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Review Article

Treatment of Advanced Systemic Mastocytosis with Midostaurin: Practical Guidance for Optimal Therapy and Management

Cristina Papayannidis[1], Vincenzo Federico[2], Luana Fianchi[3], Patrizia Pregno[4], Novella Pugliese[5], Alessandra Romano[6] and Federica Irene Grifoni[7].

[1] RCCS, Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna Italy.
[2] Haematology and Stem Cell Transplant Unit, Presidio Ospedaliero "Vito Fazzi", Lecce, Italy.
[3] Department of Radiological Sciences, Radiotherapy, and Hematology, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy.
[4] Hematology Division, Oncology and Hematology Department, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[5] Department of Clinical Medicine and Surgery, Hematology Unit, Federico II University Medical School, Naples, Italy.
[6] Division of Hematology, Azienda Ospedaliero Universitaria Policlinico - Vittorio Emanuele Catania, Catania, Italy.
[7] Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

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Abstract. Systemic mastocytosis (SM) is a rare disease with a range of clinical presentations, and the vast majority of patients have a KIT D816V mutation that results in a gain of function. The multikinase/KIT inhibitor midostaurin inhibits the D816V mutant and has a well-established role in treating advanced SM. Even if considered the standard of therapy, some open questions remain on optimizing midostaurin management in daily practice. The current review presents the opinions of a group of experts who met to discuss routine practice using midostaurin in patients with advanced SM. The efficacy and safety of midostaurin in Phase 2 trials are overviewed, followed by practical guidance for optimal therapy management and adverse events during therapy with midostaurin. Specific guidance is given for initiating therapy and evaluating response with midostaurin as general assessment and laboratory, instrumental, pathological, and molecular exams. Special consideration is given to dose interruption, reduction, and discontinuation of therapy, as well as adverse event management and supportive therapy. Patients should be informed about possible side effects and receive practical advice to avoid or limit them and antiemetic prophylaxis so that therapy with midostaurin can continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Lastly, considerations on the use of midostaurin during the ongoing Covid-19 pandemic are made. The overall scope is to provide guidance that can be useful in daily practice for clinicians using midostaurin to treat patients with advanced SM.

Keywords: Systemic mastocytosis; Midostaurin; Guidance; Management.

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Correspondence to: Cristina Papayannidis. IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Istituto di

Introduction. Mastocytosis is a rare disease characterized by a wide range of clinical presentations, symptoms, and prognosis.[1] The symptoms of mastocytosis are due to the presence and proliferation of neoplastic mast cells (MC) in one or more organs, with the skin being a frequent site, followed by bone marrow.[1,2] Systemic mastocytosis (SM) is considered a hematological neoplasm.[1,2] The WHO has classified SM into five major forms: indolent SM, smoldering SM, SM with an associated hematopoietic neoplasm (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL).[3,4] The latter three subtypes are grouped as advanced SM. Clinical findings related to organ damage deriving from MC infiltration are called C-findings and include cytopenia, liver-function abnormalities, weight loss, ascites, and osteolytic bone lesions.[5] Aggressive SM is characterized by the presence of at least one C-finding.[5]

Due partly to its rarity and diverse clinical presentations, SM can be challenging to diagnose. Therefore, diagnosis generally requires that either one major and one minor criterion are met or at least three minor criteria are satisfied.[4] The major criterion is the presence of multifocal dense infiltrates of mast cells (≥15 mast cells in an aggregate) in the bone marrow and/or extracutaneous organs. Minor criteria include: i) >25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology, or >25% of all mast cells in bone marrow aspirate smears are immature or atypical; ii) detection of *KIT* D816V mutation in bone marrow, blood, or another extracutaneous organ; iii) mast cells in bone marrow, blood, or another extracutaneous organ express CD25, with or without CD2; iv) persistent serum tryptase >20 ng/ml (in case of an unrelated myeloid neoplasm, this is not valid as an SM criterion).

It has been reported that the prevalence of SM is likely to be underestimated due to difficulties in diagnosis.[6] These difficulties may be linked to disease heterogeneity delaying the clinical suspicion[7] and requiring a multidisciplinary approach in collaboration with (or in) a center of excellence of mastocytosis involving hematologists, rheumatologists, allergologists, and gastroenterologists.[8,9] Indeed, a study from Germany reported that around one-third of patients with advanced SM are either not diagnosed or misdiagnosed, and as such greater attention should be given to tryptase levels, bone marrow histology, and genetic analyses.[10]

Among the genetic findings in SM, it has been known for some time that the vast majority of patients have a *KIT* D816V mutation that results in a gain of function and leads mast cells to uncontrolled proliferation.[11] More recently, thanks to innovative molecular techniques, mutations in *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, *JAK2*, *N/KRAS*, *CBL* and *EZH2* have also been found in a large proportion of patients with advanced disease.[12] Many of them (involving *SRSF2*, *ASXL1* and/or *RUNX1*) have been demonstrated to correlate with a bad prognosis in terms of overall survival and to be associated with adverse clinical features.[12,13] As far as treatment is concerned, Advanced SM frequently requires cytoreductive therapy[14] that includes standard chemotherapy, immunomodulating agents, and tyrosine kinase inhibitors. Among them, imatinib shows activity for wild-type KIT but is not effective on the D816V mutation, which is predominant in SM.[14,15]

In contrast, the multikinase/KIT inhibitor midostaurin is able to inhibit the D816V mutant, and its clinical utility in advanced SM has been confirmed, leading the drug to FDA, EMA, and AIFA approval as monotherapy in advanced SM patients.[15] As for chemotherapy or immunomodulating agents, in Italy, it is possible to employ subcutaneous cladribine by the law n° 648[16] or Interferon alfa-2b (IFN-a). In addition, peg-interferon alpha-2a or alpha-2b is suggested for better tolerability.[9,14] However, compared to more traditional agents such as interferon or cladribine, midostaurin can be considered a more modern and targeted approach to treating advanced SM and is now widely used.[17] New inhibitors are also becoming available, including avapritinib, a selective inhibitor of D816V, approved by the U.S. Food and Drug Administration (FDA) in June 2021 for patients with advanced SM and by the European Medicines Agency (EMA) in March 2022 for patients with advanced SM after at least one systemic therapy.[18,19]

Midostaurin is considered the standard approach for KIT inhibition in advanced SM.[18] For SM-AHN patients, a comprehensive evaluation of both SM and AHN is required to assess and correctly stage both diseases and evaluate for which treatment priority is necessary, taking into particular consideration the characteristics of the AHN component on a case-by-case basis.[20] Indeed, an AHN such as low-risk myelodysplastic syndrome (MDS) may not require immediate treatment, while it would be needed if an aggressive AHN such as acute myeloid leukemia (AML) is diagnosed. A more integrated approach, covering the biological and clinical heterogeneity of advanced SM and AHN-SM, may be more appropriate for treatment selection. However, the debate is still open on this topic, and further studies are warranted.[21,17]

From a practical perspective, some open questions remain regarding the use of midostaurin in daily routine, and there is the need for better prevention and management of adverse events to limit discontinuation or dose reduction.

