The use of midostaurin in the treatment of advanced systemic mastocytosis

Marek Hus, Aneta Szudy-Szczyrek, Justyna Kozińska, Oliwia Bachanek-Mitura

Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland

Abstract

Systemic mastocytosis (SM) is a rare myeloproliferative neoplasms (MPN) characterized by clonal growth and accumulation of mast cells in various organs, mainly in the skin, bone marrow, liver, spleen, and lymph nodes. In its advanced form, SM leads to impairment of their function. The clinical course is highly variable, ranging from slow to very aggressive with progressive multi-organ failure and a significant risk of leukemic transformation. Advanced SM is an indication for cytoreductive therapy. So far, various treatment strategies have been used, including cladribine (2-CDA), imatinib, interferon alpha (IFN-α), as well as classic cytostatics (hydroxy carboamide, cytarabine or fludarabine). However, none of the options mentioned provided satisfactory response rates. Currently, high hopes are related to midostaurin — a multi-pathway tyrosine kinase inhibitor. The drug was approved for the treatment of advanced forms of SM by the US Food and Drug Administration (FDA) in April 2017 based on the satisfactory results of phase II clinical trial #CPKC412D2201. In this paper, we present case reports of two patients diagnosed with aggressive systemic mastocytosis (ASM) and systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) treated with midostaurin as part of the early access program.

Key words: systemic mastocytosis, aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, midostaurin

Hematology in Clinical Practice 2021; 12, 2: 77–83

Introduction

According to the current 2016 World Health Organization (WHO) classification, systemic mastocytosis (SM) belongs to myeloproliferative neoplasms (MPN). It is characterized by clonal proliferation and accumulation of mast cells in various organs, mainly in the skin, bone marrow, liver, spleen, and lymph nodes. Different forms of SM are divided into two main groups: non-advanced, including indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM) and bone marrow mastocytosis (BMM); as well as advanced, which includes aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL) (Table 1) [1–4].

A key role in SM pathogenesis play activating mutations of KIT proto-oncogene, leading to stem cell factor (SCF)-independent activation of the KIT receptor and uncontrolled mast cell proliferation. In the majority of SM patients (> 90%) a somatic KIT gene mutation in codon 816 is observed [5–7].
Disease symptoms in advanced SM may result from both the release of mediators from mast cells and organ damage associated with mast cells infiltration. Clinical symptoms resulting from neoplastic infiltration (so-called “C” symptoms) include cytopenia, bone lesions, hepatomegaly with impaired liver function and/or portal hypertension, enlargement of the spleen with hypersplenism, and weight loss due to gastrointestinal involvement. Symptoms related to the release of mediators are also observed regardless of the disease form or serum tryptase concentration, including pruritus, flushing and mediator-dependent: nausea, vomiting, diarrhea, abdominal pain, hypotension episodes, fatigue, headaches, fever, dyspnea, osteopenia, osteoporosis and anaphylactic reactions. Symptoms can be mild, moderate, severe, or even life-threatening.

The cytoreductive therapy is aimed to reduction of “C” symptoms, bone marrow infiltration by mast cells, organomegaly, and mediator-related symptoms. The key is to determine whether the patient is a candidate for allogeneic hematopoietic stem cell transplantation (allo-HSCT), which is the only treatment option so far. Long-term disease control should be pursued in patients who are not eligible for transplantation. In any case, the treatment plan should be individualized [3, 8].

**Case report 1**

In May 2018, a 66-year-old man was admitted to the Endocrinology Clinic in Lublin, with a 30-year history of symptoms suggesting carcinoid syndrome, due to sudden reddening of the upper half of the face, accompanied by anxiety and fever up to 40°C. Similar episodes occurred earlier, with varying frequency, most recently about 6 years ago. Gastric and duodenal ulcer, periodic GI symptoms, chronic diarrhea, splenomegaly and depression were revealed in medical history.

