Non-Requirement to Blood Transfusion in a Patient With Myelodysplastic Syndrome Following the Oral Administration of β-D-Mannuronic Acid: A Case Report

Afshin Ghaderi1,2, Sayyed Reza Safaee Nodehi2, Tahereh Bakhtiary3, Abbas Mirshafiey3,4*

1. Department of Internal Medicine, Hematology and Medical Oncology Ward, Tehran University of Medical Sciences, Tehran, Iran.
2. Cancer Research Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
3. Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
4. Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

* Corresponding Author:
Abbas Mirshafiey, PhD.
Address: Research Center for Immunodeficiencies, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: mirshafiey@tums.ac.ir

ABSTRACT

Myelodysplastic Syndromes (MDSs) is a heterogeneous group of hematologic neoplasms that causes cytopenia and dysplasia in one or more major bone marrow cell lines. The patients with this syndrome develop clinical complications associated with progressive bone marrow destruction leading to an increased risk for acute myelogenous leukemia. In the treatment of this syndrome, repeated infusion of Red Blood Cells (RBCs) may lead to iron overload, which is associated with a reduction in the survival rate of patients. In this paper, we report a case with MDS whose risk of dependence on blood transfusion was interstitial and received 4 units of packed RBCs once every 4 weeks. He had enrolled in our current clinical trial of β-D-mannuronic acid (M2000) in Iranian MDS patients. This 68-year-old man was treated with M2000, 500-mg capsule every 12 hours for 3 months. After 3 months of treatment, he experienced a non-requirement to blood transfusion following a hemoglobin increase of more than 2.5 g/dL in his blood sample. Moreover, the patient’s life quality was improved. This case report showed that M2000 drug might be an effective treatment for transfusion-dependent MDS patients (Clinical trial identifier; IRCT20130622013739N11).
Introduction

In 1982, the French-American-British (FAB) Cooperative Group classified the Myelodysplastic Syndromes (MDSs), which are characterized by ineffective hematopoiesis with (pan) cytopenia and a normo- or hyper-cellular Bone Marrow (BM) in five categories [1]. These morphologically-based subtypes include: 1. Refractory Anemia (RA); 2. RA with Ring Sideroblasts (RARS); 3. RA With an Excess of Blasts (RAEB); 4. Chronic Myelomonocytic Leukemia (CMML); and 5. RAEB ‘in transformation’ (RAEBt). The presence of any of the following features defines RAEBt: More than 5% of blasts in the Peripheral Blood (PB), 20-30% blasts in the BM and the presence of Auer rods in the PB or BM [1].

MDS may result from the irregular proliferation of clonal hematopoietic stem cells, resulting in an abnormal mutation of myeloid cells and apoptosis in many growing cells [1, 2]. The incidence rate for myelodysplastic syndrome increases with age and at least more than 20 per 100000 people over 70 years of age are affected by this syndrome [3]. Patients with this syndrome have a variable clinical course, but many eventually develop progressive bone marrow complications leading to the increased risk of acute leukemia [4].

MDS is frequently diagnosed in older males with previous exposure to benzene, chemotherapy, or radiotherapy. About 4000 to 50000 new cases are diagnosed each year in the US alone [2], with estimating the incidence rate of 4.3 per 100000 [3]. Up to half of the patients with MDS are asymptomatic and discovered after routine laboratory blood testing. Impaired hematopoietic stem cell proliferation and differentiation lead to abnormal cell morphology and physiology with a subsequent increase in morbidity. The common symptoms vary and can include fatigue and weakness due to anemia, infections caused by neutropenia, or bleeding due to thrombocytopenia.

Anemia is the most common cytopenia associated with MDS. The current management relies on frequent Red Blood Cell (RBC) transfusions and administration of erythropoietic growth factors to alleviate symptoms. However, the dependence of patients with MDS to repeated blood transfusions often results in significant clinical and economic consequences, poor outcomes, and diminished health-related quality of life. Also, the intensity and duration of blood transfusion dependence can influence the treatment responses after disease progression. Erythropoietic growth factors may alleviate the RBC transfusion requirement in some patients with MDS, although only minorities of the patients have an appropriate response.

Emerging treatment strategies to reduce or eliminate the need for RBC transfusions in patients with MDS include immunomodulating drugs, immunosuppressive therapy, and differentiating agents. The immunomodulating drug, lenalidomide, in patients who have MDS with 5q deletion is unique among emerging approaches, in that cytogenetic remitting activity and durable erythroid responses have been achieved. Newer treatments have the potential to improve the situation of MDS patients by alleviating the clinical, economic, and quality-of-life consequences of long-term RBC transfusion dependence.

The small molecule β-D-Mannuronic acid (M2000), was patented (PCT/EP2017/067919) as a novel non-steroidal anti-inflammatory drug with the immunosuppressive property. It is prepared using the sequential acidic hydrolysis procedure based on Fattahi et al. method [5]. This drug has been tested as an anti-inflammatory and a novel immunosuppressive agent in the various and expanded in vitro and in vivo human studies since 2000.

