University of Groningen

Practical management of adverse events in patients with advanced systemic mastocytosis receiving midostaurin

Gotlib, Jason; Kluin-Nelemans, Hanneke C.; Akin, Cem; Hartmann, Karin; Valent, Peter; Reiter, Andreas

Published in:
Expert Opinion on Biological Therapy

DOI:
[10.1080/14712598.2021.1837109](https://doi.org/10.1080/14712598.2021.1837109)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gotlib, J., Kluin-Nelemans, H. C., Akin, C., Hartmann, K., Valent, P., & Reiter, A. (2021). Practical management of adverse events in patients with advanced systemic mastocytosis receiving midostaurin. *Expert Opinion on Biological Therapy*, 21(4), 487-498. <https://doi.org/10.1080/14712598.2021.1837109>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Practical management of adverse events in patients with advanced systemic mastocytosis receiving midostaurin

Jason Gotlib, Hanneke C. Kluin-Nelemans, Cem Akin, Karin Hartmann, Peter Valent & Andreas Reiter

To cite this article: Jason Gotlib, Hanneke C. Kluin-Nelemans, Cem Akin, Karin Hartmann, Peter Valent & Andreas Reiter (2021) Practical management of adverse events in patients with advanced systemic mastocytosis receiving midostaurin, Expert Opinion on Biological Therapy, 21:4, 487-498, DOI: [10.1080/14712598.2021.1837109](https://doi.org/10.1080/14712598.2021.1837109)

To link to this article: <https://doi.org/10.1080/14712598.2021.1837109>

Published online: 15 Jan 2021.

Submit your article to this journal [↗](#)

Article views: 323

View related articles [↗](#)

View Crossmark data [↗](#)

Citing articles: 4 View citing articles [↗](#)

REVIEW

Practical management of adverse events in patients with advanced systemic mastocytosis receiving midostaurin

Jason Gotlib^a, Hanneke C. Kluin-Nelemans^{ib}, Cem Akin^c, Karin Hartmann^{d,e}, Peter Valent^f and Andreas Reiter^g

^aStanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA; ^bDepartment of Hematology, University Medical Center, University of Groningen, Groningen, The Netherlands; ^cDivision of Allergy and Clinical Immunology, University of Michigan, Ann Arbor, MI, USA; ^dDivision of Allergy, Department of Dermatology, University of Basel, Basel, Switzerland; ^eDepartment of Biomedicine, University of Basel, Basel, Switzerland; ^fDepartment of Internal Medicine I, Division of Hematology and Hemostaseology, Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria; ^gUniversity Hospital Mannheim, Heidelberg University, Mannheim, Germany

ABSTRACT

Introduction: Systemic mastocytosis (SM) is characterized by the overproduction and accumulation of neoplastic mast cells (MCs) in the bone marrow, skin, and visceral organs. The *KIT* D816V mutation is found in approximately 90% of cases. In advanced SM (advSM), inferior survival often relates to MC-induced organ damage that may impact multiple organ systems. In addition, mediator symptoms related to MC activation can severely impact the quality of life. The oral multikinase/*KIT* inhibitor midostaurin was approved by the US Food and Drug Administration and the European Medicines Agency as monotherapy for advSM based on data from phase 2 clinical studies.

Areas covered: This review discusses the management of common adverse events (AEs) in patients with advSM who participated in phase 2 clinical studies that led to the approval of midostaurin.

Expert opinion: In the advSM population undergoing treatment with midostaurin, treatment-related AEs are often difficult to distinguish from disease-related symptoms, which can lead to premature discontinuation and improper dose reduction of midostaurin therapy in patients who might have benefitted from continued therapy. Here we present strategies to help optimize AE management and maximize the potential benefits of midostaurin in advSM.

