CORRESPONDENCE

Long-Term Maintenance of Hematological and Cytogenetic Remission in 5q- Syndrome After Short-Term Administration of Lenalidomide

Yuka Kawaji¹ · Hiroto Kaneko² · Takahiro Fujino¹ · Saeko Kuwahara^{1,3} · Muneo Ohshiro¹ · Yoshiko Hirakawa¹ · Toshiki Iwai¹ · Hitoji Uchiyama¹ · Junya Kuroda³ · Masafumi Taniwaki^{2,3}

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Dear Editor,

Myelodysplastic syndrome (MDS) is a disease of the hematopoietic stem cell, characterized by peripheral blood pancytopenia and morphological dysplasia of hematopoietic cells. Deletions of the long arm of chromosome 5 (5q-) are commonly found in MDS as a part of complex chromosomal abnormalities. Patients with 5q- as a sole abnormality are classified as 5q- syndrome, and are well known to present severe anemia and transfusion dependence [1]. Remarkably, lenalidomide is sensitive to 5q- syndrome by inhibiting proliferation of the 5q- clone and promoting effective erythropoiesis in non-5q- MDS progenitors [2]. The participation of various molecules has been suggested in the pathogenesis of this disease, such as SPARC, and RPS14, which are encoded on 5q31-33, the commonly deleted segment [3]. In recent years, the reports on discontinuing lenalidomide treatment for 5q- syndrome have been increasing, and we present a patient who maintains hematological complete remission over 3 years after the discontinuation of this drug.

A 67-year-old man presented to our hospital with dizziness lasting for 4 months in September 2011. His

previous medical past history included a total gastrectomy for duodenal ulcer. Physical examination revealed anemia of the skin and conjunctiva. He did not have enlarged superficial lymph nodes or hepatosplenomegaly. Vital signs were unremarkable. His blood cell count showed normocytic anemia with hemoglobin (Hb) at 8.6 g/dl. White blood cell and platelet levels remained within normal limits. Serum lactate dehydrogenase was not elevated. Serum levels of vitamin B12, folic acid, and ferritin were normal. Examination of an aspirated specimen of the bone marrow revealed hypoplasticity. The nucleated cell count was 50,000/μl, with 2.4% myeloblasts. His M/E ratio was elevated at 11.77. The blood cells exhibited abnormal morphological features; the pseudo-Pelger-Huet anomaly, and small megakaryocytes. Chromosomal analysis (Giemsa-banding stain) showed a 5q- as the sole abnormality in 12 of 20 (60%) metaphases (Fig. 1). The precise chromosomal breakpoint was unclear. He was diagnosed with refractory anemia according to the French-American-British criteria and was also classified as MDS with isolated del(5q) by the World Health Organization criteria [4].

Administration of lenalidomide at a dose of 10 mg/day was started. This treatment cycle consisted of dosing for 3 weeks, followed by 1 week of rest. Although the patient initially needed transfusion of red blood cell products once every 2 weeks, within a month after beginning the therapy, he no longer required transfusions. Adverse events included grade 2 neutropenia (according to Common Terminology Criteria for Adverse Events Ver. 4.0) and grade 3 thrombocytopenia that spontaneously improved. A grade 2 itchy skin rash also appeared on his back, which was treated with an anti-histaminergic agent and ointment.

We administered the second and third courses of lenalidomide and his Hb level increased gradually. In January 2012, after 12 weeks of treatment, lenalidomide was

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✉ Yuka Kawaji
yuka0914@koto.kpu-m.ac.jp

¹ Department of Hematology, Japanese Red Cross Kyoto Daiichi Hospital, 15-749 Honmachi, Higashiyama-ku, Kyoto 605-0981, Japan

² Department of Hematology, Aiseikai-Yamashina Hospital, 19-4 Takehana-Shichono-cho, Yamashina-ku, Kyoto 607-8086, Japan

³ Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8586, Japan

Fig. 1 Karyotypic analysis showed a deletion of chromosome 5q. Precise breakpoint is not remarkable

discontinued because of the patient's economic circumstances. However, his reticulocyte count and Hb level continued increasing. A bone marrow examination was repeated after 2 years of treatment discontinuation, which showed nucleated cell counts of 29,000/ μ l, with only 0.4% of myeloblasts, and normalized M/E ratio (2.93). No morphological abnormalities of erythroid cells and megakaryocytes were observed. Segmented mature neutrophils have also no dysplasia. On cytogenetic analysis, 5q- was observed in only 3 of 20 examined metaphases (15%), indicating that cytogenetic partial remission (PR) maintained. Currently, the patient maintains hematological complete remission (CR) without any treatment for 45 months.

He achieved only PR in cytogenetic study. We suggest that even though some 5q- clones remain in his body theoretically, a small pre-existing pool of normal hematopoietic stem cells may repopulate the myeloid and erythroid progenitor compartments because of prior lenalidomide treatment. Alternatively, the patients who can discontinue this drug, such as our patient, may have too small amount of pathological stem cells to rapidly deteriorate the disease. Based on this hypothesis, there is the possibility that achieving CR is not required to discontinue the use of this drug.

Eliminating the need for drug therapy improves the quality of patients' lives. Additionally, the long-term adverse effects of lenalidomide are not well known. To our best knowledge, only a few cases who maintain long-term hematological CR without achieving cytogenetic CR have been reported. From previous reports, discontinuation of lenalidomide treatment might tend to correlate closely with

rapid erythroid response [5]; however these unusual cases are too limited in number to investigate. Therefore, it is necessary to accumulate similar cases because of the stratification of patients recommended to discontinue lenalidomide treatment.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participant included in the study.

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