Late Hematological Improvement of Myelodysplastic Syndrome Following Treatment with 5-Azacitidine Therapy

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Abstract

Recently, 5-azacitidine has been reported to improve the survival of patients with high-risk myelodysplastic syndrome (MDS) and was approved for the treatment of MDS in Japan. We herein report a case of high-risk MDS in which the patient exhibited a hematological improvement three months after the first cycle of 5-azacitidine therapy. The second cycle of 5-azacitidine was not administered due to a severe pulmonary infection. Bone marrow aspiration revealed a decrease in the level of blast cells from 7.0% to 0.7%, and the subclassification of MDS improved from refractory anemia with excess blasts (RAEB)-1 to refractory cytopenia with unilineage dysplasia. This case demonstrates a possible late effect of 5-azacitidine treatment.

Key words: azacitidine, MDS, RAEB, RCUD, single-cycle treatment


Introduction

Myelodysplastic syndrome (MDS) is a stem cell disorder characterized by ineffective hematopoiesis and bone marrow dysplasia that, in many cases, progresses to acute myeloid leukemia (1). Treatment for MDS is variable and applied according to the risk classification based on the International Prognostic Scoring System (IPSS) (2, 3). 5-Azacitidine, a cytidine nucleoside analog, is a demethylating agent that was approved by the U.S. Food and Drug Administration for the treatment of high-risk MDS in 2004 (4-6). 5-Azacitidine was also made available locally in 2011. In an international multicenter Phase III study (the Aza-001 study), 5-azacitidine was found to achieve a better overall survival in patients with high-risk MDS compared to conventional therapies (4, 7, 8). Almost all patients were treated with more than one cycle and approximately half achieved a first response after two or more cycles (9).

We herein report the clinical course of a high-risk MDS patient who received only a single cycle of 5-azacitidine therapy (75 mg/m² for seven days) due to the development of severe pulmonary infection after the first cycle and subsequently exhibited a hematological improvement after three months of therapy. This case indicates that treatment with 5-azacitidine may achieve an effective therapeutic response within a few months of the initiation of therapy.

Case Report

A 67-year-old man presented with a three-month history of dyspnea in January 2008. A complete blood cell count (CBC) showed a white blood cell count of 2.6×10⁹/L, hemoglobin level of 10.2 g/dL and platelet count of 52×10⁹/L. Bone marrow aspiration demonstrated a blast cell level of 9.1%, with indicating bilineage dysplasia and a normal karyotype. The patient was diagnosed with MDS refractory anemia with excess blasts (RAEB)-1, IPSS intermediate-1 and WPSS (WHO-based Prognostic Scoring System) intermediate-2 (3, 10).