Management of therapy with midostaurin can also be complicated because some adverse events overlap with disease symptoms,[21] considering that the AHN component may also be responsible for the signs and symptoms.

The aim of the current report is to present the opinions

of a group of experts who met to discuss clinical issues encountered in routine practice regarding the use of midostaurin in patients with advanced SM. In particular, following a brief overview of the efficacy and safety of midostaurin, practical guidance is given for optimal therapy management and adverse events to maximize the potential benefits of midostaurin. In addition, a clinical case scenario will be used to provide a practical example of how nausea can be managed. Finally, the group of experts also presents considerations on the use of midostaurin during the ongoing Covid-19 pandemic.

The overall scope is to provide guidance that can be useful in daily practice for clinicians using midostaurin to treat patients with advanced SM.

Midostaurin in Advanced SM

Phase 2 studies. In 2016, Gotlib et al. reported the results of an open-label phase 2 trial of midostaurin in 116 patients with advanced SM.[22] In the primary efficacy population of 89 patients with mastocytosis-related organ damage, the overall response rate according to modified Valent response criteria[23] and Cheson criteria for transfusions[24,25] criteria was 60%, and 45% of patients had a major response that was independent of *KIT* mutation status. More recently, FDA and EMA assessed the efficacy with a post-hoc exploratory analysis, per the International Working Group - Myeloproliferative Neoplasms Research and Treatment - European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus criteria,[26] henceforth referred to as IWG criteria.[27,28] Out of 116 patients, 113 had a C-finding as defined by IWG response criteria (excluding ascites as a C-finding), and an overall response rate of 28.3% was reported.[27,28] Nausea, vomiting, and diarrhea were the most frequent adverse events, while neutropenia, anemia, and thrombocytopenia were seen in 24-41% of patients.[22] In addition, in 2018, DeAngelo et al. published the results of a phase II study that enrolled 26 patients with advanced SM with an overall response rate of 69% and no unexpected toxicity after a median follow-up of 10 years.[29] Overall, midostaurin was considered to be effective and to have an acceptable safety profile.[29]

Initiating Therapy with Midostaurin in Advanced SM. *Indications and recommended dosing for midostaurin.* Midostaurin was approved by FDA and EMA for newly diagnosed *FLT3* mutation-positive acute myeloid leukemia in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy for patients in complete response as single-agent maintenance therapy, and as monotherapy for the treatment of adult patients with aggressive SM, SM-AHN, or mast cell leukemia (MCL). Prophylactic antiemetics can be considered in accordance with local practice and patient tolerance. In aggressive SM, SM- AHN, and MCL, the recommended starting dose is 100 mg BID with food. No dose adjustments are needed in patients ≥65 years of age, with mild to moderate renal impairment or mild to moderate hepatic impairment.[28]

General considerations. Before initiating therapy with midostaurin, some preliminary assessments may be recommended, even if many of the exams deemed mandatory may have already been performed as part of a proper diagnostic work-up. In women of childbearing age, a pregnancy test within seven days before starting treatment is considered compulsory, considering the potential risk of harm to the fetus. In addition, women using hormonal contraceptives should also add a barrier method of contraception as it is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives. Women should discontinue breastfeeding during treatment. Complete prescription knowledge is needed since concomitant administration with strong CYP3A inducers is contraindicated, and caution is required in combination with strong inhibitors of CYP3A4. For cases where a concomitant CYP3A4 inhibitor is strongly warranted from a clinical standpoint, midostaurin is not forbidden, but frequent monitoring is required (i.e., ECG, liver tests, etc.). Patients should also be advised to take midostaurin with food since it increases midostaurin's absorption and reduces its peak concentration (Cmax).[28] Administration of food may also help to limit some adverse events.

Laboratory exams. The expert panel recommended several laboratory exams before initiating therapy with midostaurin to have pre-treatment reference values that can be used to monitor both toxicity and response to therapy (**Table 1**). In particular, full blood count, liver enzymes, creatinine, amylase, and lipase should be obtained, in addition to baseline tryptase.

Additionally, albumin and total serum protein clotting-related factors (anti-thrombin III, prothrombin, aPTT, and fibrinogen) should also be assessed. Erythrocyte sedimentation rate (ESR) and C-reactive protein should be used to exclude infections. It was also considered important to evaluate iron levels, ferritin, folate, and B12 levels to rule out deficiency anemia or treat it as needed.

Instrumental exams. Several instrumental exams should be highly recommended (**Table 2**). Since interstitial lung disease has been reported with midostaurin, it is important to have a baseline chest X-ray, which may be repeated during follow-up if required by clinical alterations. An Electrocardiogram (ECG) with an evaluation of QTc should always be performed at baseline to exclude the absence of concomitant

Table 1. Laboratory exams to carry out before initiating midostaurin and during treatment.

Parameter	Utility
Full blood count	Response, AE monitoring
Tryptase	Response
AST, ALT, GGT, ALP, bilirubin	AE monitoring, response
Amylase, lipase	AE monitoring
Albumin, PT, PTT, fibrinogen	Response
Creatinine, urea, uric acid, glycemia, electrolytes, total serum protein, urinary, glucose, HbA1c	AE monitoring
SPEP, Ig, LDH	Disease assessments, AE monitoring
ESR, CRP	Infection status
Iron, calcium, ferritin, vitamin B12	Assess deficiency

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; SPEP, serum protein electrophoresis.

Table 2. Instrumental exams to carry out before initiating midostaurin and during treatment.

Exam	Utility
Bone densitometry (DEXA, DXA)	Assess for osteoporosis
Esophagogastroduodenoscopy	Response
ECG	AE monitoring
Ultrasound	Response
CT or MRI	Response
X-ray (spinal column, pelvis)	Response*

*: in selected cases (i.e., based on symptoms) to determine the presence of new osteolytic lesions by comparing baseline.

pathologies at baseline and since QTc prolongation has been reported in midostaurin-treated patients, especially if midostaurin is taken concurrently with medicinal products that can prolong the QT interval. If a patient takes midostaurin concurrently with other medications that can prolong the QT interval, physicians should consider regularly scheduled assessments by ECG.[30] However, the expert panel suggested that, for accurate management, ECG should be carried out every three months during the first year of treatment to evaluate for toxicity, even in the absence of QT prolongation.

In order to assess skeletal disease involvement, which is frequently observed in advanced systemic mastocytosis (AdvSM) patients, a whole-body radiographic study should be carried out.

Esophagogastroduodenoscopy (EGD) and colonoscopy can be considered optional and must be performed only in patients with gastrointestinal signs to have a diagnostic confirmation of gastrointestinal involvement. EGD and colonoscopy can also help evaluate the response to therapy in these patients.