ARTICLE HISTORY

Received 29 July 2020

Accepted 12 October 2020

KEYWORDS

Advanced systemic mastocytosis; adverse events; cytopenia; *KIT* D816V mutation; mastocytosis; midostaurin; nausea; tryptase

1. Introduction

Systemic mastocytosis (SM) is a rare myeloid neoplasm caused by the increased production and accumulation of neoplastic mast cells (MCs) in the bone marrow and organs such as skin, liver, spleen, lymph nodes, and gastrointestinal tract [1–4]. Mutations in the gene encoding the *KIT* receptor tyrosine kinase (*KIT*; *KIT* D816V in ~90% of cases) [2,5,6] are a primary oncogenic driver of disease pathogenesis [7,8]. Advanced forms of the disease (advSM) include SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL) [3,9,10].

ASM is characterized by the presence of ≥ 1 C-finding (MC infiltration resulting in organ damage) [4]. MCL is defined by $\geq 20\%$ abnormal MCs on a bone marrow smear [11,12], which should not be present in ASM or SM-AHN. The vast majority of patients with MCL, but not all, present with C-findings [13]; MCL without C-findings is referred to as chronic MCL [14]. Approximately two-thirds of patients with advSM present with an associated hematologic neoplasm (AHN) [15–17]. SM-AHN is defined by SM criteria and additional criteria to diagnose an AHN. Both the SM and AHN components may contribute to organ damage and can present challenges with diagnosis, treatment, and evaluation of response due to the presence of the two related diseases [9]. Additional somatic

mutations beyond *KIT* D816V are present in >60% of the patients with advSM, particularly those with AHN [18,19]. In most patients, the AHN reflects multilineage involvement of *KIT* D816V [5]. An AHN may also be present in patients with MCL [20]. The AHNs can include a myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), MDS/MPN (predominantly chronic myelomonocytic leukemia [CMML] or MDS/MPN unclassifiable), chronic eosinophilic leukemia not otherwise specified (CEL NOS), acute myeloid leukemia (AML), and lymphoid disorders [4,21,22]. Lymphoid disorders are uncommon (<10%) AHNs and include chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphomas, as well as plasma cell dyscrasias such as monoclonal gammopathy of undetermined significance and multiple myeloma [5, 22–24].

Symptoms of advSM are associated with the degree of organ damage and MC mediator release [3,9]. MC infiltration resulting in organ damage (e.g. C-findings) can be broadly divided into nonhematologic organ damage (e.g., liver function abnormalities, hypoalbuminemia, portal hypertension, ascites, symptomatic splenomegaly, and/or large osteolysis with or without pathologic fractures) and hematologic organ damage (most frequently anemia and thrombocytopenia) [3,4,9]. Reduction in the percentage of bone marrow mast cells, as well as serum tryptase level (the most useful surrogate laboratory marker for mast cell burden and a minor

Article highlights

- In advanced systemic mastocytosis, organ damage due to accumulation of mast cells and release of mast cell mediators can produce major symptoms that have an impact on quality of life
- Advanced systemic mastocytosis may be treated with the oral multikinase/KIT inhibitor midostaurin, the only drug approved for this indication
- For patients with advanced systemic mastocytosis, treatment-related adverse events may be difficult to distinguish from disease-related events, which can result in premature discontinuation or improper dose reduction of midostaurin
- Optimizing adverse event management using the strategies described herein may allow more patients with advanced systemic mastocytosis to maximize benefit from midostaurin therapy

This box summarizes key points contained in the article.

diagnostic criterion for SM), are primary determinants of response to therapy [9]. Normalization or regression of SM-related organ damage is also used as a response criterion for clinical improvement [9,25]. More recently, changes in *KIT* D816V variant allele frequency have been incorporated into response evaluation to KIT-targeting agents [26,27].

Signs and symptoms resulting from the systemic release of proinflammatory MC mediators include pruritus, flushing, diarrhea, nausea, vomiting, anaphylaxis, headache, hypotension, syncope, fatigue, depression, and cognitive impairment [28,29], with flushing and anaphylaxis being significantly more frequent in patients with nonadvanced types of SM, such as indolent SM (ISM) [30,31]. Many patients with advSM report a negative impact on their health-related quality of life due to symptoms of MC burden and MC mediator release [32–34].

