Case Report

Myelodysplastic Syndrome with Transfusion Dependence Treated with Venetoclax

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Myelodysplastic syndromes are characterized by ineffective hematopoiesis in one or more lineages of the bone marrow. They are a group of heterogeneous clonal stem cell malignancies with a high risk to progress to acute myeloid leukemia (AML). Majority of adult MDS cases arise de novo; however, some are due to genotoxic damage from ionizing radiation or chemotherapy treatments [1]. In the United States, the incidence of MDS is 3-4 cases per 100,000 population per year and increases with age with 30 cases per 100,000 population per year among individuals of 70 years of age and older [2]. The prevalence of MDS is growing in part due to an ageing population and an increased awareness of these syndromes [3]. Prognosis of MDS is highly variable based on risk stratification ranging from several years in low-risk patients to several months in patients with high-risk disease [4].

Currently, there are no curative FDA-approved medications for MDS. Hematopoietic cell transplantation (HCT) is potentially the only curative option; however, treatment with HCT is often unavailable due to age and comorbidities or is not tolerated due to potential side effects. Hypomethylating agents (HMA), Azacitidine and Decitabine, and the immunomodulatory agent Lenalidomide are the only three FDA approved drugs for the treatment of MDS, all of which are noncurative. Venetoclax, an inhibitor of the antiapoptotic protein BCL-2 used to treat chronic lymphocytic leukemia, is currently being evaluated in clinical trials as a monotherapy in high-risk myelodysplastic syndromes/acute myeloid leukemia. We present a patient with transfusion-dependent myelodysplastic syndrome refractory to the current standard of care treatment not a candidate for hematopoietic cell transplantation who responded well to monotherapy treatment with venetoclax and has since remained transfusion-independent.

1. Introduction

Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis in one or more lineages of the bone marrow. They are a group of heterogeneous clonal stem cell malignancies with a high risk to progress to acute myeloid leukemia (AML). Majority of adult MDS cases arise de novo; however, some are due to genotoxic damage from ionizing radiation or chemotherapy treatments [1]. In the United States, the incidence of MDS is 3-4 cases per 100,000 population per year and increases with age with 30 cases per 100,000 population per year among individuals of 70 years of age and older [2]. The prevalence of MDS is growing in part due to an ageing population and an increased awareness of these syndromes [3]. Prognosis of MDS is highly variable based on risk stratification ranging from several years in low-risk patients to several months in patients with high-risk disease [4].
2. Case Presentation

A 53-year-old male with past medical history of hypertension, hyperlipidemia, peptic ulcer disease, gout, coronary artery disease, and sleep apnea underwent a CABG procedure in December 2011. Following CABG, the patient’s blood counts remained low, and in March of 2012, he was referred to Hematology at the VA for further evaluation. His CBC at that time demonstrated pancytopenia with a white count of $2100 \times 10^9/L$, hemoglobin of $9.7 \times 10^9/L$, and platelet count of 123,000 per microliter. He had 3% circulating blasts. The bone marrow demonstrated a hypercellular marrow with multilineage dysplasia. Cyto genetics were significant for translocation between chromosome 2 and 11 (t(2; 11)(p21; q23)). At that time, he was diagnosed with MDS (refractory anemia with excess blasts, intermediate I) and was found to have a revised IPSS (International Prognostic Scoring System) score of 3. The initial bone marrow blast count was 4% and the cytogenetics was 46, XY, t(2; 11). A repeat bone marrow showed a blast count of 3% and the cytogenetics was 46, XY, t(2; 11).

The patient was started on Azacitidine in September of 2012. This was complicated by elevated liver function tests as well as prolonged neutropenia. The bilirubin peaked at approximately 5–6 mg/dL. In November 2012, he received a 20% dose reduction of Azacitidine which was again complicated by acute hepatitis and renal failure with a creatinine of approximately 6 mg/dL, a total bilirubin peaked at 10 mg/dL and AST and ALT of 401 and 414 units per liter. His CBC demonstrated pancytopenia, however, was stable and he had not required any further blood transfusions. The licensed indication for the use of Azacitidine in Europe is IPSS Int-2 and high; therefore, its use was off-label. He had a response to Azacitidine for almost 10 months. In May 2013, CBC and high; therefore, its use was off-label. He had a response to Azacitidine for almost 10 months. In May 2013, CBC and high; therefore, its use was off-label. He had a response to Azacitidine for almost 10 months. 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there is currently an ongoing Phase 1b, open-label, multi-center study evaluating the safety and pharmacokinetics as a monotherapy or in combination with hypomethylating agents for the treatment of relapsed/refractory myelodysplastic syndrome with an estimated completion date of August 2020 (ClinicalTrials.gov identifier: NCT02966782).

**Figure 1:** Red blood cell and white blood cell count recorded during Venetoclax monotherapy treatment from December 2018 to January 2020. The treatment initially began on November 28, 2018 at 100 mg and after one month was increased to 200 mg.

**Figure 2:** Hemoglobin recorded during Venetoclax monotherapy treatment from December 2018 to January 2020. The treatment initially began on November 28, 2018 at 100 mg and after one month was increased to 200 mg.

**Figure 3:** Platelet count recorded during Venetoclax monotherapy treatment from December 2018 to January 2020. The treatment initially began on November 28, 2018 at 100 mg and after one month was increased to 200 mg.
A recently accepted abstract to the American Society of Hematology (ASH) 2019 Annual meeting presented preliminary results demonstrating that venetoclax in combination with HMAs led to high rates of marrow remission (55%) and hematologic improvement (38%) in a very high-risk and heavily treated MDS population after performing a retrospective review [13].

In this case, a patient with myelodysplastic syndrome refractory to current standard of care treatments with contraindications to alloSCT was treated with Venetoclax as the sole agent. After three months of treatment, the patient became transfusion independent. As of June 2019, he has not required further transfusions, however, remains mildly neutropenic. The development of new therapeutic strategies for MDS refractory to HMAs is an important avenue of research and is being extensively studied in clinical trials. Our case aims to demonstrate the feasibility of Venetoclax monotherapy for refractory MDS in hopes that in conjunction with the results of current and future clinical trials will become a standard of care option for these patients.

Disclosure

This case was presented at the Northern New England Clinical Oncology Society Annual Meeting on October 19, 2019, in Rockport, Maine.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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