Pathology and molecular assessments. The pathologist, with strong expertise in hematological diseases, plays a relevant role in the management of SM as, in practice, morphological examination of bone marrow (both biopsy and aspiration) is required for a right diagnosis and may also detect an associated hematologic neoplasm, if present.[5] Moreover, in the context of SM-AHN, not only morphological but also cytogenetic and molecular analyses are of particular value.[5]

Dialogue between experienced pathologists and clinicians is strongly recommended for optimal diagnosis and management of SM patients, particularly for SM-AHN cases, because clinical data and laboratory alterations should be matched. Biopsy of affected disease sites, such as gastrointestinal mucosa or localized bone lesions, is also possible, but it is infrequently pursued.[5] Lastly, it is recommended that diagnosis and subclassification of SM and the potential AHN component be carried out in dedicated reference centers to avoid misclassification and allow adequate diagnosis.[31]

Molecular testing, particularly *KIT* D816V using highly sensitive and quantitative PCR techniques such as digital PCR[32] and mast cell immunophenotyping by flow cytometry and/or immunohistochemistry are mandatory. Next-generation sequencing (NGS) can be considered in specialized centers for full mutational screening (*TET2*; *SRSF2*; *ASXL1*; *RUXN1*), and in selected cases, if *KIT* D816V with ASO-qPCR and PNA-mediated PCR is negative, as this may have prognostic value. Indeed, when concomitant hematological neoplasia is present, NGS is required to obtain a complete characterization of

the disease and to have detailed information on staging at baseline. If eosinophilia is present, the pathologist should screen for *FIP1L1-PDGFRA* molecular rearrangement. Cytogenetic assessment is important in assessing for the presence of other hematological neoplasms. The pathologist is responsible for the collection and archival of tissue samples that will be needed for future analyses in accordance with the hematologist.

From a therapeutic standpoint, bone marrow biopsy and aspiration with morphology, flow-cytometry, and quantification of *KIT* allele burden also have a role in monitoring response to the therapy; however, there is no established standard at present.[33]

Therapy, Follow-Up and Evaluation of Response. With midostaurin, based on clinical trials and real-life experiences, a rapid response is seen in many patients when given in the first line.[22] As advanced SM is a highly heterogeneous disease in terms of clinical manifestations and symptoms, timing and modalities of follow-up should be individualized and based on the characteristics of the disease and patient. While tryptase is a fundamental indicator of response, in a real setting, many exams are needed to monitor the patient's response to therapy, as detailed below. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.[28]

Response criteria. Defining global response criteria for mastocytosis remains a challenge due to the diverse clinical presentations of this condition.[34] Criteria for evaluation of response were first published in 2003 by Valent et al. and were subsequently modified in 2013 by IWG-MRT and ECNM.[26,35,36] The IWG-MRT-ECNM criteria are employed mostly for clinical trials and are mainly based on a TKI approach.[26]

Additionally, in this context, new response criteria for advanced SM have been recently proposed[37] following a modular approach and creating a tiered response evaluation of pathologic, molecular, and clinical responses.[38]

While the IWG-MRT-ECNM criteria and the latest approach mentioned are particularly relevant in the context of clinical trials and to assess response if an AHN component is present, in daily clinical practice, the response is still usually monitored using C-findings, and is broadly classified as a major response, partial response, clinical improvement and no response.[35] A version of these criteria, known as "modified Valent criteria", was used to assess response to midostaurin treatment within clinical trials[22,23] and is described hereafter and in **Table 3**. A major response is designated as the resolution of one or more C-findings and further subcategorized as complete (no organ infiltrates, tryptase < 20 ng/ml, no organomegaly), incomplete (>50% decrease in organ infiltrates, tryptase, and organomegaly), or pure clinical remission (no significant change in organ infiltrates and organomegaly, and tryptase decreased by 0-50%). In addition, a partial response is considered good when one or more C-findings have improved by more than 50%, and minor when improved by >20 to ≤50%. Lastly, no response is considered when one or more C-findings either show a constant range or have worsened by >20%. Unfortunately, the selected criteria for response evaluation are not always exhaustive for mastocytosis overall.[34]

Laboratory, instrumental, and pathology exams. Among blood and laboratory tests, full blood count, tryptase, albumin, PT, PTT, alkaline phosphatase, and fibrinogen are useful to monitor response to therapy (the latest if baseline values are abnormal).

Bone marrow biopsy and aspiration with morphology,

Table 3. Modified Valent Response Criteria*.

Response **	Subcategory ***	MC infiltrate in organ	Tryptase level	Organomegaly	C-Finding(s) (CF)
MR	CR	disappeared [*and*] ↓< 20 ng/ml [*and*] disappeared			≥ 1 CF resolved; *and* no CF↑
	IR	decrease [*and/or*] ↓> 50% [*and/or*] ↓> 50%			≥ 1 CF resolved; *and* no CF ↑
	PCR	no significant change	↓ ≤ 50% - 0%	no significant change	≥ 1 CF resolved; *and* no CF ↑
PR	GPR	N/A	N/A	no significant change	≥ 1 CF ↓by > 50%; no CF ↑
	MinR	unchanged	unchanged	no significant change	≥ 1 CF↓ by > 20% - ≤ 50%; no CF ↑
NR	SD	unchanged	unchanged	unchanged	CFs ti by +/- 0-20%
	PD	unchanged or worsened	unchanged or worsened	unchanged or worsened	≥ 1 CF ↑by > 20%

* Derived from ref. 23. ** MR: Major Response; PR: Partial Response; NR: No Response. *** CR: Complete Remission; IR: Incomplete Remission; PCR: Pure Clinical Response; GPR: Good Partial Response; MinR: Minor Response; SD: Stable Disease; PD: Progressive Disease. ≥ 1 CF: more than one C-Finding … ↓: decrease/ regression [to …] ↑: increase/ progression [to …].

flow-cytometry, and the quantifications of *KIT* allele burden also have a role in monitoring response to therapy. Relative reduction by ≥25% in the expressed *KIT* D816V allele has been associated with improved prognosis.[39] However, the experts held that while evaluation of allelic burden is useful, there is still no consensus on the timing and method to use. It should also be kept in mind that cytogenetic alterations have a prognostic impact on overall survival (OS).[40]

Concerning instrumental exams, ultrasound, CT, or MRI can be used to assess organomegaly and have an important role in monitoring its reduction.[13] In addition, only in selected cases (i.e., based on symptoms) can skeletal X-rays be used to determine the presence of new osteolytic lesions by comparing images taken before initiating therapy, as no current evidence that midostaurin improves bone disease in SM has been reported to date.[41]

The expert panel agreed that laboratory and clinical evaluation should be monitored at baseline and at least at 1, 3, 6, and 12 months from the start of therapy. However, the schedule may vary depending on the baseline severity of blood counts and the degree of emergent cytopenia.[30]

Dose interruption, reduction, and discontinuation. In advanced SM patients who receive midostaurin, treatment-related adverse events (AEs) are often difficult to distinguish from disease-related symptoms, which can lead physicians to prematurely discontinue drug administration or inadequately reduce the dosage in patients who might have benefitted from continued therapy. Therefore, it is important to assess the criteria to identify and manage AEs, in order to maximize the potential benefits of midostaurin.

