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Effective midostaurin treatment in a patient with aggressive systemic mastocytosis

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Abstract

Systemic mastocytosis (SM) is a rare neoplastic disease of the hematopoietic system characterized by the presence of a somatic mutation in the KIT gene, leading to excessive proliferation of pathological mast cells. This results in abnormal growth of mast cells in the skin and other organs. There are following variants of SM: SM with an associated hematological neoplasm (SM-AHN), aggressive SM (ASM) and mast cell leukemia (MCL), they all are referred to as advanced SM (AdvSM). The drug of choice in the treatment of ASM in Poland is cladribine, which, however, is not approved in this indication, unlike the multikinase inhibitor — midostaurin and imatinib. The latter drug can be used when c-KIT D816V mutation remains negative or unknown.

A 61-year-old female with ASM, accompanied by pancytopenia, hepatosplenomegaly and bone marrow fibrosis with sclerotic bone lesions was reported. The patient was initially treated with cladribine, but due to lack of efficacy after 3 cycles, midostaurin was used as a second option. Initially, the patient developed neutropenia, which led to dose reduction. Treatment continuation resulted in improvement of blood counts and regression of organ changes. Finally, the patient achieved a partial response and the drug was well tolerated. Midostaurin remains a promising treatment option in a patient with ASM and cladribine ineffectiveness.

Key words: aggressive systemic mastocytosis, cladribine, midostaurin

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Introduction

Mastocytosis is a rare neoplastic disease of the hematopoietic system which, according to the 2016 World Health Organization (WHO) classification, belongs to the group of myeloid neoplasms [1]. The exact prevalence and incidence is unknown but based on retrospective European studies it is estimated that 1 in 10,000 people suffer from mastocytosis [2]. Symptoms in patients with mastocytosis are diverse and depending on the form of the disease, they may be limited to skin lesions or may be systemic, resulting from infiltration of organs and their dysfunction. Systemic mastocytosis (SM) includes the following forms: indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with accompanying hematological cancer (SM-AHN), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL). SM-AHN, ASM and MCL are classified as advanced systemic mastocytosis (AdvSM) [1]. Almost all patients, regardless of the

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Table 1. Criteria for the diagnosis of systemic mastocytosis (SM) (source [1])

Major criteria	Minor criteria
Presence of multifocal mast cell infiltrates (≥ 15 in aggregate) in bone marrow biopsy or other organs outside the skin	Abnormal morphology (spindle cells) > 25% of mast cells in trepanobiopsy or other organ outside the skin or > 25% of all mast cells in bone marrow aspirates that show immature or atypical morphology
	Presence of activating *c-KIT* gene mutation at codon 816 (usually D816V mutation) in bone marrow, peripheral blood or material sampled from another organ outside the skin
	CD25 antigen expression with or without the presence of CD2 antigen on the surface of mast cells isolated from bone marrow, peripheral blood or other organ outside the skin
	Increased serum tryptase level > 20 ng/mL (except for accompanying hematopoietic neoplasm)
SM diagnosis: 1 major + 1 minor or 3 minor criteria	

Table 2. B and C symptoms (source [1])

B symptoms	C symptoms
Presence of bone marrow mast cell infiltration (> 30%) in the form of focal dense aggregates with total blood tryptase level > 200 ng/mL	Abnormal bone marrow function in the form of single or multi-line cytopenia (PLT < 100 × 10^9/L, Hb < 10 g/dL, ANC < 1 × 10^9/L)
Presence of dysplasia or myeloproliferation symptoms in a lineage other than the mast cell line, which, however, do not meet the criteria for the diagnosis of another hematopoietic neoplasm with normal CBC and blood smears	Hepatomegaly in physical examination with elevated liver enzymes with ascites and/or portal hypertension
	Splenomegaly in physical examination with features of hypersplenism
Hepatomegaly without liver dysfunction and/or splenomegaly in physical examination without evidence of hypersplenism and/or lymphadenopathy in physical or imaging examination (> 2 cm)	Skeletal system involvement with large foci of osteolysis with or without pathological fractures (osteoporosis with bone fractures is not C symptom)
	Malabsorption with weight loss
	Life-threatening damage to another organ by local mast cell infiltration

ANC — absolute neutrophil count; Hb — hemoglobin; PLT — platelets

disease subtype, have an autoactivating somatic *KIT* gene mutation. In 90% of cases it is the D816V mutation. Other *KIT* gene mutations (i.e. V560G, D815K, D816Y) occur sporadically [3]. The criteria for systemic mastocytosis are presented in Table 1 [1]. The decision to start treatment should be based on the presence or absence of the so-called B and C symptoms — Table 2 [1]. The first choice drug in the treatment of patients with advanced systemic mastocytosis in the world is midostaurin, while in Poland — cladribine, which is not registered in this indication. Other therapeutic options include peginterferon alfa, imatinib (when the *c-KIT* D816V mutation is absent or the mutation status is unknown), or hydroxycarbamide [4].