The patient’s medical records showed that a carcinoid tumor was suspected only on the basis of clinical symptoms and ambiguous results of laboratory tests from 2000: increased 5-hydroxyindole acetic acid level (5-HIAA) — 11.8 mg/day (normal range 5.5–10.3) and serotonin — 0.89 μg/mL (normal range 0.55–0.75).

In the last few months pain in the lumbar region of the spine, weakness, and weight loss by several kilograms were also observed. For this reason, in March 2018, a radiographic (X-ray) and computed tomography (CT) scan of the bones were performed, showing heterogeneous osteolytic sclerotic remodeling (Figure 1), and a scintigraphy that showed increased diffuse tracer accumulation (Figure 2). Based on the results of imaging studies, the presence of metastatic lesions was suggested.

Control chromogranin A, neuron-specific enolase (NSE), serotonin and 5-HIAA measurements showed normal results. No lesions with increased expression were found in somatostatin receptor scintigraphy. Presented results ruled out carcinoid tumor and highlighted the necessity to extend the diagnosis towards the primary tumor.

PET-CT study performed in August 2018 showed enlarged spleen (longitudinal dimension 170 mm), sclerotic skeleton remodeling, disseminated lytic lesions with the largest in L1 vertebra with diameter of 29 mm, and increased radioisotope accumulation in the right hip joint area (SUVmax 5.9).

In November 2018, a diagnostic bone marrow biopsy was performed. In the material from the iliac bone plate, numerous foci and fields of spindle cells (CD117+, CD45+ weak, panCK–) corresponding to mast cells were described.

Then the patient was qualified for trepanobiopsy. The obtained material showed increased marrow cellularity (approx. 70–80% of surface pits), with red blood cell (glycoporphin+) and granulocytic systems (MPO+, CD34+ in single cells < 1%) proportionally represented with preserved maturatio. There were a few megakaryocytes (FVIII+)
per pits, with scattered, medium-sized cells with multilobed nuclei. Lymphocytes (CD45+) were small, diffuse, constituting approximately 20% of cells. Among the marrow weaving, the mast cells (CD117+) with normal morphology and fusiform cells were present, forming large fields or scattered, with an accompanying increase in the number of reticulated fibers, accounted for approximately 40% of the weaving.

_D816V KIT_ and _D816H KIT_ mutations were detected in the molecular test.

According to the current criteria, the diagnosis of ASM was established (Table 2).

The first-line treatment was chemotherapy with cladribine in a dose of 10 mg intravenous (i.v.) on days 1–5 of 28-day cycles. The treatment was well tolerated.

The disease stage was assessed after the completion of the 3<sup>rd</sup> chemotherapy cycle. In the control trepanobiopsy, the bone marrow infiltration by mast cells was 50%. The immunophenotypic evaluation revealed 2.34% mast cells (CD17+, CD2+, CD25+, CD33+) in bone marrow and 0.23% in the peripheral blood. The control tryptase level was 99.8 μg/L. The decision was made to discontinue cladribine and to qualify the patient for second-line chemotherapy.

The patient started the treatment with midostaurin in May 2019. The recommended dose was 2 × 100 mg per os (p.o.), with prophylaxis of bone disease with IV bisphosphonates (disodium pamidronate every 4 weeks). Grade 3 pneumonia with pulmonary embolism occurred in the second month of treatment. The treatment included broad-spectrum antibiotics (ceftriaxone, levofloxacin), and anticoagulants (low molecular weight heparin). The clinical condition improved, and chemotherapy was resumed after a 10-day break. The side effects of nausea and vomiting were maintained throughout the treatment period.
The use of antiemetic drugs (ondansetron) and modification of depression treatment of (duloxetine) provided clinical benefit.

After 6 treatment cycles, there was a significant reduction in bone marrow infiltration by pathological mast cells to approximately 15% of weaving in trepanobiopsy and 0.37% in immunophenotyping. The control tryptase level was 21.6 μg/L. The patient continues treatment at the appropriate dose. He has now completed the 17th treatment cycle. The patient is in good general condition and reports well-being. So far, no increased symptoms associated with mast cell mediators have been observed. The clinical response persists.