Dose interruption and reduction during therapy can be considered in several scenarios. These include reductions in absolute neutrophil count, platelet count, hemoglobin, Grade 3/4 nausea and vomiting, and other Grade 3/4 non-hematological toxicities such as diarrhea (**Table 4**).

In the case of hematological toxicity at the grade specified in **Table 4**, the dose is interrupted until the ANC, platelet count, or hemoglobin level improves.[28] Midostaurin is then resumed at 50 mg BID and subsequently increased to 100 mg BID.[28] Midostaurin should be discontinued if low levels of ANC, platelet count, or hemoglobin persist for >21 days.[28]

Midostaurin can cause nausea, vomiting, and diarrhea.[28] Patients should be reminded to take midostaurin with food, and the soft capsules should not be chewed but swallowed whole.[42] In the case of Grade 3/4 nausea and vomiting, midostaurin should be interrupted for three days (6 doses) and then resumed at 50 mg BID; if tolerated, the dose can be gradually increased to 100 mg BID. For other Grade 3/4 non-hematological toxicities, midostaurin should be interrupted until the event has resolved to grade ≤2 and then resumed at 50 mg BID; if tolerated, the dose can be increased to 100 mg BID. Midostaurin should be discontinued if toxicity is not resolved to Grade ≤2 within 21 days or if severe toxicity recurs at the reduced dose.

As pulmonary toxicity has occurred in patients treated with midostaurin monotherapy or in combination with chemotherapy,[28] patients should be counseled about

Table 4. Dose interruption, reduction and discontinuation recommendations for midostaurin in patients with advanced SM.[28]

Criteria	Dosing
ANC <1.0 x 10^9/l attributed to midostaurin in patients without MCL, or ANC <0.5 x 10^9/l in patients with baseline ANC of 0.5-1.5 x 10^9/l.	Interrupt until ANC ≥1.0 x 10^9/l, then resume at 50 mg BID and, if tolerated, increase to 100 mg BID. Discontinue if low ANC persists for >21 days and is suspected to be related to midostaurin.
Platelet count <50 x 10^9/l attributed to midostaurin in patients without MCL, or platelet count <25 x 10^9/l attributed to midostaurin in patients with baseline platelet count of 25-75 x 10^9/l.	Interrupt until platelet count ≥50 x 10^9/l, then resume at 50 mg BID and, if tolerated, increase to 100 mg BID. Discontinue if low platelet count persists for >21 days and is suspected to be related to midostaurin.
Hemoglobin <8 g/dl attributed to midostaurin in patients without MCL, or life-threatening anemia attributed to midostaurin in patients with baseline hemoglobin of 8-10 g/dl.	Interrupt until hemoglobin ≥8 g/dl, then resume at 50 mg BID and, if tolerated, increase to 100 mg BID. Discontinue if low hemoglobin persists for >21 days and is suspected to be related to midostaurin.
Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy.	Interrupt for 3 days (6 doses), then resume at 50 mg BID and, if tolerated, gradually increase to 100 mg BID.
Other Grade 3/4 non-hematological toxicities.	Interrupt until event has resolved to Grade ≤2, then resume at 50 mg BID and, if tolerated, increase to 100 mg BID. Discontinue if toxicity is not resolved to Grade ≤2 within 21 days or severe toxicity recurs at a reduced dose.

ANC, absolute neutrophil count; MCL, mast cell leukemia.

possible signs and symptoms such as new or worsening cough and dyspnea. In addition, Midostaurin should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease or pneumonitis that are ≥ Grade 3 (NCI CTCAE).[28]

Adverse event management and supportive therapy. Midostaurin demonstrated clinical benefit in advanced SM with a high rate of response accompanied by reduced mast cell infiltration of bone marrow and decreased serum tryptase levels.[43] More recently, it has been shown that midostaurin improves the quality of life and SM-associated symptoms.[44] Moreover, a pooled analysis of the two phase-2 studies found that midostaurin reported an increase of about two-fold in OS versus historical controls from a patient registry (42.6 vs. 24.0 months, respectively). Propensity scoring was used for supportive analyses to match patients in the registry and provided consistent results (hazard ratio (HR)=0.381 [95% CI, 0.169-0.960]; P=.101).[45] To help patients optimize midostaurin's potential benefits, it is thus important to utilize strategies to minimize treatment-related adverse events such as nausea and vomiting. Indeed, the panel noted that these latter events are among the main adverse events that lead to discontinuation of therapy and dose reduction in daily practice. Therefore, proper management of hematologic and nonhematologic adverse events, including diarrhea, may help to avoid unnecessary dose reduction, interruption, or discontinuation of midostaurin in patients who might otherwise benefit from the continuation of therapy.[30]

Management of nausea and vomiting. As mentioned, patients taking midostaurin are frequently expected to experience nausea. However, the expert panel noted that these symptoms might improve over time, particularly when managed correctly. It has also been observed that patients typically experience nausea to a far lesser extent after the evening dose compared to the morning dose.[26] In particular, antiemetic prophylaxis should be administered as needed, and patients should be given practical diet advice and reminded to take midostaurin with food. Some practical tips that can be used to avoid nausea and vomiting include opening the blister pack away from the face and/or applying a strong-smelling ointment under the nose.[42] In addition, any comedications, which may cause nausea and vomiting, should be carefully evaluated.[42] Moreover, in this context, the expert panel highlighted the usefulness for patients to keep a food and symptoms diary that, beyond monitoring possible trigger foods, can help to identify whether consumed products are linked to an increase in nausea and/or vomiting. Of note, when prescribing midostaurin with other medications that can prolong the QT interval (e.g., some of the most commonly used antiemetics, such as ondansetron or granisetron), physicians should consider regularly scheduled assessments by ECG.

The group of experts referred that they all used ondansetron in their centers; a dose of 8 mg taken 1 hour prior to midostaurin has been previously suggested.[30] Some of the experts referred that they also used granisetron transdermal plasters to avoid further increasing the number of tablets to be taken, with changes every five days, as described in the real-life case scenario. However, ondansetron can be useful when initiating therapy during the first week since the patch takes longer to demonstrate full efficacy. As highlighted by the panel, adequate supportive therapy is undoubtedly helpful in mitigating midostaurin-related nausea and vomiting and is associated with good adherence to therapy.