Case Presentation

A 68-year-old man was suffering from fatigue and chronic macrocytic anemia (hemoglobin level of 70 g/L and the mean corpuscular volume of 103.3 fl). He was not suffering from any serious illness and only used vitamin B12, folic acid, and vitamin B6. His initial medical examination was normal. The number of white blood cells, based on differential counts, was equal to 5.2×10^9/L, and his platelet count was equal to 163×10^9/L. In this patient, serum levels of vitamin B12, folate, and thyroid stimulating hormone, as well as the liver enzymes, were normal. Anemia was exacerbated in this patient, and his hemoglobin level was less than 80 g/L since three years ago. Therefore, he needed blood transfusions and received 4 units of packed red blood cells every 4 weeks.

Bone marrow aspiration and biopsy performed four years earlier revealed hypercellular bone marrow with dysplastic changes in the erythroid cell line, which is one of the categories of dysplastic changes. There were less than 5% blasts, and the karyotype was normal male. The patient was diagnosed with myelodysplastic syndrome (according to the World Health Organization, subtype of resistant cytopenia with the single-line dysplasia, refractory anemia). The primary grade of the patient in the international scoring system was 3.5 (interstitial risk).
He continued his dependence on blood transfusion and received almost 4 blood units every 4 weeks.

After receiving more than 40 units of packed red blood cells, his serum ferritin reached 2500 µg/L. The patient received 1000 mg oral deferasirox (20 mg/kg) per day at this stage. Three months after the onset of iron chelation therapy, his serum ferritin level reached less than 600 µg/L. The patient, who had previously been dependent on blood transfusion, received 100 units of packed red blood cells over 30 months. With this clinical history, he started the oral intake of 500-mg M2000 capsules (with the clinical trial code of IRCT20130622013739N11) every 12 hours for 3 months.

The patient was examined every 2 weeks, and blood transfusion was performed when his hemoglobin declined to less than 9 g/dL. In the first month, the patient received 4 units of blood just before taking the medication. Interestingly, in the second month, the hemoglobin level reached 8.7 g/dL, so that the transfusion of only one unit of packed red blood cells was carried out in the second month. In the third month, when the hemoglobin level reached 9.6 g/dL, the patient did not need any blood transfusion (Table 1). In the second month, the patient’s need for blood transfusion reduced from 4 units per month to 1 unit per month; in the third month, there was no need for blood transfusion. Since the patient was not dependent on blood transfusion, his quality of life improved. He experienced less fatigue and showed more tolerance in the exercise test.

### Table 1. The profile of hematologic determinants before and after treatment with M2000 in our MDS case

| Hematological Determinants | Before Treatment | One Month After Treatment | Two Months After Treatment | Three Months After Treatment | Normal Range |
|----------------------------|------------------|---------------------------|----------------------------|----------------------------|---------------|
| White blood cells          | 5.2              | 5.5                       | 5.8                        | 6                          | 3.6-11.0 K/uL |
| Red blood cells            | 2.8              | 2.7                       | 3.1                        | 3.5                        | 3.80-5.60 M/uL|
| Hemoglobin                 | 7                | 7.6                       | 8.7                        | 9.6                        | 11.6-16.8 g/dL|
| Hematocrit                 | 20               | 21                        | 25                         | 27                         | 35.1-50.0%    |
| Mean corpuscular volume    | 103              | 100                       | 103                        | 96                         | 73.5-96.5 fl  |
| Mean corpuscular hemoglobin| 23               | 23                        | 25                         | 26                         | 23.9-33.6 pg  |
| Mean corpuscular hemoglobin concentration | 33               | 32                        | 33                         | 33                         | 32-35 g/dL    |
| Red cell distribution width| 14               | 15                        | 14                         | 15                         | 12.1-16.5%    |
| Platelets                  | 163              | 178                       | 158                        | 155                        | 150-375 K/uL  |

Discussion

M2000 was introduced in a published paper as a novel Non-Steroidal Anti-Inflammatory Drug (NSAID) with immunosuppressive property based on its effects on Cyclooxygenase (COX)-1 and COX-2 gene expression and activity, as well as its potential efficacy was evaluated in phase I/II randomized clinical trial on ankylosing spondylitis [6, 7]. The results of a study showed that M2000 as a novel NSAID with immunosuppressive properties could improve hematological parameters through an increase in the count of RBCs and hemoglobin concentration in anemic patients with rheumatoid arthritis [8].

In another study, our results demonstrated that M2000 could decrease the gene expression and gelatinolytic activities of MMP-2 and MMP-9 in PMA-differentiated THP-1 cell line probably through inhibiting CD147 [9]. Hosseini et al. demonstrated that M2000 therapy not only prevents the formation of chronic inflammatory response but also inhibits crosstalk between tumor cells and their microenvironment, which is associated with the reduction of tumor growth and metastasis arrest [10]. Rastegari-Pouyani et al. illustrated that M2000 could be considered as an anti-angiogenic molecule which probably exerts its activity mainly via indirect effects on endothelial cells and its anti-inflammatory effects may partly be attributable to its anti-angiogenic activity.

