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Long-term hematologic response after azacitidine treatment in a lower-risk myelodysplastic syndrome patient: A case report

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ABSTRACT

We report results of a 65-year-old patient with lower-risk myelodysplastic syndrome and multilineage dysplasia treated with hypomethylating agents. After failure of erythropoietin and thalidomide, the patient received azacitidine and achieved hematological remission for 95 months. In 2016, the treatment was switched to decitabine with promising results. These data showed that azacitidine used as a third-line treatment resulted in an exceptionally long-lasting positive hematological response after standard first- and second-line therapies had failed. Additionally, the patient experienced a good quality of life with no complications related to profound cytopenia, and continues to do so at the time of this report's preparation.

1. Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous hematopoietic disorder characterized by clonal hematopoiesis, abnormal cellular maturation, and cytopenia of one or more peripheral blood cells [1]. Based on the International Prognostic Scoring System and the revised International Prognostic Scoring System, patients with MDS are often broadly grouped into those with a lower or a higher risk of transformation to acute myeloid leukemia [1]. This stratification along with other factors, such as patient comorbidities, helps to tailor initial patient therapy [2,3].

Treatment goals of lower- and higher-risk MDS differ: treatment of lower-risk MDS aims at reducing cytopenia and improving quality of life, while treatment of higher-risk MDS aims at delaying leukemic progression and improving survival [1,4]. First-line therapy in lower-risk MDS patients without chromosome 5q deletion includes the use of erythropoiesis-stimulating agents to treat refractory anemia [3]; however, no clear guidance exists regarding the choice of treatment following its failure [4]. Moreover, the most appropriate treatment approach is even less clear for lower-risk MDS patients who have other severe cytopenia beyond anemia [5]. Nevertheless, thalidomide or its derivatives such as lenalidomide have been successfully used in lower-risk MDS patients with and without chromosome 5q deletion [3,6].

Hypomethylating agents (HMTs), including azacitidine and decitabine, are the standard of care for higher-risk MDS [2,4]. These drugs have also been used as second-line therapy after failure of erythropoiesis-stimulating agents in lower-risk MDS patients with cytopenia of multiple blood cells [2,3]; however, reports have shown mixed results with HMTs. Some studies have indicated limited efficacy of azacitidine in these patients [7,8], while others have shown azacitidine to be safe and effective [9–11]. In fact, an expected event-free survival of up to 14 months has been reported for lower-risk MDS patients treated with azacitidine [12,13]. However, no reports are available on a good response to HMTs over a longer follow-up period.

To our knowledge, this is the first report of an exceptional patient with lower-risk MDS who showed an unexpectedly long-lasting positive hematological response to azacitidine used as a third-line therapy.

2. Case presentation

A 65-year-old male patient underwent an emergency hemorrhoidectomy in February 2007. Routine blood tests performed before and after the procedure revealed mild macrocytic anemia (hemoglobin concentration of 10.5 g/dL and mean corpuscular volume of 99 fL) and thrombocytopenia (106,000/μL). He was referred to a general practitioner in 2006 for further evaluation of his anemia. The patient had a history of hemorrhoids with recurrent insignificant blood loss and of a basal cell carcinoma on the upper left part of his lip, which was completely excised in 2003. He was not taking regular medication, and

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his family history was clear of malignancies.

The patient remained asymptomatic while his blood counts deteriorated after hemorrhoidectomy. His peripheral blood contained low granulocyte (1.2×10^9/L) and thrombocyte (83,000/μL) counts and erythroblasts made up 9 % of the cells. An abdominal ultrasound revealed no signs of liver cirrhosis or hepatosplenomegaly, and hepatitis B and C serology tests were negative. C-reactive protein levels remained within the normal range, and serum protein electrophoresis analysis returned normal values. Vitamin B12 (197 pmol/L) and folic acid (10.9 nmol/L) were also within normal range. However, levels of lactate dehydrogenase (252 U/L) and alanine aminotransferase (46 U/L) were above normal, while erythropoietin levels were low (27 U/L).

Later, a bone marrow biopsy revealed dysplasia of the erythroid and megakaryocytic cells. His hemoglobin concentration was 10.5 g/dL, the absolute neutrophil count (ANC) 1.52×10^9/L, and the thrombocyte count 62,000/μL. The analysis showed less than 1 % ringed sideroblasts, 2 % blasts in the bone marrow, and 0.5 % blasts in the peripheral blood, without Auer rods, with a normal karyotype (46,XY), and without 5q deletion. These findings met the 2016 criteria for MDS multilineage dysplasia [14]; the patient was given a lower-risk prognosis, according to the International Prognostic Scoring System, and very low risk prognosis according to the revised International Prognostic Scoring System.