Case Scenario and Management of Nausea. This female patient was born in 1975. Her symptoms began in 2007, and she was diagnosed with aggressive SM in January 2016. The patient presents with a high disease burden with a BM biopsy showing > 30% infiltration of MC as focal, dense aggregates and serum tryptase level > 200 ng/ml, skeletal involvement, and malabsorption with weight loss due to MC infiltrates (both as C-findings). Midostaurin was started at 100 mg BID in December 2018 as second-line therapy following interferon. The patient experienced Grade 3/4 nausea during the first months of therapy that was not resolved with ondansetron. The dose of midostaurin was thus reduced to 50 mg BID. Using a granisetron plaster allowed for resolution of nausea, and consequently, the dose of midostaurin was successfully increased to 100 mg BID. Treatment at 100 mg BID has been ongoing for 28 months, and the patient has not experienced other adverse events.

Management of diarrhea. Among nonhematologic toxicities, diarrhea was reported in 54% of patients treated with midostaurin.[22] However, gastrointestinal (GI) symptoms are commonly present in SM patients due to the release of MC mediators and, in advanced forms, by MC infiltration of the gut causing malabsorption.[46] Indeed, 33-45% of patients reported diarrhea as a manifestation of their disease.[47,48] In addition, in patients treated with midostaurin, substantial improvements in MC mediator–related symptoms, including diarrhea, were reported.[44] Therefore, it is crucial to distinguish between disease- and midostaurin-related diarrhea. In this context, some clinical "clues" were described to be helpful:[30] appropriate therapy (i.e., histamine H2 receptor blockers or cromolyn sodium) may offer relief to disease-related diarrhea; in case of no response, it is more probable that the diarrhea is related to midostaurin.

Furthermore, a temporal increase in the frequency and/or severity of diarrhea compared to baseline disease-

related or new onset of diarrhea with the initiation of midostaurin may also favor the correlation with this agent. In these cases, a dose reduction of midostaurin or concomitant use of antidiarrheal agents (e.g., diphenoxylate/atropine, loperamide) are potential options for diarrhea management. In general, determining the bowel involvement by SM (through endoscopy and/or colonoscopy with biopsies and staining for CD117, tryptase, and CD25) may be useful.[30] Finally, as already suggested for nausea and vomiting management, diet monitoring with a food and symptoms diary may help to identify potential food intolerance as a source of GI symptoms.

Management of cytopenia. Cytopenia is not uncommon in patients receiving midostaurin, but it may sometimes be difficult to understand if the cytopenia is related to the treatment or the disease. If the serum tryptase level and bone-marrow mast cell infiltration realistically compare with the degree of cytopenia, then it is likely that the low blood counts are related to the disease itself.[30] However, if there is only a small amount of mast cell infiltration in bone marrow, an associated hematological neoplasm may account for cytopenia. On the other hand, cytopenias may be determined by midostaurin if other disease markers (e.g., bone marrow MC burden, serum tryptase level, organ damage) improve, but cytopenia does not improve or even worsens upon treatment start.[30] Therefore, monitoring complete blood count every 1-2 weeks during the first 2 months of therapy is generally recommended, with monitoring intervals after that determined individually.[30] Both red blood cell and platelet transfusions should be given when clinically warranted; also, in case of anemia, erythropoiesis-stimulating agents may be considered, even though this was not evaluated in clinical trials.[30] In addition, patients should be given supportive care with G-CSF and antibiotics according to local practice recommendations.[30] The steps to take in terms of dose reduction and discontinuation of midostaurin for cytopenia (neutropenia, anemia, and thrombocytopenia) are described in **Table 4**.

Other. Hyperglycemia is the most frequent non-hematological laboratory abnormality found in up to 94% of patients.[28] Since diabetes is a potential risk factor for cardiovascular disease, in the event of hyperglycemia, the patient should be evaluated for glucose intolerance and referred to a diabetologist. In addition, patients should receive education on cardiac risk factors optimization, while oral hypoglycemic agents or insulin may be considered if clinically indicated.[30] No midostaurin dose adjustments have been required for patients with hyperglycemia;[30] however, dose interruption and reduction can be considered for Grade 3/4 non-hematological toxicities as described in Table 4 and/or on a case-by-case basis. Hyperlipasemia is also a frequent finding, usually asymptomatic.[29,30] Therefore, lipase should be monitored, and if elevated, patients should be followed up, given supportive care as clinically indicated, and advised to avoid all consumption of alcohol. No midostaurin dose adjustments were reported as necessary;[30] however, dose interruption and reductions should be made according to **Table 4** or on a case-by-case basis. Skin rash is also very common, affecting more than 10% of patients; in these cases, topical corticosteroids and H1 antihistamines may be administered if needed.[30] Dose modifications for these alterations should be made on a case-by-case basis. In studies with advanced SM, photosensitivity was reported in a small analysis of 28 patients in a transitory-use authorization program in France[49] and as in a case report,[50] but not in other studies.[28] If there is concern about photosensitivity, patients can be advised to wear sunscreen and suitable protective clothing.

Management of Midostaurin in SM During the Covid-19 Era and Vaccination. The ongoing Covid-19 pandemic has severely disrupted healthcare systems worldwide, but now the situation is slowly returning to normality. While advanced SM does not appear to place patients at greater risk of SARS-CoV-2 infection or severe Covid-19 in itself, many patients have many comorbidities or other characteristics that may predispose them to severe Covid-19, for example, male sex, age >65 years, type 2 diabetes, and obesity.[51]

General recommendations include avoiding any situation associated with increased risk of acquiring or transmitting infection.[51] In the case of Covid-19 infection, it has also been suggested that immunosuppressants, aggressive cytoreductive therapy, and drugs that deplete lymphocytes should be avoided or postponed if possible (e.g., rituximab, alemtuzumab, cladribine).[51]

However, treatment with anti-mediator drugs, bisphosphonates, and inhibitors of KIT kinase, such as midostaurin, should be continued, which has been done in clinics in Italy. The indications for interruption and discontinuation of therapy should be based on the best clinical judgment. Moreover, during the pandemic, patients with SM were followed according to the recommendations of the Italian Society for Hematology and the Italian Group for Bone Marrow Transplantation.[52]

At the end of 2020, effective COVID-19 vaccinations were developed and made available. Since then, some reports on the use of vaccines against SARS-CoV-2 in patients with SM have been published.[53,54] The authors suggested that this provides evidence that the vaccine is safe in patients with mastocytosis. These reports, together with the current knowledge of the safety profile of COVID-19 vaccinations, were followed by the publication of the ECNM and American Initiative in

Mast Cell Disease (AIM) recommendations on COVID-19 Vaccination in mastocytosis patients.[55] In summary, the panel of experts acknowledges that severe adverse reactions from COVID-19 Vaccination are rare, even in patients with mastocytosis. Therefore, the general use of COVID-19 Vaccination in these patients is recommended. The only well-established exception is known or suspected allergy against a vaccine constituent. However, it is suggested to consider some safety measures, including premedication and postvaccination observation, in all patients with mastocytosis, depending on the individual risk. Indeed, guidance from the expert panel results in a stratification of risk and recognizes three categories of patients at low, mild, and high risk of Vaccination which will require differentiated safety measures. These recommendations are based on expert opinion and have not been evaluated with regard to effectiveness.

