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CASE REPORT

The use of midostaurin in aggressive systemic mastocytosis (ASM) with the *c-KIT* D816V mutation within The Emergency Access to Drug Technologies Programme

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Abstract

Aggressive systemic mastocytosis (ASM) is a very rare subtype of systemic mastocytosis (SM) and, together with systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL), it belongs to advanced systemic mastocytosis (AdvSM). Different strategies of systemic treatment are used in patients with AdvSM. The protocols base on the cladribine, interferon, allogeneic hematopoietic stem cell transplantation, polychemotherapy or the midostaurin — the only approved drug therapy in AdvSM. Options available in Poland — cladribine and interferon — are characterized by a non-lasting effect and, unfortunately, midostaurin still remains unreimbursed for patients. On October 5, 2018, The Polish Agency for Health Technology Assessment and Tariff System approved the midostaurin to be financed within The Emergency Access to Drug Technologies Programme in ASM with the c-KIT D816V mutation. Based on a case report, the following manuscript describes authors' experiences with the use of midostaurin. The aim of the article is to present an overview of the current status of midostaurin in the treatment of ASM and to summarize the results of clinical trials, focusing on its effectiveness and safety. Authors, hereby, report a case of a patient diagnosed in 2000 with cutaneous mastocytosis (CM), that developed a transformation to ASM in 2015. The following lines of treatment were used: cladribine, pegylated interferon alpha, dasatinib. Significant side effects were observed after each line, without obtaining a lasting response to treatment. In July 2020, patient began a therapy with midostaurin. Afterwards, a normalization of peripheral blood count parameters together with reduction of serum tryptase level were observed, without noticing any adverse effects.

Key words: midostaurin, mastocytosis, systemic mastocytosis, KIT, FLT3, cladribine, tryptase

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Introduction

Aggressive systemic mastocytosis (ASM) is a very rare form of the disease, accounting for approximately 5% of all systemic mastocytosis (SM) cases and together with systemic mastocytosis with an associated hematological neoplasm (SM-AHN) and mast cell leukemia (MCL) belongs

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to the group of advanced systemic mastocytosis (AdvSM). According to the 2016 World Health Organization (WHO) hematological neoplasms classification, ASM is classified as a myeloproliferative neoplasm [1, 2].

Various systemic treatment strategies are used in patients with AdvSM. The current protocols are based on allogeneic hematopoietic cell transplantation, polychemotherapy, cladribine (2Cd-A), interferon or midostaurin — the only approved drug in AdvSM therapy [3, 4]. Avapritinib, a selective KIT and PDGFRα inhibitor and a kinase inhibitor DCC-2618 are during clinical development [5, 6] The therapeutic options available in Poland — cladribine and interferon — are characterized by a non-lasting effect [7–9], and midostaurin is still under reimbursement procedure. Other drugs: dasatinib, nilotinib or brentuximab vedotin, to the current knowledge are not effective in the treatment of AdvSM, despite the promising results of preclinical studies [10, 11]. On October 5, 2018, the Agency for Health Technology Assessment and Tariffs gave a positive opinion on the legitimacy of financing the drug Rydapt® (midostaurin) in ASM with the *c-KIT* D816V mutation as part of emergency access to drug technology (EADT) [12]. Based on the case report, the authors present clinical experience with the use of midostaurin in ASM *c-KIT* D816V+ patient financed under EADT.

Case report

Diagnosis

We present the case of 61-year-old female patient diagnosed with cutaneous mastocytosis (CM) in 2000. Until 2015, she remained under the care of an allergy clinic and required only supportive treatment: proton pump inhibitors (PPIs) and antihistamines.

In May 2015, anemia (Hb 9.6 g/dL) and thrombocytopenia (PLT 47×10^9/L) were recorded in the routinely performed complete blood count (CBC) and the patient was referred to a hematology clinic.

There were multifocal, dense mast cell infiltrates (> 15 cells in the aggregate) in the trepanobiopsy; a point mutation in codon 816 of the *c-KIT* gene was detected; 80% of bone marrow was infiltrated by mast cells, showing CD25 expression; the serum tryptase level was 274 ng/mL. Based on the presence of C symptoms (anemia and thrombocytopenia), the patient was diagnosed with ASM [13] and qualified for systemic treatment. The main complaints reported by the patient were bone pain and fatigue.

Systemic treatment

From May 2015 to September 2015, the patient received 5 full 7-day cycles: 2Cd-A 10 mg intravenous (i.v.)/day. Treatment was discontinued due to thrombocytopenia and anemia requiring blood transfusion. In the post-cycle control test the serum tryptase level was 200 ng/mL.

Between September 2015 and November 2015, the patient received treatment with pegylated interferon alfa at a dose of 2×3 MU/week — treatment was discontinued due to complications such as grade 2 depression, suicidal ideation and cognitive disorders. At the end of therapy, serum tryptase level was 251 ng/mL, CBC revealed thrombocytopenia (PLT 61×10^9/L) and anemia (Hb 10.4 g/dL).

Until June 2016 the patient was under observation, and between June 2016 to September 2016 she received 3 full 7-day cycles: 2Cd-A 10 mg i.v./day. Treatment was discontinued due to a complication e.g. thrombocytopenia and anemia requiring blood transfusion. After the 3rd (8th in total) cycle, the serum tryptase level was 169 ng/mL. The result of control histopathological examination of bone marrow specimens taken during trepanobiopsy was stable in relation to the baseline examination at diagnosis. CBC revealed thrombocytopenia (PLT 34×10^9/L) and anemia (Hb 8.6 g/dL).

