-dependent anaemia and was free from transfusion. However, after 8 months, DPO lost effectiveness. She then received CERA and recovered from anaemia. Her haemoglobin level remained >10 g/dl for 3 years and 4 months. However, even CERA lost effectiveness, and she received roxadustat treatment with CERA, leading to recovery from anaemia again. Although further evidence is required, the extension of the no-transfusion period provided by ESAs and roxadustat is important and is awaited among low-risk MDS patients.

INTRODUCTION

Myelodysplastic syndrome (MDS) is characterized by ineffective erythropoiesis, caused by excessive premature apoptosis of haematopoietic precursors [1]. Anaemia is a major risk factor of poor prognosis in MDS. Primary supportive care includes red blood cell (RBC) transfusion, which is an independent risk factor of poor MDS prognosis and is associated with impaired quality of life (QoL), increased cardiovascular risks and iron overload [2]. Anaemia treatment and reduction of transfusion-need are, therefore, major therapeutic goals in patients with low-risk MDS. Erythropoiesis-stimulating agents (ESAs) are widely used to reduce the need for RBC transfusion in low-risk patients with MDS. In particular, darbepoetin alpha (DPO) improves the patient response rate. However, ESAs lose their effectiveness within 12 months in many responders [3]. Treatment options after ESA failure are limited in MDS cases.

Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor [4], is used for anaemia treatment in patients undergoing dialysis and is under investigation in a Phase III trial for anaemia treatment in low-risk patients with MDS

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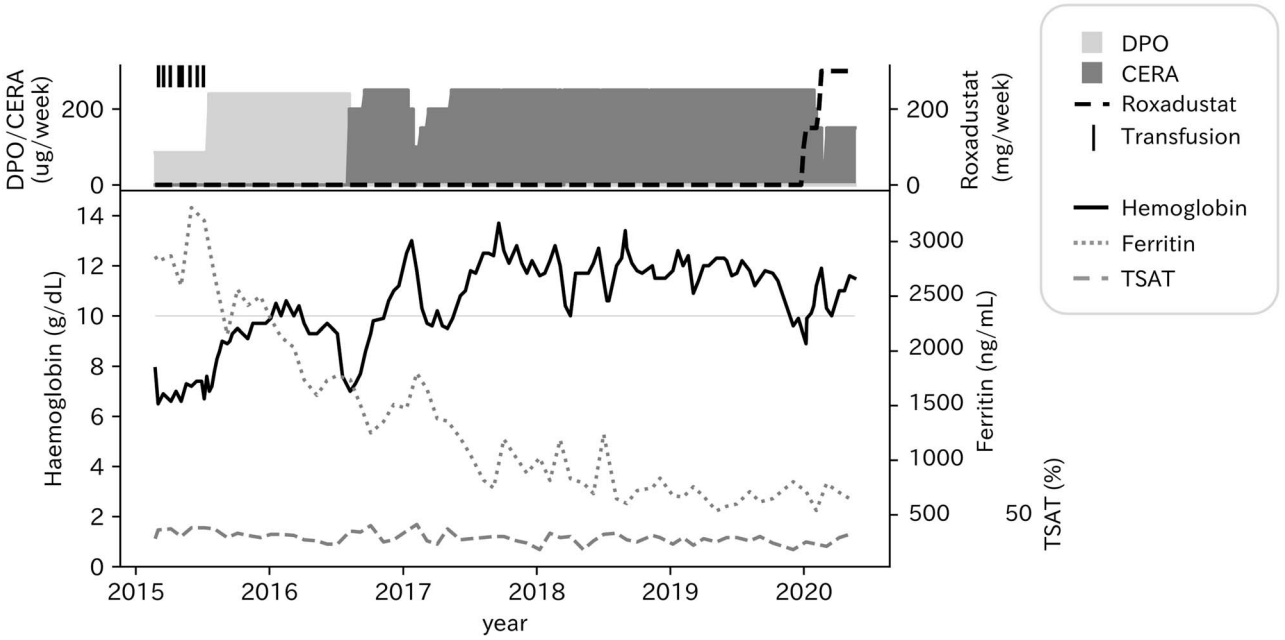

Figure 1: clinical course of the patient. The upper graph shows the administration course of drugs and transfusions per week. The lower graph shows the changes in examination data. The total values of DPOα and EPOα are represented by light grey shadows; CERA (epoetin β pegol), dark grey shadow; and roxadustat, bold dashed line in the upper graph. The transfusions are represented by whiskers. The total values of DPOα and EPOα are calculated after converting EPOα (200 IU) into DPOα (1 µg). The haemoglobin concentration is represented by the solid line, ferritin by the dotted line and transferrin saturation by the dashed line in the lower graph.

(NCT03263091) [4, 5]. Our previous study reported a continuous erythropoietin receptor activator, continuous epoetin β pegol, an erythropoietin receptor activator (CERA), as a therapeutic option after DPO failure [6]. Herein, we provide further information regarding treatment after DPO failure among low-risk patients with MDS and report our experience of long-term CERA use and treatment after CERA failure.