Case report 2

In May 2019, a 32-year-old female patient diagnosed with multiple myeloma was admitted to the Department of Hematooncology and Marrow Transplantation in Lublin, after completing first-line chemotherapy to qualify for auto-HSCT. The patient was initially diagnosed and treated in Lviv and came without full medical documentation. The disease was diagnosed on the basis of a biopsy from a tumor of the femur and bone marrow in December 2018. The treatment included 3 cycles of VCD chemotherapy (bortezomib, cyclophosphamide, dexamethasone). Despite the treatment, severe bone pain was still observed. In order to verify the disease stage, a control trepanobiopsy and bone CT were performed prior to the planned auto-HSCT (May 2019). The CT image of the skeleton showed scattered osteolytic-sclerotic foci up to 28 mm in diameter within the bones of the skull, bodies of cervical, thoracic and lumbar vertebrae and hip bones. The largest lesion of approximately 42 × 31 mm, containing areas of both sclerotic thickening and dilution, was visualized in the intercaval region and in the proximal femoral shaft (Figure 3). In trepanobiopsy focal, nodular and epithelial clusters of mast cells (CD117+, CD45+ weak) with typical morphology and fusiform clusters, including > 15 cells/cluster, as well as scattered polyclonal plasmocytes were described. Systemic mastocytosis was suspected.

In August 2019, a biopsy of the femoral tumor was performed; the histopathological examination showed a positive CD138 and an equivocal CD117 test results. There was no c-KIT mutation in the bone marrow biopsy material, 0.1% of plasmocytes (CD 138+) and 0.4% of mast cells (CD2+/CD117+/CD 25+) (normal range 0.005–0.024%) were detected in the immunophenotypic evaluation. Serum protein electrophoresis revealed the presence of IgA kappa M-protein 0.47 g/dL, immunoglobulins and serum free light chain (sFLC) levels were normal. Serum tryptase level was 31.1 μg/L (normal range 5–11.4 μg/L). The diagnosis of systemic mastocytosis accompanying hematological neoplasm - multiple myeloma (SM-AHN) was established (Table 2). Prophylaxis of bone disease with bisphosphonates (i.v. disodium pamidronate every 4 weeks) and prophylaxis of symptoms related to mediators release with H1 and H2 receptor antagonists (fexofenadine + famotidine) were implemented. The patient was qualified for palliative pelvic radiotherapy, and a dose of 20 Gy was administered in 5 fractions in December 2019. An application has been issued for treatment with midostaurin under the Early Access Program. After the quick approval of the application, the therapy with midostaurin was started at a dose of 2 × 100 mg p.o. During the first 10 days of treatment, severe diarrhea occurred with a weight loss of approximately 6 kg. The drug dose was reduced to 2 × 50 mg p.o. Simultaneously with the initiation

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of multifocal mast cell infiltrates (≥ 15 in aggregate) in bone marrow biopsy or other organs outside the skin</td>
<td>Abnormal morphology (spindle cells) &gt; 25% of mast cells in trepanobiopsy or other organ outside the skin or &gt; 25% of all mast cells in bone marrow aspirates that show immature or atypical morphology</td>
</tr>
<tr>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>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</td>
<td>Increased serum tryptase level &gt; 20 ng/mL (except for accompanying hematopoietic neoplasm)</td>
</tr>
</tbody>
</table>

SM diagnosis: 1 major + 1 minor or 3 minor criteria
of the treatment, an increase in the IgA kappa M-protein from 0.47 g/dL to 1.05 g/dL, sFLC kappa from 33.07 mg/L to 62.03 mg/L was observed in laboratory tests. Taking into account the entire clinical picture, it was decided to continue the treatment with midostaurin at a dose of 2 × 50 mg p.o. in combination with bortezomib at a dose of 1.3 mg/m² s.c. on days 1, 4, 8, 11 and dexamethasone 20 mg p.o. on days 1–4, 8–11 in 28-day cycles.