Treatment of advSM is challenging due to the heterogeneity and complexity of the disease [2,35]. Historically, treatment options were limited to palliative therapies that were directed toward relieving symptoms of MC degranulation or anaphylaxis (e.g. antihistamines, MC stabilizers, corticosteroids, epinephrine for anaphylaxis), and cytoreductive therapies directed at MC debulking (e.g. interferon- α , cladribine, or multi-agent chemotherapy) [2,35,36]. The multikinase/KIT inhibitor midostaurin demonstrated clinical benefit in two phase 2 studies in patients with advSM, regardless of *KIT* mutation status [15,16,37,38], which led to its approval in 2017 by the US Food and Drug Administration and the European Medicines Agency as a single agent for the treatment of patients with advSM [39,40]. Today, midostaurin is widely used in patients with advSM.

2. Overview of midostaurin efficacy and safety

Recommended dosing of midostaurin for patients with advSM is 100 mg twice daily with food; this dosage is twice as high as the dose recommended for the treatment of patients with *FLT3*

mutation-positive AML (i.e. 50 mg twice daily in combination with chemotherapy and as single-agent maintenance therapy) [39,40]. The efficacy and safety of midostaurin in patients with advSM was evaluated in an international, multicenter, open-label, phase 2 study (D2201; NCT00782067), in which patients received midostaurin 100 mg twice daily in continuous 4-week cycles until protocol-defined disease progression, death, unacceptable toxicity, or withdrawal of consent [15]. Of the 116 patients enrolled in the study, 89 were evaluable for response, and all patients were evaluable for safety. The overall response rate was 60%, including 45% of patients with complete resolution of ≥ 1 C-findings (i.e. major response). Responses were observed across all advSM subtypes (SM-AHN, ASM, and MCL) and were independent of *KIT* mutation status or prior therapy. Decreases in bone marrow MC burden $\geq 50\%$ were observed in 57% of evaluable patients. Collective decreases in serum tryptase levels and bone marrow MC burden were reported in 78% of patients. Reduction in spleen volume was observed in 77% of the 39 patients with evaluable baseline splenomegaly. Patient-reported symptom burden, measured using the Memorial Symptom Assessment Scale, decreased in 30 of the 32 symptoms reported. Since midostaurin not only suppresses the growth of neoplastic mast cells but also the immunoglobulin E-dependent mediator release from mast cells and basophils [41,42], it is possible that mitigation of patients' symptoms may be in part also related to this mechanism [38].

The most frequently reported adverse events (AEs) were grade 1/2 gastrointestinal (GI) events (i.e. nausea, vomiting, and diarrhea) (Table 1 and Table 2) [15]. New or worsening hematologic AEs (i.e. AEs reported at a higher grade while on treatment vs at baseline) included anemia, neutropenia, and thrombocytopenia, all of which were most common in patients with preexisting cytopenias. With a median duration of exposure of 11.4 months (range, 0.3–51.5 months), 65 patients (56%) had ≥ 1 dose reduction, most frequently due to AEs (48 of 65 patients [74%]). Overall, 18 patients (21%) discontinued midostaurin due to AEs, mostly nonhematologic. Any-grade AEs that led to discontinuation in >1 patient were QT prolongation ($n = 3$) and ascites, nausea, vomiting, and increased amylase level ($n = 2$ each). Discontinuation due to grade 3/4 thrombocytopenia and neutropenia occurred in 1 patient each.

An additional phase 2 study evaluated single-agent midostaurin in 26 patients with advSM (A2213; NCT00233454) who were treated with 100 mg twice daily in continuous 28-day cycles for ≤ 12 cycles, with treatment continued for patients deriving clinical benefit [16]. The overall response rate was 69% (50% major response; 19% partial response). The most frequently reported nonhematologic AEs were grade 1/2 GI events; hematologic abnormalities were also reported in most patients (Table 1; Table 2). Decreases in bone marrow MC burden, serum tryptase levels, splenomegaly, and reversion of disease-related organ damage (e.g. weight gain, reduction in ascites) were also observed, consistent with the D2201 trial. Nausea and vomiting were reported in 88% and 69% of enrolled patients, respectively, and led to midostaurin dose reduction in 8% of patients; discontinuations due to nausea and vomiting were not reported.