Case report

A 61-year-old female patient was first admitted to the hematology department in June 2019 due to pancytopenia. Medical history revealed a profuse, prolonged bleeding after an elective gynecological procedure in 2006, since then the patient was under the supervision of a hematologist. Due to increasing pressure pain under the left costal margin, in October 2014 she saw an internist; in a physical examination the spleen protruding approximately 3 cm from under the costal arch. Computed tomography (CT) of the chest, abdomen and pelvis showed enlarged spleen (bipolar dimension 153 mm), otherwise the examination was normal. In a follow-up CT scan in March 2019, additionally with hepatomegaly in physical examination, bipolar spleen dimension was 140 mm, the liver was significantly enlarged, with an anterior-posterior (AP) dimension of 203 mm. In addition, in the pelvic assessment, the attention was drawn to the generalized sclerotization of the bone structures concerning mainly the hip bones, and in the chest, single subpleural nodules in both lungs and quite numerous non-enlarged mediastinal lymph nodes up to 7 mm in the short axis. From May 2019, pancytopenia was observed in complete blood count (CBC) [platelets (PLT) = 120 × 10^9/L, hemoglobin (Hb) = 9.7 g/dL, white blood cells (WBC) = 2.9 × 10^9/L, absolute neutrophil count (ANC) = 1.34 × 10^9/L]. Vitamin

B12, folic acid and iron deficiencies of were excluded. In order to extend the diagnosis, with the suspicion of a hematopoietic neoplasm, the patient was referred to the hematology department.

During the first hospitalization in June 2019, CBC showed further decreases in blood counts (PLT = 100 × 10^9/L, Hb = 8.5 g/dL, WBC = 2.4 × × 10^9/L, ANC = 1.15 × 10^9/L). No significant abnormalities were found in the peripheral blood smear and biochemical test results. Palpating the spleen protruding 5 cm from under the costal arch. In abdominal ultrasound examination (US), enlarged spleen (bipolar dimension 178 mm), liver dimensions as before. Bone marrow aspiration difficult with aspicular bone marrow, not for cytological evaluation; trepanobiopsy was performed. The immunophenotype showed no blasts, and 28.6% mast cells with pathological phenotype CD117+, CD2+/CD25+ were found. The histopathological evaluation of the bone marrow showed diffuse grade 3 reticulin fibrosis and focal collagen grade 1 fibrosis in all interstellar spaces (Masson +). In addition, about 80% of bone marrow was occupied by dense, diffuse, multifocal mast cell infiltrates (CD117+) with predominant spindle cells. Real-time polymerase chain reaction (RT-PCR) did not detect JAK2 V617F and BCR/ABL oncogenes in peripheral blood.

During the next hospital stay CBC showed stable pancytopenia (PLT = 114 × 10^9/L, Hb = 9.7 g/dL, WBC = 3.4 × 10^9/L, ANC = 2.6 × 10^9/L), peripheral blood smear was normal. Biochemical tests showed a slightly increased alkaline phosphatase (ALP) activity = 154.5 IU/L, N: 30–120). The presence of *KIT* gene D816V mutation in the bone marrow was confirmed by RT-PCR and an increased serum tryptase level (245 ng/mL, N: < 11.4 ng/mL) was found. As a first-line treatment cladribine (2-CdA) was used at a dose of 0.14 mg/ /kg body weight for 5 days (50 mg per cycle). The treatment was fairly well tolerated, but the patient required a red blood cell (RBC) concentrates between hospitalizations. After 3 cycles of 2-CdA therapy, CBC showed increasing pancytopenia (PLT = 88 × 10^9/L, Hb = 8.1 g/dL, WBC = 2.56 × 10^9/L, ANC = 1.28 × 10^9/L), the patient more often indicates RBC-transfusion-dependence, for 8 weeks she required 4 units of RBC concentrate. The results of additional tests highlighted the features of hemolysis: increased free bilirubin level (23.54 μmol/L, N: 1.7–17.7), decreased haptoglobin level (< 0.07 g/L, N: 0.3–2), and increased reticulocytosis (6.94%, N: 0.5–2). On palpation, the spleen reached the iliac fossa. The abdominal ultrasound showed a further increase in the spleen size (220 mm) and the liver AP dimension (160 mm). Due to hemolysis, the treatment with prednisone 20 mg/ /day was introduced. Control tryptase level after 3 cladribine cycles was 142 μg/L.

Due to progression of mastocytosis, in mid--May 2020, the treatment was switched to midostaurin at a due dose of 2 × 100 mg/day. After a month of midostaurin introduction CBC showed PLT = = 112 × 10^9/L, Hb = 9.3 g/dL, WBC = 1.7 × 10^9/L, ANC = 0.98 × 10^9/L. According to the Summary of Product Characteristics (SmPC), the drug was withdrawn for two weeks due to neutropenia, and after reaching ANC > 1.0 × 10^9/L, midostaurin was reintroduced at a reduced dose of 2 × 50 mg/ /day. The treatment was well tolerated, the patient did not require transfusions of blood and its components. Moreover, no side effects were observed during six months of drug administration. The patient remains under the control of a hematology clinic, monitored at least once a month. During the last assessment stable values of morphotic parameters were found, abdominal ultrasound showed a significant regression in liver and spleen size (liver AP dimension 115 mm, bipolar spleen dimension 132 mm). The patient denies any conditions and side effects of the drug. Based on good outcome and absence of side effects, the dose 2 × 50 mg/ /day was maintained. Currently, the patient does not consent to the proposed procedure of hematopoietic stem cell allotransplantation.