The response was noted already after 2 treatment cycles, no serum M protein was found, the sFLC and tryptase levels decreased to normal values (sFLC kappa 16.34 mg/L; tryptase to 8.4 μg/L). A trepanobiopsy performed after the 4th treatment cycle showed the bone marrow with reduced cellularity, occupying up to 5–10% of surface pits. The granulocytic system (MP0+, CD15+, CD34+) relatively numerous with preserved maturation. The red blood cell system (glycophorin+) is scantily represented. A few megakaryocytes (FVIIT+) per pits, scattered medium-sized and small cells. Single mast cells (CD117+) in the preparation (1%). Plasmocytes (CD138+, kappa+ immunoglobulin light chains) scattered, constituting about 10% of bone marrow cells. Lymphocytes (CD45+) small, diffuse, accounting for approximately 15% of all cells. The arrangement of the mesh fibers is correct.

During the treatment, clinical improvement was observed and bone pain subsided. There were no complications. Treatment was continued for up to 6 cycles.

The patient was qualified for allo-HSCT from a brother compatible according to human leukocyte antigens (HLA) system. The conditioning included the CyBuMEL chemotherapy regimen (cyclophosphamide, busulfan, melphalan). In July 2020, 2 preparations of 3 × 10⁶ CD34+ were transplanted. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 oral mucositis was observed in the post-transplant period. On +12 day following allo-SCT, acute graft-versus-host disease (GvHD) occurred, treatment with methotrexate 10 mg/kg and topical glucocorticosteroids was introduced. The correct regeneration of hematopoiesis was observed, the patient did not require transfusion of blood products.

On +32 day control bone marrow biopsy was performed. Medium-rich bone marrow with hematopoietic systems with preserved maturation were described, in the immunophenotypic test monoclonal plasmocytes constituted 0.09%, and mast cells 0.01%. Donor chimerism accounted for 99.8%. Tryptase concentration — 11 μg/L, M protein was not found, sFLC was normal. From +40 day after transplantation, maintenance treatment with midostaurin at a dose of 2 × 50 mg/day was initiated.

In September 2020, the patient suffered a pathological subtrochanteric fracture of the left femur without displacement at the site of the primary infiltrative lesion. Surgical treatment was abandoned. There was no disease progression.

In the examination on +100 day after allo-HSCT, 99.7% of donor chimerism and disease remission were recorded. In the assessment, immunophenotypic monoclonal plasmocytes constituted 0.09%, no mast cells were found. A normal picture of complete blood counts is observed. The patient is in good general condition and does not report any significant complaints.

Discussion

The treatment of patients with advanced SM is a major challenge for clinicians. Clear treatment algorithms are still lacking and treatment experience is still very limited.

Cladribine (2-CdA) showed therapeutic activity in all SM subtypes, including MCL. In the Mayo Clinic trial, 22 patients treated with cladribine had an overall objective response rate (ORR) of 55% complete response (CR) 5%, minimal response (MR) 32% and partial response (PR) 18%, with a mean duration of 11 months (range 3–74). The main side effects were myelosuppression and infections [9]. In further trial Barete et al. observed an improvement in response rates: in a study of 68 patients (36 with ISM, and 32 with advanced SM) treated with 2-CdA, ORR was 72%, 92% in patients with ISM (by reducing symptoms and seizure skin),
and 50% in patients with advanced SM. The median duration of response was 3.7 and 2.47 years for ISM and advanced SM, respectively. The administered dose was 0.14 mg/kg intravenously or subcutaneously for 5 days, repeated after 4–12 weeks, with a median number of cycles of 3.7 (range 1–9). Leukopenia and opportunistic infections were among the most serious side effects [10].

In presented case, the use of cladribine did not bring the expected therapeutic effect.