Table 1. Frequency of nonhematologic (occurring in $\geq 15\%$ of patients in the pooled analysis) and new or worsening hematologic adverse events observed in patients with advSM treated with midostaurin in clinical studies [15,16,39].

Events	Patients With AdvSM (N = 142)	
	All Grades, %	Grade ≥ 3 , %
Nonhematologic AEs (occurring in $\geq 15\%$ of patients) ^a		
Nausea	82	6
Vomiting	68	6
Diarrhea	54	8
Edema	40	7
Musculoskeletal pain	35	4
Abdominal pain	34	6
Fatigue	34	9
URI	30	1
Constipation	29	< 1
Pyrexia	27	4
Headache	26	1
Dyspnea	23	7
Arthralgia	19	2
UTI	16	3
Cough	18	< 1
New or worsening hematologic abnormalities (occurring in $\geq 45\%$ of patients)		
Lymphopenia	66	42
Leukopenia	61	19
Anemia	60	38
Thrombocytopenia	50	27
Neutropenia	49	22
New or worsening laboratory abnormalities (occurring in $\geq 35\%$ of patients)		
Hyperglycemia	80	18
Elevated AP	39	9
Hypocalcemia	39	2
Elevated lipase	37	18
Hyperuricemia	37	11
Elevated GGT	35	9

AE, adverse event; AP, alkaline phosphatase; GGT, γ -glutamyl transferase; URI, upper respiratory tract infection; UTI, urinary tract infection.

^aAcross both studies, the rate of any-grade QT prolongation was 11%, and the rate of grade ≥ 3 QT prolongation was < 1%.

Similarly, a study with 28 patients with advSM reported nausea and vomiting as common AEs occurring in 89% of patients and leading to treatment discontinuation in 18% despite the use of antiemetics [43].

The following two case studies highlight issues related to the evaluation of AEs on midostaurin in patients with advSM and are followed by detailed recommendations for optimal management of specific AEs.

3. Case studies

3.1. Case 1

A 65-year-old man presented with SM associated with CMML and *KIT* D816V and *SRSF2* mutations (with mutant allele burdens of 42% and 36%, respectively). The patient experienced abdominal bloating and discomfort, with a weight loss of 4.5 kg over 3 months. In addition, he presented with diarrhea 2 to 3 times daily and paracentesis-dependent ascites (every 2 weeks). On physical examination, performed between episodes of paracentesis, splenomegaly of 8 cm below the left costal margin and hepatomegaly of 5 cm were evident. His complete blood count revealed a white blood cell count of $14.8 \times 10^9/L$, hemoglobin level of 10.4 g/dL, and platelet count of $108 \times 10^9/L$. His differential revealed 40% neutrophils, 20% lymphocytes, and 38% monocytes, for an absolute monocyte count of $5.62 \times 10^9/L$. A bone marrow core biopsy showed MC involvement of 40% as well as CMML-1 with a marrow blast count of 6%. The serum tryptase level was 220 ng/mL (normal, <11.4 ng/mL). An increase in serum alkaline phosphatase (AP) to 340 IU/L was noted [normal, <130 IU/L]. Liver biopsy as well as random biopsies via upper

Table 2. Hematologic and nonhematologic adverse events occurring in $\geq 10\%$ of patients in clinical studies of midostaurin in advSM.