Therefore, it could be recommended as a candidate for prevention and treatment of cancer, chronic in-
Inflammatory diseases, and other angiogenesis-related disorders [11].

In our case, his need for blood transfusion reduced 50% in the second month, and non-blood-dependent treatment was administered in the third month. This patient, based on the criteria of the International Working Group (IWG) [12] for modifying erythroid response received the blood transfusion 4 units per month so that his hemoglobin had increased to 7.0 g/dL before the start of mannuronic acid. Our new treatment protocol increased his hemoglobin level to 9.6 g/dL after 3 months of treatment, meaning that it was elevated more than 2 g/dL, which was an appropriate erythroid response according to IWG criteria (Table 1).

Drug M2000 as a novel NSAID with immunosuppressive properties had been previously introduced as a hematologic modifier based on the results of phase I/II clinical trial of this drug in patients with rheumatoid arthritis. In this case report, we clearly show this potent effect (transfusion-dependent) in one of our MDS patients.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declared no conflict of interest.

References:

[1] Pirayesh A, Verbunt R, Kluin PM, Meinders A, De Meijer P. Myelodysplastic syndrome with vasculitic manifestations. Journal of Internal Medicine. 1997; 242(5):425-31. [DOI:10.1046/j.1365-2796.1997.00213.x] [PMID]

[2] Tefferi A, Vardiman JW. Myelodysplastic syndromes. New England Journal of Medicine. 2009; 361(19):1872-85. [DOI:10.1056/NEJMra0902908] [PMID]

[3] Ma X. Epidemiology of myelodysplastic syndromes. American Journal of Medicine. 2012; 125(7):52-5. [DOI:10.1016/j.amjmed.2012.04.014] [PMID] [PMCID]

[4] Germing U, Küngdén A. Prognostic scoring systems in MDS. Leukemia Research. 2012; 36(12):1463-9. [DOI:10.1016/j.leukres.2012.08.005] [PMID]

[5] Fattahi MJ, Abdollahi M, Agha Mohammadi A, Rastkari N, Khorasani R, Ahmadi H, et al. Preclinical assessment of β-D-mannuronic acid (M2000) as a non-steroidal anti-inflammatory drug. Immunopharmacology and Immunotoxicology. 2015; 37(6):535-40. [DOI:10.3109/08923973.2015.1113296] [PMID]

[6] Mirshafiey A, Taeb M, Mortazavi-Jahromi S, Jafarnezhad-Ansariha F, Rehm BH, Esposito E, et al. Introduction of β-D-mannuronic acid (M2000) as a novel NSAID with immunosuppressive property based on COX-1/COX-2 activity and gene expression. Pharmacological Reports. 2017; 69(5):1067-72. [DOI:10.1016/j.pharep.2017.04.015] [PMID]

[7] Fattahi MJ, Jamshidi AR, Mahmoudi M, Vojdanian M, Yekaninejad MS, Jafarnezhad-Ansariha F, et al. Evaluation of the efficacy and safety of β-D-mannuronic acid in patients with ankylosing spondylitis: A 12-week randomized, placebo-controlled, phase II/II clinical trial. International Immunopharmacology. 2018; 54:112-7. [DOI:10.1016/j.intimp.2017.11.003] [PMID]

[8] Ahmadi H, Jamshidi AR, Mahmoudi M, Gharibdoost F, Vojdanian M, Fattahi MJ, et al. Hematological improvement of patients with active rheumatoid arthritis by β-D-mannuronic acid (M2000) as a novel NSAID with immunosuppressive property. Iranian Journal of Allergy, Asthma and Immunology. 2017; 16(5):433-42.

[9] Farahani MM, Motevaseli E, Maghsood F, Heidari-Kharaji M, Mirshafiey A. Anti-inflammatory property of β-D-mannuronic acid (M2000) on expression and activity of matrix metalloproteinase-2 and 9 through CD147 molecule in phorbol myristate acetate-differentiated THP-1 cells. Iranian Journal of Allergy, Asthma and Immunology. 2017; 16(5):443-51.

[10] Hosseini F, Hassannia H, Mahdian-Shakib A, Jadidi-Niaragh F, Enderman SE, Fattahi M, et al. Targeting of crosstalk between tumor and tumor microenvironment by β-D mannuronic acid (M2000) in murine breast cancer model. Cancer Medicine. 2017; 6(3):640-50. [DOI:10.1002/cam4.1013] [PMID] [PMCID]

[11] Rastegari-Pouyani M, Mostafaeia M, Mansouri K, Mortazavi-Jahromi S, Mohammad-Motlagh HR, Mirshafiey A. Anti-angiogenesis effect of β-D-mannuronic acid (M2000) as a novel NSAID with immunosuppressive properties under experimental model. Clinical and Experimental Pharmacology and Physiology. 2018; 45(4):370-6. [DOI:10.1111/1440-1681.12907] [PMID]

[12] Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006; 108(2):419-25. [DOI:10.1182/blood-2005-10-1419] [PMID]