Between February 2017 and May 2017, the patient received dasatinib at a dose of 100 mg//day — the course of treatment was complicated by upper respiratory tract and urinary tract infections and repeated episodes of anaphylaxis secondary to the mast cell activation syndrome (MCAS) [14], therefore the dose of dasatinib was reduced. At the time of dose reduction, the serum tryptase level was 196 ng/mL. CBC revealed thrombocytopenia (PLT 39×10^9/L) and anemia (Hb 8.4 g/dL).

Between May 2017 and August 2017, the patient received dasatinib in a dose of 100 mg every other day. Despite the dose reduction, the course of treatment was also complicated by upper respiratory tract and urinary tract infections and MCAS, which was reported twice. At the end of treatment, the serum tryptase level was 180 ng/mL. For the first time since the diagnosis of ASM, the hemoglobin level was normalized (Hb 12.0 g/dL), but thrombocytopenia persisted (PLT 90×10^9/L).

Due to the exhaustion of available therapeutic options and the need for further systemic treatment, an application was made to the Ministry of Health for financing midostaurin under the EADT. After obtaining the consent, therapy with Rydapt® was started in the dose 2×100 mg/day

per os (p.o.) Tryptase level decreased to 35 ng/mL after 5 weeks of treatment and to 26 ng/mL after 10 weeks. The patient had been receiving treatment continuously for 16 weeks with very good tolerance. Importantly, no adverse effects were reported during this period. The patient declared that fatigue and bone pain subsided, as well as improved quality of life based on SF-12 questionnaire [15]. There was no need to modify the dose during this period. After 16 weeks, there was an increase in hemoglobin and platelets levels (Hb 12.5 g/dL; PLT 123×10^9/L).

Due to the peak period of the COVID-19 pandemic and the delayed processing of the application for extension therapy funding under EADT, the patient had an unplanned 7-week break in therapy. Over this period, tryptase levels increased to 97 ng/mL. This proves the need for the drug to be used continuously and uninterruptedly. At the time of manuscript preparation, the treatment was continued. To date, no side effects have been reported.

Discussion

The efficacy of midostaurin has been well documented in clinical trials. The first, historical study, was a phase II trial in 26 AdvSM patients with median age 62 years (24–79) [16]. Response to treatment was standardized according to the algorithm proposed by Valent [17]. Overall response rate (ORR) was 69% (18/26 patients); 10 patients (38%) achieved a major response (MR) [including 6 incomplete remissions (IR) and 4 pure clinical responses (PCR)], 5 patients (19%) achieved good partial response (GPR), and 3 patients (12%) achieved minor partial response (MPR). Of the 8 patients who did not respond, 4 (15%) had stable disease (SD) and another 4 (15%) had progressive disease (PD).

The pivotal study included 89 patients (16 ASM, 57 SM-AHN, 16 MCL) who received the drug at a dose of 100 mg twice daily. ORR was 60%, 45% of patients achieved MR. No significant side effects were observed; among grade 3–4 non-hematological side effects gastrointestinal symptoms, i.e. nausea, vomiting and diarrhea (6-8%) were dominant. Grade 3–4 hematological symptoms included worsening of prior or first appearance of neutropenia (24%), anemia (41%), and thrombocytopenia (29%) [3, 18].

The results of the NCT00782067 study are important from the clinical practice perspective, which proved that patients treated with midostaurin experience a significant improvement in the quality of life evaluated with the SF-12 objective tools and the Memorial Symptom Assessment Scale, and less frequently experience negative symptoms of mastocytosis [19]. This is confirmed in the present case report.

In another study involving 28 AdvSM patients, the mean duration of response was 17 months and the ORR was 71% (MR — 57%, PR — 14%). In the midostaurin-naive and age at diagnosis- and AdvSM subtype-matched control group, the risk of death after reaching the median follow-up was more than twice as high as in the midostaurin-treated cohort (hazard ratio 2.2; p = 0.02) [20].

In April 2017, midostaurin was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with FLT3+ acute myeloid leukemia (AML) in combination with standard chemotherapy and as monotherapy in the treatment of patients with ASM, SM-AHN or MCL [14]. According to the Summary of Product Characteristics (SmPC), midostaurin inhibits numerous tyrosine kinase receptors, including FLT3 and KIT kinase, and also FLT3 receptor signaling pathway and induces cell cycle arrest and apoptosis in leukemia cells expressing mutant FLT3 ITD or TKD receptors, or overexpressing wild-type FLT3 receptors. In addition, midostaurin inhibits other receptors with tyrosine kinase activity, such as platelet-derived growth factor receptor (PDGFR) or vascular endothelial growth factor receptor 2 (VEGFR2), as well as members of the protein kinase C (PKC) family belonging to serine-threonine kinases [21]. It is clinically significant that it has the potential to inhibit *KIT* signaling pathways (wild-type and D816V mutant), cell proliferation and histamine release and induce apoptosis in mast cells [22].

The clinical challenge for the future remains the detailed understanding of the mechanisms of resistance to midostaurin and the development of therapeutic strategies that will allow for its avoidance and overcoming. In this context the combination of cladribine and midostaurin is a promising direction, supported by the results of in vitro studies [23, 24].

Due to the proven effectiveness, positive impact on the quality of life and an acceptable safety profile, midostaurin can be successfully used in the first and subsequent lines of AdvSM treatment [25]. However, the availability of midostaurin remains a separate issue. At the time of writing this article, its funding is based solely on the EADT. The community of hematologists and the Association of Patients with Mastocytosis look forward to

covering midostaurin with reimbursement under the drug program [26], which will provide Polish patients with continuous and uninterrupted access to this therapy, which has been successfully used in the world for several years.

Authors contribution

In order.

Conflict of onterest

The authors collaborate with Novartis Oncology.

Financing

Work co-financed by Novartis Oncology.

Ethics

The article was prepared according to the principles of the Helsinki Declaration, EU directives and the unified requirements for biomedical journals.

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