	D2201 [15] N = 116		A2213 [16] N = 26	
Protocol-defined guidance on dose interruption	<div><div><ul style="list-style-type: none">• Dose interruption for ≤ 21 days until recovery to grade ≤ 2 for:<ul style="list-style-type: none">◦ Drug-related grade 3/4 hematologic abnormalities^{a,b}◦ Grade 3/4 nonhematologic toxicities◦ Nausea/vomiting lasting 3 days despite antiemetic use◦ Grade 3/4 diarrhea despite optimal medication</div><div><ul style="list-style-type: none">• Dose interruption for ≤ 14 days until recovery to grade ≤ 1 for:</div></div>			
Protocol-defined guidance on dose reduction/discontinuation	<div><ul style="list-style-type: none">• Resume treatment at 50-mg reduced dose; if tolerated, resume 100-mg dose in subsequent cycles• Discontinue if toxicity does not resolve during specified duration of interruption or if grade 3/4 AEs recur at 50-mg dose</div>			
AEs, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nausea	92 (79)	7 (6)	23 (88)	0
Vomiting	77 (66)	7 (6)	18 (69)	0
Diarrhea	63 (54)	9 (8)	7 (27)	0
Peripheral edema	40 (34)	5 (4)	–	–
Abdominal pain	33 (28)	4 (3)	4 (15)	0
Fatigue	32 (28)	11 (9)	9 (35)	2 (8)
Pyrexia	31 (27)	7 (6)	–	–
Constipation	28 (24)	1 (1)	12 (46)	0
Headache	27 (23)	2 (2)	8 (31)	0
Back pain	23 (20)	2 (2)	–	–
Pruritis	22 (19)	4 (3)	–	–
Arthralgia	20 (17)	2 (2)	–	–
Cough	19 (16)	1 (1)	–	–
Dyspnea	18 (16)	5 (4)	5 (19)	2 (8)

(Continued)

Table 2. (Continued).

	D2201 [15] N = 116		A2213 [16] N = 26	
Musculoskeletal pain	18 (16)	5 (4)	–	–
Nasopharyngitis	17 (15)	0	–	–
UTI	14 (12)	2 (2)	–	–
Dizziness	13 (11)	0	–	–
Epistaxis	13 (11)	3 (3)	–	–
Pleural effusion	13 (11)	4 (3)	–	–
QT prolongation	12 (10)	1 (1)	–	–
Lower extremity edema	–	–	9 (35)	0
Lipase increased ^c	–	–	5 (19)	4 (15)
AP elevated	–	–	5 (19)	2 (8)
Hyperglycemia	–	–	5 (19)	1 (4)
Lightheadedness	–	–	4 (15)	0
Hypokalemia	–	–	4 (15)	1 (4)
Decreased concentration	–	–	3 (12)	0
Gas/bloating	–	–	3 (12)	0
Tremors	–	–	3 (12)	0
Hematologic abnormalities, n (%)				
Anemia	73 (63)	48 (41)	7 (27)	3 (12)
Thrombocytopenia	60 (52)	33 (29)	6 (23)	2 (8)
Neutropenia	56 (48)	28 (24)	3 (12)	2 (8)

AdvSM, advanced systemic mastocytosis; AE, adverse event; AP, alkaline phosphatase; UTI, urinary tract infection.

^aIn D2201, no dose modification was made for grade 3/4 hematologic abnormalities in patients with grade 3/4 cytopenias at baseline.

^bOn repeat determination 7 days apart.

^cAsymptomatic without evidence of clinical pancreatitis.

endoscopy and colonoscopy confirmed involvement by SM. Midostaurin therapy (100 mg twice daily) was initiated, with the patient reporting moderate nausea starting 30 minutes after the morning dose and lasting for 1 hour, resulting in 1 episode of vomiting.

3.2. Case 2

A 58-year-old man was diagnosed with SM-CEL, NOS with a *KIT* D816V mutation (variant allele frequency, 28%). The patient complained of moderate fatigue and night sweats and was found to have splenomegaly of 6 cm below the left costal margin. Laboratory values included a white blood cell count of $25 \times 10^9/L$, hemoglobin level of 9.8 g/dL, and platelet count of $89 \times 10^9/L$, with differential showing eosinophilia of 55%. The serum tryptase level was 180 ng/mL. A bone marrow core biopsy showed 30% MC involvement and marked marrow eosinophilia. Midostaurin therapy (100 mg twice daily) was started. After 4 weeks, the patient's hemoglobin and platelet levels decreased to 8.8 g/dL and $54 \times 10^9/L$, respectively, with an accompanying reduction in eosinophilia to 18%. The serum tryptase level decreased to 105 ng/mL; fatigue was improving (despite the hemoglobin drop) and night sweats decreased. In addition, splenomegaly decreased to 3 cm below the left costal margin.

