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The Patient with Primary Myelofibrosis who Developed *Acute Myeloid Leukemia*: a Clinical Case Approach

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Abstract: MPNs are acquired clonal disorders of the hematopoietic stem cells characterized by the hyperplasia of one or several myeloid lineages. The aim of this study is evaluation of treatment a patient with AML after primary MF during her treatment. A 46-year-old female patient was presented to us 4 years ago with a one-month history of fatigue, night sweats, and abdominal distention. The biopsy results were reported as myelofibrosis. In the past history the assays for JAK2 V617F was positive and the Philadelphia chromosome was negative. We investigated the secondary myelofibrosis events, but all of them were negative. Treatment of myelofibrosis-related anemia was started with androgen (danazol). Afterwards, treatment with thalidomide (100 mg/day) was started. The patient was followed under thalidomide treatment for about 6 months. Thalidomide treatment was stopped and then we applied for compassionate use of ruxolitinib and splenic irradiation. At the beginning of ruxolitinib treatment, the constitutional symptoms regressed, but at the end of the sixth month her disease transformed to acute myeloblastic leukemia (AML). She was treated with low dose cytarabine 20 mg/day subcutaneous combined with ruxolitinib for two months with transfusion support. The patient died 3 months after recent rehospitalization, because of invasive aspergillosis. PMF is a serious bone marrow disorder and asymptomatic and its treatment is difficult. We can use other treatment methods like immunomodulating drugs, oncogenic pathways and target epigenetic and HSCT.
Keywords: AML, JAK2, Ruxolitinib, Primary MF.

INTRODUCTION

MPNs are acquired clonal disorders of the hematopoietic stem cells (HSCs) characterized by the hyperplasia of one or several myeloid lineages. Non-BCR-ABL classical MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). The *V617F* mutation of the protein kinase JAK2 is the most prevalent genetic abnormality in the 3 types of MPNs (95% in PV and ~50% in ET and PMF) [1]. Over the last 3 decades many therapies have been evaluated in myelofibrosis, including JAK inhibitors (e.g., ruxolitinib, fedratinib, pacritinib), immunomodulatory drugs (e.g., thalidomide, lenalidomide), DNA methyltransferase (DNMT) inhibitors (e.g., 5-azacytidine, decitabine), chemotherapeutic agents (e.g, hydroxyurea, cladribine), and biologic-response modifiers (e.g., androgens, erythropoietin) [2]. The International Prognostic Scoring System (IPSS) for PMF uses five risk factors consisting of age (>65 years), anemia (Hb <10 g/l), leukocyte count (>25 x 109/l), circulating blasts (>1%) and the presence of constitutional symptoms to categories patients in either a high (≥3 risk factors), intermediate-high (2 risk factors), intermediate low (1 risk factor) or low (no risk factors) risk group with a median survival of 27, 48, 95, or 135 months, respectively [3]. Clinical presentation for PMF may include splenomegaly, anemia, and multiple burdensome chronic symptoms such as night sweats, pruritus, early satiety, abdominal pain, left sub costal pain, bone pain, profound fatigue (irrespective of presence or degree of concomitant anemia), and cachexia [4]. Activating mutations in JAK2, MPL, and calreticulinare found in 60%, 8%, and 15% to 25% of PMF patients, respectively [5]. Ruxolitinib, an oral JAK1/JAK2 inhibitor (formerly INCB018424; Incyte Corporation, Wilmington, DE, USA), is approved in the US for the treatment of patients with intermediate or high-risk MF. Outside the US, ruxolitinib is approved forth treatment of MF in 42 countries worldwide [6]. An important cause of death in high-risk MF is transformation to acute myeloid leukemia (AML, i.e., myeloproliferative neoplasm [MPN] blast phase), which occurs in 8%-23% of patients with MF in the first 10 years after diagnosis [4,5]. Patients with MF that transform to AML have a dismal outcome [6], with an OS ranging from 3 to 8 months and a 1-year survival rate of 5%-10% [7]. The aim of this study is evaluation

of treatment a patient with AML after primary MF during her treatment.