Treatment with regular transfusions of red blood cells (RBCs) was commenced in March 2009, and the CBC subsequently showed a white blood cell count of 1.7×10⁹/L (blast cells: 0.0%), hemoglobin level of 5.9 g/dL and plate-
let count of 25×10^9/L with 15% blast cells in the bone marrow. Bone marrow aspiration revealed unilineage dysplasia with erythroid megaloblastic changes. A chromosomal analysis showed 47, XY, +1, der (1;7)(q10;p10), +8[1]/46, XY[19]. At that time, the diagnosis was MDS RAEB-2, while the IPSS score was high and the WPSS score was very high. Allogeneic stem cell transplantation was not performed due to the patient’s elderly age and impaired respiratory function resulting from his past medical history of pulmonary tuberculosis. Regular platelet transfusions were also started in February 2010, with RBC transfusions performed monthly. In September 2009, vitamins D and K were administered without a noticeable effect. During this period, the patient was admitted with febrile neutropenia several times. 5-Azacitidine treatment was therefore administered at a dose of 75 mg/m^2 for seven days starting in April 2011 (day 1), as it then became available in Japan. On this admission, the CBC showed a white blood cell count of 0.5×10^9/L (blasts: 0.0%), hemoglobin level of 7.6 g/dL and platelet count of 5.0×10^9/L. Prior to the administration of this therapy, bone marrow aspiration demonstrated a nuclear cell count of 0.1×10^10/L, with a blast cell level of 7.0% and a normal karyotype. The diagnosis was MDS RAEB-1, IPSS intermediate-1 and WPSS high. After the first cycle of 5-azacitidine therapy, the patient suffered from febrile neutropenia, followed by severe bacterial pneumonia in the beginning of May. He received broad-spectrum antibiotics; however, a maximum of 6 L/min of oxygen was required and granulocyte colony-stimulating factor (G-CSF) was administered from day 36 (neutrophils: 0.01×10^9/L) to day 54 (neutrophils: 0.71×10^9/L). The patient ultimately recovered in association with an increase in the neutrophil count, at 1.3×10^9/L on day 73. The platelet count and hemoglobin level gradually increased starting in July; therefore, no further platelet transfusions were administered after day 79 and no RBC transfusions were required after day 93 (Figure). Eventually, a hematological improvement was observed in the levels of erythroid cells, platelets and neutrophils, according to the criteria of the International Working Group 2006 (11), and bone marrow aspiration performed on day 127 showed a nuclear cell count of 2.5×10^9/L, with a blast cell level of 0.7% and a normal karyotype. Erythroid megaloblastic changes were observed. The diagnosis was changed from RAEB-1 to refractory cytopenia with unilineage dysplasia (RCUD). However, the second cycle of treatment was postponed due to worsening of the previous severe pulmonary complications.

The patient’s hematological response did not persist, and he consequently returned to a transfusion-dependent state, receiving platelets on day 138 and RBCs on day 192, in association with a decrease in the level of neutrophils. In due course, he suffered from multiple pulmonary infections and received broad-spectrum antibiotic treatment. G-CSF was administered every few days from day 220 to day 241; however, no hematological response was observed. The patient ultimately died of bacterial pneumonia on day 242.

**Discussion**

This report describes a rare case of 5-azacitidine efficacy after a long treatment interval. Hematological improvements in the levels of RBCs, platelets and neutrophils were obtained after three months of a single cycle of therapy, result-
ing in independence from RBC and platelet transfusions. The nuclear cell count increased in association with a decrease in the blast cell count in the bone marrow, and the diagnosis improved from RAEB-1 to RCUD, with persistent unilineage dysplasia involving erythroid megaloblastic changes. A recovery in the capacity for differentiation among malignant cells may be obtained via demethylation. Our findings suggest that the treatment efficacy of 5-azacitidine may become evident within an interval of several months after the single use of this agent. In the present case, G-CSF was administered after the therapy; therefore, it is possible that the patient’s hematological improvement was attributable to G-CSF treatment. However, no hematological recovery was observed after the readministration of G-CSF. Since the administration interval of G-CSF was different in this case, there is also the possibility that the G-CSF treatment interval triggered the hematological improvement. Another possibility is that the patient’s infectious disease was related to his hematological improvement, as previously reported (12). However, he did not show any hematological improvements prior to the administration of 5-azacitidine despite suffering from severe pneumonia and colitis.

A single cycle of 5-azacitidine therapy was administered in this case. Valentiny and colleagues reported the case of a 75-year-old woman with acute myeloid leukemia who achieved complete remission approximately six weeks after a single cycle of 5-azacitidine therapy (13). One additional 5-azacitidine cycle was administered seven months after a relapse occurred, although it resulted in a slight and short-term increase in the levels of thrombocytes and granulocytes, corresponding to a nonresponse according to the criteria of the International Working Group. Garcia-Manero et al. also reported that most MDS patients show a reversal in the expression interval triggered the hematological improvement. An-ther possibility is that the patient’s infectious disease was related to his hematological improvement, as previously re-ported (12). However, he did not show any hematological improvements prior to the administration of 5-azacitidine despite suffering from severe pneumonia and colitis.

The authors state that they have no Conflict of Interest (COI).

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References