Midostaurin (PKC412) is the first multi-pathway tyrosine kinase inhibitor. It demonstrates the ability to inhibit signaling and cell proliferation pathways through the FLT3 receptor. It induces the mechanisms of apoptosis in leukemic cells that show mutations in the FLT3 gene with tandem duplication in the internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations. It has the ability to inhibit KIT signaling pathways (wild-type and D816V mutant), cell proliferation and histamine release, and induce apoptosis in mast cells. In vitro, inhibits the activity of several other receptor tyrosine kinases such as PDGFRα/β, VEGFR2, and the PKC kinases family [11].

Pivotal midostaurin study CPKC412D2201 enrolled 116 patients with advanced SM. The efficacy of treatment was assessed in 89 patients, including 16 with ASM, 57 with SM-AHN and 16 with MCL. The drug was administered at a dose of 100 mg orally twice a day. The median follow-up was 26 months (range 12–54). Overall ORR was estimated at 60%, with 45% patients achieving MR and 15% achieving PR. The median overall survival (OS) was 28.7 months and the median PFS was 14.1 months. In the responders group the median duration of response (DOR) was 24.1 months, and the median OS was 44.4 months, with the best response observed in patients with ASM (75%), and the mean DOR not reached. Responses occurred regardless of the D816V mutation status in the KIT gene. During treatment, resolution of hypoalbuminemia (58%), independence from red blood cell (40%) and platelets (100%) transfusions, improvement in liver function (44–58%) and/or weight gain (25%) were observed. Significant (> 50%) reductions in mast cells bone marrow infiltration and a decrease in tryptase levels were noted. Dose reduction related to drug toxicity was required in 56% of patients; a further increase of the starting dose was possible in 32% of patients. The most common adverse events were nausea, vomiting, and diarrhea. Hematological complications — grade 3 or 4 neutropenia, anemia, and thrombocytopenia — occurred in 24%, 41%, and 29% of patients, respectively, mainly those with pre-existing cytopenia [12].

The use of midostaurin in the presented patient with ASM brought clinical benefit, improved general condition, relief of mediator-related symptoms, as well as a significant decrease in serum tryptase level and bone marrow infiltration by malignant mast cells. The nausea and vomiting observed during treatment are sporadic and most often disappear after the use of symptomatic medications, as in presented case. The occurrence of a complication in the form of pulmonary embolism is not typical for midostaurin. Nevertheless, this is valuable knowledge for practicing clinicians, and the possible risk of thromboembolic complications requires further monitoring. Midostaurin in combination with bortezomib was used in patients diagnosed with refractory/recurrent acute myeloid leukemia (AML) in the phase I clinical trial NCT01174888. The patients were divided into two groups: receiving midostaurin 50 mg twice daily and increasing doses of bortezomib (1 to 1.3 mg/m2) and receiving midostaurin and bortezomib after MEC chemotherapy (mitoxantrone, etoposide, cytarabine). No dose-limiting toxicities (DLT) or clinical response were observed in any of the patients enrolled in chemotherapy with midostaurin/bortezomib. Among patients enrolled in intensified therapy, DLT included peripheral neuropathy, decreased ejection fraction, and diarrhea. On the other hand, CR was observed in 56.5% of patients, and ORR was 82.5% (CR + CR with incomplete regeneration of neutrophils or platelets) [13].

To the best of the authors’ knowledge, there are no reports in the literature on the use of midostaurin with bortezomib and dexamethasone in patients with SM-AHN. Our observations seem to be the first in the world. It must be admitted that the diagnosis of SM with multiple myeloma itself is extremely rare, and the knowledge about the strategy of management in this group of patients is based solely on case reports [14, 15]. The highly aggressive clinical course, the picture of the active components of the disease, and the young age of the patient forced an individualized approach to treatment. The aim of the therapy was to achieve remission of the disease with subsequent allo-HSCT, which is the only chance for a cure [16]. The use of combined chemotherapy with midostaurin with bortezomib and dexamethasone brought a satisfactory effect, without side effects.
Conclusions

Diagnosing and treating patients with advanced SM is a big challenge. Low awareness of the disease, atypical, diverse clinical picture cause delays in correct diagnosis. Treatment should be multidisciplinary and patient-tailored.

Sources of funding/participation in grants

Not applicable.

References