Conclusions. Tyrosine kinase inhibitors such as midostaurin have revolutionized the treatment of advanced SM. Notwithstanding, treatment of advanced SM with midostaurin can add a further challenge to disease management, which is complex and requires the involvement of a multidisciplinary team (hematologists, pathologists, allergologists, dermatologists, rheumatologists, and gastroenterologists), and a multitude of laboratory, instrumental, and pathological exams prior to initiating therapy. Most tests are required as part of proper diagnostic work-up and during follow-up to monitor therapeutic response and emergent toxicities. However, the timing and modalities of follow-up may vary based on individual patient and disease characteristics. To achieve the most out of treatment with midostaurin in the advanced SM population, prescribers must be aware of its side effect profile and be able to recognize disease-related symptoms versus treatment-related adverse events, in particular nausea and vomiting. As the expert panel noted, optimal management of AEs may limit premature discontinuation and improper dose reduction of midostaurin and maximize the potential benefit of this treatment. With the intent to further refine a personalized approach in advanced SM, new treatments are developing and will extend the available therapeutic opportunities. Future research should also focus on combining KIT-targeting agents with AHN-directed agents since SM-AHN still represents an unresolved challenge. New approaches need to be able to address the remaining unmet needs in advanced SM.

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References:

1. Radia DH, Green A, Oni C and Moonim M. The clinical and pathological panoply of systemic mastocytosis. Br J Haematol. 2020;188:623-640. https://doi.org/10.1111/bjh.16288 PMid:31985050
2. Horny HP, Sotlar K and Valent P. Mastocytosis: state of the art. Pathobiology. 2007;74:121-132. https://doi.org/10.1159/000101711 PMid:17587883
3. Valent P, Akin C and Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129:1420-1427. https://doi.org/10.1182/blood-2016-09-731893 PMid:28031180 PMCid:PMC5356454
4. Swerdlow SH. WHO classification of tumours of haematopoietic and lymphoid tissues 4th ed (revised). IARC Press; Lyon, France. 2017.
5. Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. Am J Hematol. 2021;96:508-525. https://doi.org/10.1002/ajh.26118 PMid:33524167
6. Martelli M, Monaldi C, De Santis S, Bruno S, Mancini M, Cavo M and Soverini S. Recent Advances in the Molecular Biology of Systemic Mastocytosis: Implications for Diagnosis, Prognosis, and Therapy. Int J Mol Sci. 2020;21:3987. https://doi.org/10.3390/ijms21113987 PMid:32498255 PMCid:PMC7312790
7. Hermans MAW, Rietveld MJA, van Laar JAM, Dalm VASH, Verburg M, Pasmans SGMA, van Wijk RG, van Hagen PM and van Daele PLA. Systemic mastocytosis: A cohort study on clinical characteristics of 136 patients in a large tertiary centre. European Journal of Internal Medicine. 2016;30:25-30. https://doi.org/10.1016/j.ejim.2016.01.005 PMid:26809706
8. Valent P, Akin C, Gleixner KV Sperr WR, Reiter A, Arock M and Triggiani M. Multidisciplinary Challenges in Mastocytosis and How to Address with Personalized Medicine Approaches. Int J Mol Sci. 2019; 20(12):2976. https://doi.org/10.3390/ijms20122976 PMid:31216696 PMCid:PMC6627900
9. Zanotti R, Tanasi I, Crosera L, Bonifacio M, Schena D, Orsolini G, Mastropaolo F, Olivieri E and Bonadonna P. Systemic mastocytosis: multidisciplinary approach. Mediterr J Hematol Infect Dis. 2021;13(1):e2021068. https://doi.org/10.4084/MJHID.2021.068 PMid:34804442 PMCid:PMC8577553
10. Schwaab J, Cabral do OHN, Naumann N, Jawhar M, Weiss C, Metzgeroth G, Schmid A, Lübke J, Reiter L, Fabarius A, Cross NCP, Sotlar K, Valent P, Kluin-Nelemans HC, Hofmann WK, Horny HP, Panse J and Reiter A. Importance of Adequate Diagnostic Workup for Correct Diagnosis of

Advanced Systemic Mastocytosis. J Allergy Clin Immunol Pract. 2020;8:3121-3127.
https://doi.org/10.1016/j.jaip.2020.05.005
PMid:32422371

11. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y and Metcalfe DD. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci U S A. 1995;92:10560-10564.
https://doi.org/10.1073/pnas.92.23.10560
PMid:7479840 PMCid:PMC40651
12. Jawhar M, Schwaab J, Schnittger S, Meggendorfer M, Pfirrmann M, Sotlar K, Horny HP, Metzgeroth G, Kluger S, Naumann N, Haferlach C, Haferlach T, Valent P, Hofmann WK, Fabarius A, Cross NCP, Reiter A. Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V(+) advanced systemic mastocytosis. Leukemia. 2016;30:136-143.
https://doi.org/10.1038/leu.2015.284
PMid:26464169
13. Jawhar M, Schwaab J, Hausmann D, Clemens J, Naumann N, Henzler T, Horny HP, Sotlar K, Schoenberg SO, Cross NCP, Fabarius A, Hofmann WK, Valent P, Metzgeroth G and Reiter A. Splenomegaly, elevated alkaline phosphatase and mutations in the SRSF2/ASXL1/RUNX1 gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. Leukemia 2016;30:2342-2350.
https://doi.org/10.1038/leu.2016.190
PMid:27416984
14. Pardanani A. Systemic Mastocytosis in Adults: 2021 Update on Diagnosis, Risk Stratification and Management. Am J Hematol. 2021;96:508-525.
https://doi.org/10.1002/ajh.26118
PMid:33524167
15. Gilreath JA, Tchertanov L and Deininger MW. Novel approaches to treating advanced systemic mastocytosis. Clin Pharmacol. 2019;11:77-92.
https://doi.org/10.2147/CPAA.S206615
PMid:31372066 PMCid:PMC6630092
16. Agenzia Italiana del Farmaco (AIFA). Legge n.648/1996.
17. Mannelli F. Catching the clinical and biological diversity for an appropriate therapeutic approach in systemic mastocytosis. Ann Hematol. 2021;100:337-344.
https://doi.org/10.1007/s00277-020-04323-9
PMid:33156374 PMCid:PMC7646220
18. Piris-Villaespesa M and Alvarez-Twose I. Systemic Mastocytosis: Following the Tyrosine Kinase Inhibition Roadmap. Front Pharmacol. 2020;11:443.
https://doi.org/10.3389/fphar.2020.00443
PMid:32346366 PMCid:PMC7171446
19. Ayvakyt. Summary of Product Characteristic. Available at:
https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf
(Accessed 26 June, 2022)
20. Gotlib J, Gerds AT, Bose P, Castells MC, Deininger MW, Gojo I, Gundabolu K, Hobbs G, Jamieson C, McMahon B, Mohan SR, Oehler V, Oh S, Padron E, Pancari P, Papadantonakis N, Pardanani A, Podoltsev V, Rampal R, Ranheim E, Rein L, Snyder DS, Stein BL, Talpaz M, Thota S, Wadleigh M, Walsh K, Bergman MA and Sundar H. Systemic Mastocytosis, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16:1500-1537.
https://doi.org/10.6004/jnccn.2018.0088
PMid:30545997
21. Reiter A, George TI and Gotlib J. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. Blood. 2020;135:1365-1376.
https://doi.org/10.1182/blood.2019000932
PMid:32106312
22. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, Awan FT, Hexner E, Mauro MJ, Sternberg DW, Villeneuve M, Huntsman Labed A, Stanek EJ, Hartmann K, Horny HP, Valent P and Reiter A. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016;374:2530-2541.
https://doi.org/10.1056/NEJMoa1513098
PMid:27355533
23. Valent P, Akin C, Sperr WR, Escribano L, Arock M, Horny HP, Bennett JM and Metcalfe DD. Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. Leuk Res. 2003;27(7): 635-41.
https://doi.org/10.1016/S0145-2126(02)00168-6
24. Cheson BD, Bennett JM, Kantarjian H, Pinto A, Schiffer CA, Löwenberg B, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Wijermans PW, Gore S, Greenberg PL, World Health Organization (WHO) international working group. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood. 2000;96(12):3671-74.
25. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, Pinto A, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Gore SD, Schiffer CA and Kantarjian H. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2): 419-25.
https://doi.org/10.1182/blood-2005-10-4149
PMid:16609072
26. Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, Kluin-Nelemans H, Hartmann K, Sperr WR, Brockow K, Schwartz LB, Orfao A, DeAngelo DJ, Arock M, Sotlar K, Horny HP, Metcalfe DD, Escribano L, Verstovsek S, Tefferi A and Valent P. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood. 2013;121:2393-2401.
https://doi.org/10.1182/blood-2012-09-458521
PMid:23325841 PMCid:PMC3612852
27. Tzogani K, Yu Yang, Meulendijks D, Herberts C, Hennik P, Verheijen R, Wangen T, Håkonsen GD, Kaasboll T, Dalhus M, Bolstad B, Salmonson T, Gisselbrecht C and Pignatti F. European Medicines Agency review of midostaurin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis. ESMO Open. 2019;4(6):e000606.
https://doi.org/10.1136/esmoopen-2019-000606
PMid:32392175 PMCid:PMC7001097
28. Midostaurin. Summary of Product Characteristic. Available at:
https://www.ema.europa.eu/en/documents/product-information/rydapt-epar-product-information_en.pdf
(Accessed 26 June, 2022)
29. DeAngelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, Westervelt P, Merker JD, Berube C, Coutre S, Liedtke M, Medeiros B, Sternberg D, Dutreix C, Ruffie PA, Corless C, Graubert TJ and Gotlib J. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia. 2018;32:470-478.
https://doi.org/10.1038/leu.2017.234
PMid:28744009
30. Gotlib J, Kluin-Nelemans HC, Akin C, Hartmann K, Valent P and Reiter A. Practical management of adverse events in patients with advanced systemic mastocytosis receiving midostaurin. Expert Opin Biol Ther. 2021:1-12.
https://doi.org/10.1080/14712598.2021.1837109
PMid:33063554
31. Jawhar M, Schwaab J, Horny HP, Sotlar K, Naumann N, Fabarius A, Valent P, Cross NCP, Hofmann WK, Metzgeroth G and Reiter A. Impact of centralized evaluation of bone marrow histology in systemic mastocytosis. Eur J Clin Invest. 2016;46:392-397.
https://doi.org/10.1111/eci.12607
PMid:26914980
32. Greiner G, Gurbisz M, Ratzinger F, Witzeneder N, Simonitsch-Klupp I, Mitterbauer- Hohendanner G, Mayerhofer M, Müllauer L, Sperr WR, Valent P and Hoermann G. Digital PCR: A Sensitive and Precise Method for KIT D816V Quantification in Mastocytosis. Clin Chem. 2018;64:547-555.
https://doi.org/10.1373/clinchem.2017.277897
PMid:29237714 PMCid:PMC7115889
33. Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escribano L, Kristensen TK, Kluin-Nelemans HC, Hermine O, Dubreuil P, Sperr WR, Hartmann K, Gotlib J, Cross NCP, Haferlach T, Garcia-Montero A, Orfao A, Schwaab J, Triggiani M, Horny HP, Metcalfe DD, Reiter A and Valent P . KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia. 2015;29:1223-1232.
https://doi.org/10.1038/leu.2015.24
PMid:25650093 PMCid:PMC4522520
34. Criscuolo M, Fianchi L, Maraglino AME and Pagano L. Mastocytosis: One Word for Different Diseases. Oncol Ther. 2018;6:129-140.
https://doi.org/10.1007/s40487-018-0086-2
PMid:32700030 PMCid:PMC7360005
35. Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, Castells M, Sperr WR, Kluin-Nelemans HC, Hamdy NAT, Lortholary O, Robyn J, van Doormaal J, Sotlar K, Hauswirth AW, Arock M, Hermine O, Hellmann A, Triggiani M, Niedoszytko M, Schwartz LB, Orfao A, Horny HP and Metcalfe DD. Standards and standardization in

mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest. 2007;37:435-453.
https://doi.org/10.1111/j.1365-2362.2007.01807.x
PMid:17537151
36. Valent P, Akin C, Sperr WR, Horny HP, Arock M, Lechner K, Bennett JM and Metcalfe DD. Diagnosis and treatment of systemic mastocytosis: state of the art. Br J Haematol. 2003;122:695-717.
https://doi.org/10.1046/j.1365-2141.2003.04575.x
PMid:12930381
37. Gotlib J, Reiter A. ECNM 2020 Annual Meeting, Vienna, Austria.
38. Shomali W and Gotlib J. Response Criteria in Advanced Systemic Mastocytosis: Evolution in the Era of KIT Inhibitors. Int J Mol Sci. 2021;22:2983.
https://doi.org/10.3390/ijms22062983
PMid:33804174 PMCid:PMC8001403
39. Jawhar M, Schwaab J, Naumann N, Horny HP, Sotlar K, Haferlach T, Metzgeroth G, Fabarius A, Valent P, Hofmann WK, Cross NCP, Meggendorfer M and Reiter A. Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. Blood. 2017;130:137-145.
https://doi.org/10.1182/blood-2017-01-764423
PMid:28424161
40. Naumann N, Jawhar M, Schwaab J, Kluger S, Lubke J, Metzgeroth G, Popp HD, Khaled N, Horny HP, Sotlar K, Valent P, Haferlach C, Göhring G, Schlegelberger B, Meggendorfer M, Hofmann WK, Cross NCP, Reiter A and Fabarius A. Incidence and prognostic impact of cytogenetic aberrations in patients with systemic mastocytosis. Genes Chromosomes Cancer. 2018;57:252-259.
https://doi.org/10.1002/gcc.22526
PMid:29341334
41. Knapper S, Cullis J, Drummond MW Evely R, Everington T, Hoyle C, McLintock L, Poynton C and Radia D. Midostaurin a Multi-Targeted Oral Kinase Inhibitor in Systemic Mastocytosis: Report of An Open-Label Compassionate Use Program in the United Kingdom. Blood. 2011:118(21):5145.
https://doi.org/10.1182/blood.V118.21.5145.5145
42. Galinsky I, Coleman M and Fechter L. Midostaurin: Nursing Perspectives on Managing Treatment and Adverse Events in Patients With FLT3 Mutation-Positive Acute Myeloid Leukemia and Advanced Systemic Mastocytosis. Clin J Oncol Nurs. 2019;23:599-608.
https://doi.org/10.1188/19.CJON.599-608
PMid:31730602
43. Chandesris MO, Damaj G, Lortholary O and Hermine O. Clinical potential of midostaurin in advanced systemic mastocytosis. Blood Lymphat Cancer. 2017;7:25-35.
https://doi.org/10.2147/BLCTT.S87186
PMid:31360083 PMCid:PMC6467340
44. Hartmann K, Gotlib J, Akin C, Hermine O, Awan FT, Hexner E, Mauro MJ, Menssen HD, Redhu S, Knoll S, Sotlar K, George TI, Horny HP, Valent P, Reiter A and Kluin- Nelemans HC. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis. J Allergy Clin Immunol. 2020;146:356-366.e4.
https://doi.org/10.1016/j.jaci.2020.03.044
PMid:32437738
45. Reiter A, Kluin-Nelemans HC, George T, Akin C, DeAngelo DJ, Awan F, Hexner E, Mauro M, Schwaab J, Jawhar M, Sternberg D, Berkowitz N, Niolat J, Huntsman Labed A, Hartmann K, Horny HP, Valent P and Gotlib J. Pooled survival analysis of midostaurin clinical study data (D2201+A2213) in patients with advanced systemic mastocytosis compared with historical controls. Haematologica. 2017;102(s2):321.
46. Zanelli M, Pizzi M, Sanguedolce F et al. Gastrointestinal Manifestations in Systemic Mastocytosis: The Need of a Multidisciplinary Approach. Cancers. 2021;13(13):3316.
https://doi.org/10.3390/cancers13133316
PMid:34282774 PMCid:PMC8269078
47. Sokol H, Georgin-Lavialle S, Canioni D et al. Gastrointestinal manifestations in mastocytosis: A study of 83 patients. Journal of Allergy and Clinical Immunology. 2013;132(4): 866-873.e3
https://doi.org/10.1016/j.jaci.2013.05.026
PMid:23890756
48. Lee P, George TI, Shi H, et al. Systemic mastocytosis patient experience from Mast Cell Connect, the first patient-reported registry for mastocytosis. Blood. 2016;128(22). [abstract 4783].
https://doi.org/10.1182/blood.V128.22.4783.4783
49. Chandesris MO, Damaj G, Canioni D, Brouzes C, Lhermitte L, Hanssens K, Frenzel L, Cherquaoui Z, Durie I, Durupt S, Gyan E, Beyne-Rauzy O, Launay D, Faure C, Hamidou M, Besnard S, Diouf M, Schiffmann A, Niault M, Jeandel PY, Ranta D, Gressin R, Chantepie S, Barete S, Dubreuil P, Bourget P, Lortholary O, Hermine O and CEREMAST Stydy Group. Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016;374:2605-2607.
https://doi.org/10.1056/NEJMc1515403
PMid:27355555
50. Cura P, Salomon G, Bulai Livideanu C, Tournier E et al. Midostaurin-induced lichenoid photoallergic reaction in a patient with systemic mastocytosis. Photodermatol Photoimmunol Photomed. 2022.
https://doi.org/10.1111/phpp.12778
PMid:35103335
51. Valent P, Akin C, Bonadonna P, Brockow K, Niedoszytko M, Nedoszytko B, Butterfield JH, Alvarez-Twose I, Sotlar K, Schwaab J, Jawhar M, Reiter A, Castells M, Sperr WR, Kluin-Nelemans HC, Hermine O, Gotlib J, Zanotti R, Broesby-Olsen S, Horny HP, Triggiani M, Siebenhaar F, Orfao A, Metcalfe DD, Arock M and Hartmann K. Risk and management of patients with mastocytosis and MCAS in the SARS-CoV-2 (COVID-19) pandemic: Expert opinions. J Allergy Clin Immunol. 020;146:300-306.
https://doi.org/10.1016/j.jaci.2020.06.009
PMid:32561389 PMCid:PMC7297685
52. SIE/GITMO. Available at:
https://www.siematologia.it/suggerimenti-pratici-per-la-gestione-dei-pazienti-oncoematologici-nella-seconda-pandemia
(Accessed 11 Feb, 2020)
53. Rama TA, Moreira A and Castells M. mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis. J Allergy Clin Immunol. 2021;147:877-878.
https://doi.org/10.1016/j.jaci.2021.01.004
PMid:33485650 PMCid:PMC7816615
54. Lazarinis N, Bossios A and Gülen T. COVID-19 vaccination in the setting of mastocytosis-Pfizer-BioNTech vaccine is safe and well tolerated. J Allergy Clin Immunol Pract. 2022;Feb 3:S2213-2198(22)00117-9.
55. Bonadonna P, Brockow K, Niedoszytko M, Elberink HO, Akin C, Nedoszytko B, Butterfiel JH, Alvarez-Twose I, Sotlar K, Schwaab J, Jawhar M, Castells M, Sperr WR, Hermine O, Gotlib J, Zanotti R, Reiter A, Broesby-Olsen S, Bindslev-Jensen C, Schwarts LB, Horny HP, Radia D, Triggiani M, Sabato V, Carter MC, Siebenhaar F, Orfao A, Grattan C, Metcalfe DD, Arock M, Gulen T, Hartmann K and Valent P. COVID-19 Vaccination in Mastocytosis: Recommendations of the European Competence Network on Mastocytosis (ECNM) and American Initiative in Mast Cell Diseases (AIM). J Allergy Clin Immunol Pract. 2021;9:2139-2144.
https://doi.org/10.1016/j.jaip.2021.03.041
PMid:33831618 PMCid:PMC8019658