CASE PRESENTATION

A 46-year-old female patient was presented to us 4 years ago with a one-month history of fatigue, night sweats, and abdominal distention. Huge splenomegaly was detected on physical examination; her spleen was 20 cm below the costal margin and with hepatomegaly .There was no lymphadenopathy. White blood cell (WBC) count was 2500 mm^3, hemoglobin level was 7.0 g/dL with MCV of 86 fL, hematocrit was 22% platelet count was 15000*10^9/L, and lactate dehydrogenase was 845 IU/L. Peripheral blood smear showed normocytic anemia, tear drop-shaped red blood cells (RBCs) (dacryocytes), and leuko erythroblastosis (nucleated RBCs and granulocyte precursors) and immature blastic cell. The bone marrow aspirate was a dry tap. Bone marrow biopsy revealed an increased number of megakaryocytes and a moderate increase of reticulin fibers. The biopsy results were reported as myelofibrosis. In the past history the assays for JAK2 V617F was positive and the Philadelphia chromosome was negative. We investigated the secondary myelofibrosis events, but all of them were negative. These findings showed that the patient had primary myelofibrosis. The prognostic score of the patient was calculated as intermediate-2 according to the International Prognostic Scoring System. Treatment of myelofibrosis-related anemia was started with androgen (danazol, 600 mg/day). After treatment with danazol for 3 months, it became clear that there was no increase in hemoglobin levels and so danazol treatment was stopped immediately. Treatment of myelofibrosis-related anemia was then started with hydroxyurea but myelosuppression began, and so hydroxyurea treatment was also stopped. In place of hydroxyurea, treatment of myelofibrosis-related anemia was started with interferon- alpha at 3 million IU subcutaneously 3 times/week, but the patient could not tolerate it. In the meantime, she became transfusion-dependent again and needed, on average, 4-6 units of erythrocyte suspension per month. Afterwards, treatment with thalidomide (100 mg/day) was started. After this treatment his constitutional symptoms regressed and hemoglobin levels increased, but the splenomegaly never regressed. The patient was followed under thalidomide treatment for about 6 months. During this period of time, on average, 2 units of erythrocyte suspension per month. However, in the 19th month, hemoglobin levels decreased to 6 g/dL and her spleen became enlarged. She gained weight, night sweats, and became transfusion-dependent again after 4 months. Thalidomide treatment was stopped and then we applied for compassionate use of ruxolitinib. During the application procedure, the patient's spleen size increased progressively; because of trouble with spleen infarctions, she is not eligible for splenectomy procedure and decided to splenic irradiation. Following the first month after splenic irradiation, ruxolitinib at 10 mg/day was given to the patient, who had a poor prognosis and still needed erythrocyte suspensions. At the beginning of ruxolitinib treatment, the constitutional symptoms regressed; the patient put on some weight and at the end of the first month. She required on average, 1 units of erythrocyte suspension per month. In the third month of treatment, the weight of the patient increased returned and all of her laboratory values were in the near normal reference range. She was followed with minimal symptom for 4 months, but at the end of the sixth month her disease transformed to acute myeloblastic leukemia (AML). She was rehospitalized and due to poor cardiac function not eligible for classic 7+3 chemotherapy. She was treated with low dose cytarabine 20 mg/day subcutaneous combined with ruxolitinib (10 mg/day) for two months with transfusion support. The patient died 3 months after recent rehospitalization, because of invasive aspergillosis.

DISCUSSION

MFs a challenging myeloid malignancy to treat effectively, limited by advanced age in the majority of patients, the presence of competing comorbid conditions, and the availability of tolerable disease-modifying agents [8]. Primary myelofibrosis (PMF) belongs to the group of Philadelphia chromosome negative (Ph-) chronic myeloproliferative neoplasms caused by a clonal stem cell disorder presenting with myeloproliferation and fibrosis [9]. Furthermore, the median age patients are diagnosed with MF is 67 years, which limits the possibility to use allogeneic stem cell transplantation as a curative option in a substantial number of the patients [10]. In addition, lenalidomide, other agents such as pomalidomide and danazol may improve hematopoiesis thereby mitigating JAK2 inhibitor mediated myelosuppression and are being evaluated in combination with ruxolitinib (NCT01644110, NCT01732445) [11]. The prognostic score of our patient was calculated as intermediate-2 according to the IPSS. Treatment of myelofibrosis-related anemia was started with androgen (danazol) and then started with hydroxyurea and the patient was followed under thalidomide treatment for about 6 months. Thalidomide treatment was stopped and then we applied for compassionate use of ruxolitinib. Treatment with thalidomide induces a clinical response in almost half of the patients but appears to be poorly tolerated. As discussed by the authors, others found this regime to be more tolerable in combination with prednisone [12]. Interestingly, a new IMID, pomalidomide, either alone or in combination with prednisone, was recently demonstrated to be effective in reducing anaemia in patients with PMF without serious side effects such as neuropathy or severe

myelosuppression [9]. The molecular mechanisms regulating the progression from MF to AML are incompletely understood. Mutations to several genes encoding epigenetic modifiers such as those involved in DNA hydroxy methylation (eg, TET2, IDH1/2), in the regulation of his ton modifications (eg, ASXL1), IZF1, or TP53 have also been linked to AML transformation [13]. Also our patient in end of the sixth month her disease transformed to AML.

CONCLUSION

PMF is a serious bone marrow disorder and asymptomatic and its treatment is difficult. We can use other treatment methods like immunomodulating drugs, oncogenic pathways, target epigenetic and HSCT.

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