At the time of diagnosis, first-line treatment for lower-risk MDS did not include HMTs. The patient was therefore first treated with erythropoietin for 22 weeks starting in April 2007, which was stopped due to ineffectiveness. Anemia did not improve, with a hemoglobin concentration between 9.5 and 10.5 g/dL, ANCs between 0.5 x and 1.2×10^9/L, and thrombocyte counts ranging from 30,000 to 60,000/μL. This was characterized as a primary failure per International Working Group 2006 treatment response criteria for hematological improvement [8].

After erythropoietin, the patient received thalidomide (50 mg once daily) for 16 weeks. He was also prescribed daily prednisone for overt fatigue, dyspnea, and weakness, which improved his general condition. The patient presented with jaundice due to ineffective erythropoiesis and a maculopapular skin rash, which showed perivascular mixed lineage on histological examinations, consistent with partially neutrophilic cutaneous vascular inflammation. The thalidomide treatment was eventually stopped due to ineffectiveness and persistent anemia, with a hemoglobin concentration between 9.4 and 11 g/dL. ANCs (0.5–0.7 ×

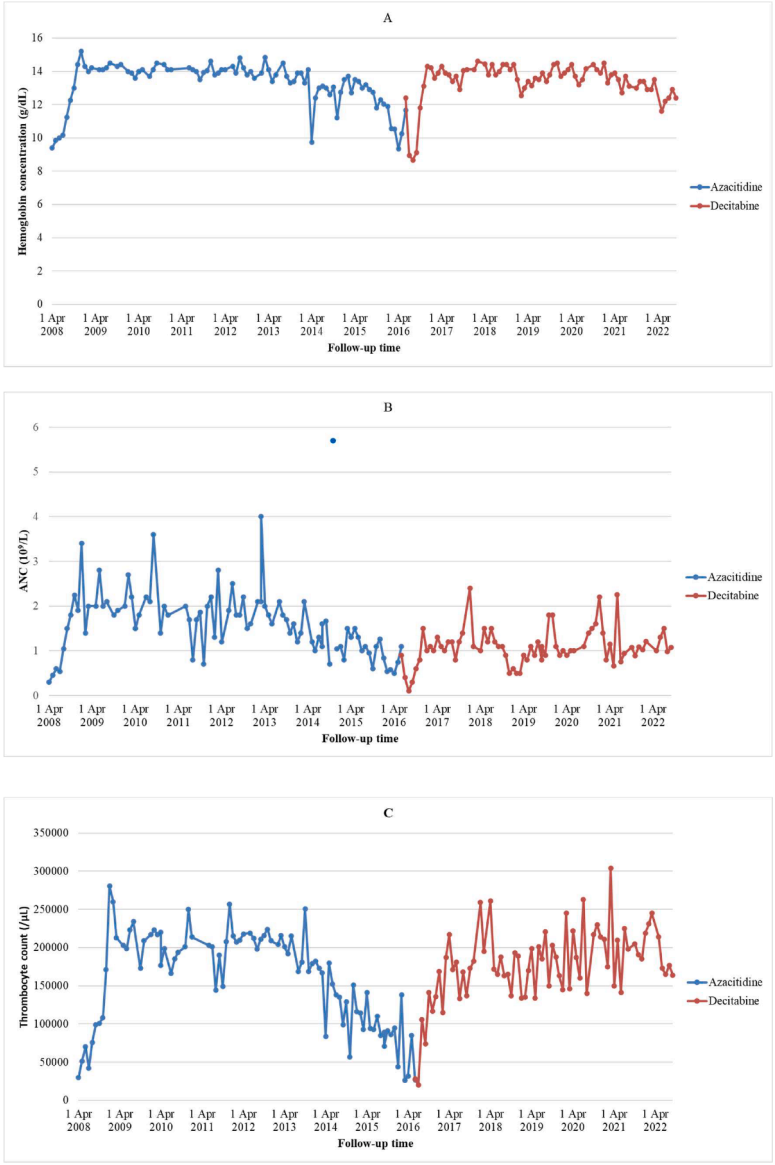

Fig. 1. Hemoglobin concentration (A), ANC (B), and thrombocyte count (C) after treatment with azacitidine and decitabine. Mean values are shown where multiple values were available in a month. The isolated dot in graph B depicts an outlier.