CASE REPORT

A 65-year-old Japanese woman, whose detailed clinical information has been published [6], was diagnosed with MDS via bone marrow aspiration in 2008. She had refractory anaemia, as defined by the World Health Organization and was categorized by the IPSS (the International Prognostic Scoring System) as belonging to the low-risk group (IPSS low or Int-1). She had diabetes since 1991; with resultant renal insufficiency, haemodialysis was initiated in January 2015. She was transfusion dependent, with haemoglobin levels maintained at 6.5 g/dl via transfusion every week 44 during the predialysis period. Frequent transfusions resulted in congestive heart failure and secondary hemochromatosis; she was diagnosed with transfusion-associated circulatory overload. Accordingly, treatment with epoetin α (9000 IU/week) plus DPO (40 µg/week) was started with haemodialysis initiation. However, even after ESA initiation, she continued to require transfusion. In July 2015, we increased the DPO dose to 240 µg/week. After 2 weeks of DPO treatment, the anaemia resolved; she no longer needed transfusions, and the haemoglobin concentration was maintained at >10 g/dl. From March 2016, she gradually developed resistance to DPO treatment. In July 2016, her haemoglobin concentration rapidly decreased to 6.8 g/dl and she needed transfusions again. We then switched the ESA from DPO to CERA (250 µg/week) in August 2016. After switching, the haemoglobin concentration again gradually increased, and she no longer needed further transfusions. No progression of anaemia was observed for 3 years and 4 months; her haemoglobin concentration was stable at >10 g/dl. In December 2019, although her iron metabolism was stable and anaemia treatment did not change, her haemoglobin concentration fell to <10 g/dl, reaching 8.9 g/dl in January 2020. Throughout this period, no obvious physical changes or particular adverse events were observed. Accordingly, we suspected that the drop was caused by CERA treatment failure and initiated roxadustat treatment. First, roxadustat at 150 mg/week was initiated along with CERA (150 µg/week), and the roxadustat dose was later increased to 300 mg/week. Her haemoglobin concentration increased again, and we decided to gradually switch the drug to roxadustat alone and decreased CERA to 50 µg/week. However, this change resulted in a decrease in the haemoglobin concentration. Therefore, we administered both CERA (150 µg/week) plus roxadustat (300 mg/week). Her haemoglobin level is currently maintained at >10 g/dl for over a year (Fig. 1).

DISCUSSION

The clinical course of our patient provides two important indications: (i) CERAs may be able to reduce the transfusion-need among low-risk patients with MDS and (ii) roxadustat when used along with ESAs may be able to control anaemia.

The introduction of CERA in MDS treatment may be favourable for low-risk patients with MDS. In our case, CERA treatment led to a long-term freedom from transfusions. ESAs lose their effectiveness with regard to anaemia treatment in low-risk patients with MDS in a few years. Epoetin loses its effectiveness in 0.42 years and DPO in 0.75 years [3]. Prevention from transfusion-dependent anaemia leads to improved QoL and overall survival in low-risk MDS patients. In low-risk

MDS patients, the utility scores from which quality-adjusted life-years (QALYs) are calculated are higher for transfusion independence than for transfusion dependence, with a difference of 0.24 [7]. Furthermore, as she avoided treatment for iron overload caused by transfusions, she obtained a utility score of at least 0.21 [8]. Thus, she achieved 1.65 QALYs after CERA treatment.

Roxadustat may compensate for the loss of effectiveness of CERA in low-risk MDS patients if anaemia results from the loss of effectiveness of CERA. In our case, although adding roxadustat to CERA resulted in recovery from anaemia, when we stopped CERA treatment, the anaemia recurred. Although the starting dose was low (1.67 mg/kg), roxadustat may not induce sufficient effects as a single agent [9]. Roxadustat as well as granulocyte colony stimulating factor may achieve a 30% improvement in ESA resistance [10] and reduce ESA resistance among low-risk patients with MDS by suppressing apoptosis of haematopoietic stem cells.

The following points should be noted when interpreting this case report: first, anaemia progression while using CERA may not have resulted from ESA resistance. However, the abovementioned discussion about the combination of ESA and roxadustat holds because reducing the dose of ESAs diminished the effects of roxadustat, leading to the promotion of anaemia. Second, the safety of using roxadustat in patients with MDS has not been confirmed. Roxadustat should not be used for solid tumours, and the results of a phase III trial concerning its use in low-risk MDS patients are awaited.

In our case, we examined the long-term use of CERA in a low-risk patient with MDS having anaemia and found that after the failure of CERA, supplementation with roxadustat was effective. Although further evidence is required, ESAs may extend the no-transfusion period among low-risk patients with MDS.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

Keijin-kai Institutional Review Board (IRB) approved this report (IRB Log Number: 8).

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

GUARANTOR

All authors guarantee this case report.

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