Discussion

Aggressive systemic mastocytosis is a rare form of systemic mastocytosis, accounting for app. 5% of all MS cases [5]. The diagnosis of ASM is often a serious diagnostic challenge, even for experienced clinicians, as most patients do not have typical skin lesions and the systemic symptoms are not very specific. The prognosis in this subtype is much worse than in the ISM or SSM. The median survival is approximately 41 months and the risk of transformation into acute leukemia is 5% [6].

In every patient with SM suspicion, a peripheral blood smear should be assessed to exclude the presence of concomitant/other hematological neoplasms or to look for mast cells. In the presented case, no abnormalities were found in the peripheral blood. The next step in assessing the cause of pancytopenia and hepatosplenomegaly is bone marrow examination. Typically, histopathological examination in SM patients reveals spindle-shaped mast cells, and the mast cell infiltration is interspersed

with lymphohistiocytic cells, eosinophilic granulocytes, and plasma cells. Infiltrates often accumulate around blood vessels and are accompanied by a dense network of reticulin fibers. Excessive angiogenesis is observed in the majority of patients with mast cell infiltration. The lymphocytic component can be very pronounced in some cases, so that the diagnosis of indolent non-Hodgkin lymphoma, especially in the form of ISM, may initially be mistakenly suspected. Patients with one of the aggressive SM subtypes may have more numerous, larger, and sometimes confluent mast cell infiltrates. Extensive bone marrow infiltration may be accompanied by cytopenia, involving all cellular elements of the blood [7]. Neoplastic bone marrow mast cells have been shown to produce vascular endothelial growth factor, which is consistent with the finding of excessive angiogenesis described above. Myelofibrosis is particularly intense in AdvSM, which was observed in presented case [8]. Hepatosplenomegaly occurs in half of SM patients, and its diagnosis is difficult because, as this is nonspecific symptom, and may indicate other systemic diseases than hematopoietic malignancies, including autoimmune, cardiovascular, solid tumors/metastases or infectious diseases [9]. The results of imaging tests, such as magnetic resonance imaging (MRI) or CT, are not very characteristic in mastocytosis, and suspected neoplastic changes in the liver or spleen must first be differentiated from metastatic changes. The patient's hepatosplenomegaly was most likely due to mast cells infiltration of the liver and spleen, which worsened the functions of these organs. As a result of liver damage, increased alkaline phosphatase level was observed. This abnormality is common in SM patients [10]. Mayo researchers analyzed 580 SM patients and found platelet count $< 150 \times 10^9$/L, anemia below sex-adjusted normal range, and elevated ALP levels as three risk factors that determined survival in both ISM/SSM and advanced SM, independent of age and morphological category [11].

The occurrence of generalized sclerotization of bone structures in presented case should be highlighted, as these changes occur only in about one third of ASM cases [10]. In any case, however, they would require histological confirmation.

In therapy, regardless of SM type, it is important to avoid factors that can activate mast cells, including allergenic substances, and to treat patients symptomatically. Midostaurin is a potent FLT3 tyrosine kinase inhibitor, active against mutated *KIT* proto-oncogene receptor tyrosine kinase in advanced forms of the disease [12]. The patient was first treated with 2-CdA. Until midostaurin received marketing authorization, cladribine was first choice drug due to the high efficacy in all variants of AdvSM. Response rates are 50–60% depending on the SM variant and are slightly higher in patients with SM-AHN compared with ASM patients. So far, no head-to-head studies have been conducted that would allow comparison of cladribine and midostaurin in terms of the effectiveness in AdvSM treatment [13]. The patient tolerated the drug infusion well, however, worsening pancytopenia was observed between subsequent cycles and the patient became RBC-transfusion-dependent. Additionally, hemolysis occurred in laboratory tests. Mastocytosis progression determined the change of treatment and the switch to midostaurin therapy. After a month of its use, the drug had to be temporarily discontinued due to neutropenia. Grade 3 neutropenia was the only side-effect of midostaurin treatment in presented case. This symptom occurs in 24% of patients. Statistically, treatment with midostaurin is most often accompanied by gastrointestinal symptoms (nausea, vomiting, diarrhea), followed by peripheral cytopenias [14]. In a midostaurin pivotal trial with 89 patients (16 ASM, 57 SM-AHN and 16 MCL), the most common adverse events were nausea, vomiting and low-grade diarrhea. Newly diagnosed or worsening grade 3/4 neutropenia, anemia and thrombocytopenia occurred in 24%, 41% and 29% of patients, respectively, mainly in subjects with pre-existing cytopenia. The overall response rate in this study was 60%. The median overall survival was 28.7 months and the median PFS was 14.1 months [15].

Conclusion

Midostaurin remains an effective drug in a patient with advanced mastocytosis and prior failure of cladribine.

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