10^9/L) and thrombocyte counts (19,000–41,000/μL) were also low.

The patient's only sibling was not human leukocyte antigen-compatible, and thus an allogeneic transplantation was not possible. Following the exhaustion of standard treatment options and the known success, even though short-term, of HMTs in lower-risk MDS patients, the patient was subsequently placed on azacitidine (100 mg/m^2 given intravenously over the course of 1 h or subcutaneously daily for 5 days) in 2008. The treatment cycle was repeated every 4 weeks. Overall, the patient experienced a response duration of 95 months, corresponding to 84 cycles of azacitidine treatment.

The patient's hemoglobin concentration, thrombocyte counts, and ANCs clearly improved over the course of treatment with azacitidine (Fig. 1). The hemoglobin concentration improved from 9.3 to 11.4 g/dL after three treatment cycles (nearly 3 months), with a mean hemoglobin concentration of 12.9 g/dL. Thrombocyte counts increased from 18,000 to 165,000/μL after six treatment cycles (nearly 5 months), reaching a peak count of 281,000/μL and a mean count of 144,000/μL. Finally, ANCs improved from 0.3 to 1.5 $\times$ 10^9/L after five treatment cycles (nearly 5 months), with a mean of 1.6 $\times$ 10^9/L.

The patient's hemoglobin concentration, thrombocyte counts, and ANCs began to decline after the 60th cycle but remained within the normal range. After the 70th cycle, the patient became cytopenic. Around the 95th cycle of azacitidine, the hemoglobin concentration (9.9 g/dL), thrombocyte counts (55,000/μL), and ANCs (0.4 $\times$ 10^9/L) were low. Clinically, the patient was asymptomatic and tolerated treatment well (without dyspnea and weakness) for nearly 8 years. Nevertheless, he experienced sporadic infections during the last treatment cycles and a hematoma in the pelvic area before the final treatment cycle.

In 2016, treatment was switched to decitabine (30 mg/m^2), which was administered intravenously over the course of 1 h daily for 5 days with treatment cycles repeated every 4 weeks. The patient continued this treatment at the time of this report's preparation. The hemoglobin concentration (13.5 g/dL), ANCs (1.2 $\times$ 10^9/L), and thrombocyte counts (135,000/μL) increased after 22 treatment cycles with decitabine.

3. Discussion

In this case report, we described a unique lower-risk MDS patient who had an exceptional 95-month long positive hematological response to azacitidine after failure of first- and second-line treatment with erythropoiesis-stimulating agents and thalidomide. The patient tolerated the treatment well; he experienced a good quality of life over the course of the treatment and showed no complications related to profound cytopenia. Both goals of lower-risk MDS treatment were successfully met.

To our knowledge, this is the first study to present a lower-risk MDS patient treated with azacitidine with such a long-lasting positive response. Not only did the patient improve, in contrast to those in some studies where azacitidine displayed limited efficacy [7,8] or no survival benefit for lower-risk MDS patients [15], but he greatly surpassed the short-term event-free survival of up to 14 months previously reported [12,13] in cases where azacitidine had been efficient and safe in lower-risk MDS patients [9–11]. Furthermore, the patient's sustained positive response to decitabine has already exceeded the overall and event-free survival of up to 44 months published in the literature for lower-risk MDS [13,16]. Additionally, some studies have hinted that lower doses of azacitidine and decitabine administered with a shorter treatment schedule than the standard (3 days versus 5 days) are effective and well tolerated in lower-risk MDS patients [12,16]; however, the patient in this case report responded well with no complications despite receiving a standard treatment schedule. Even though the results presented here come from just one patient, this study indicates the potential of HMTs in lower-risk MDS patients and deserves further exploration.

4. Conclusion

In conclusion, this case report highlights two findings. First, azacitidine used as a third-line treatment resulted in an exceptionally long-lasting positive hematological response after standard first- and second-line therapies for lower-risk MDS had failed. Second, the patient experienced a good quality of life with no complications related to profound cytopenia, and continues to do so at the time of this report's preparation. These findings could benefit other patients with similar diagnosis, necessitating further research on the use of HMTs in the management of lower-risk MDS.

Authors contributions

KL was involved in writing the original draft. All authors reviewed and edited the final manuscript.

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Ethics approval

The study followed the institutional protocol.

Informed consent

The patient signed an informed consent for participation in this case report.

Declaration of competing interest

None.

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