4. Management of cytopenias, gastrointestinal adverse events, and selected other adverse events

In the pivotal midostaurin studies, the most common grade 1/2 AEs were GI events, whereas the most common grade 3/4 AEs included cytopenias, asymptomatic hyperlipasemia, fatigue, dyspnea, elevated AP, and pyrexia (Table 1; Table 2) [15,16]. Elevation of the serum AP level is the most common

manifestation of liver involvement by SM. With midostaurin treatment, it typically normalizes over time; in the D2201 clinical trial, the median level of AP at baseline (441 U/L) declined over a 6-month period to a median level of 186 U/L and often declined to normal levels in patients who had elevated values at baseline [15]. Other grade 1/2 AEs commonly reported with midostaurin therapy included many of the same symptoms associated with MC mediator release, such as headache and fatigue. Therefore, it can be difficult

Table 3. Clinical clues to help distinguish disease-related symptoms from midostaurin-related AEs.

Symptom/AE	Midostaurin Related vs Disease Related
Nausea and vomiting	<ul style="list-style-type: none"> Midostaurin-related nausea and vomiting usually follow the 'after 1 hour for 1 hour' rule, that is, they begin within 30 minutes to 1 hour after taking the midostaurin dose and last for 1 hour; AEs are more frequent with the morning dose than the evening dose of midostaurin Disease-related nausea and vomiting do not often occur in a discernible pattern
Diarrhea	<ul style="list-style-type: none"> Midostaurin-related diarrhea may be more frequent than baseline disease-related diarrhea Disease-related diarrhea may often show improvement or complete resolution with successful therapy
Cytopenias (anemia, neutropenia, and thrombocytopenia)	<ul style="list-style-type: none"> Cytopenias may be midostaurin related if other surrogate disease markers (e.g. bone marrow MC burden, serum tryptase level, organ damage) improve but cytopenia does not improve or even worsens

Table 4. Summary of hematologic and nonhematologic adverse events and their management.

Event	Trial Data	Management Recommendations
Hematologic adverse events		
Anemia	<ul style="list-style-type: none"> Although most patients experienced anemia, no patients in the D2201 or A2213 studies discontinued due to anemia [15,16] 	<ul style="list-style-type: none"> If hemoglobin <8 g/dL attributed to midostaurin occurs in patients without MCL or life-threatening anemia attributed to midostaurin occurs in patients with baseline hemoglobin level of 8–10 g/dL [39,40]: <ul style="list-style-type: none"> Interrupt midostaurin until hemoglobin is ≥ 8 g/dL, then resume midostaurin at 50 mg twice daily; if tolerated, increase back to 100 mg twice daily Although the studies required discontinuation of midostaurin if a low hemoglobin level (<8 g/dL) persisted for >21 days and was suspected to be related to midostaurin, discontinuation may not be required in daily practice where physicians may consider red blood cell transfusions as well as the use of erythropoiesis-stimulating agents, although the latter was not evaluated in clinical studies
Neutropenia	<ul style="list-style-type: none"> In the D2201 and A2213 studies, 22% of patients on midostaurin experienced grade ≥ 3 neutropenia, but patients rarely discontinued midostaurin therapy [39] 	<ul style="list-style-type: none"> Patients may benefit from treatment with granulocyte-colony stimulating factor If ANC is $< 1 \times 10^9/L$ and <ul style="list-style-type: none"> to add to midostaurin in a patient with baseline ANC value of $0.5\text{--}1.5 \times 10^9/L$ [39,40]: <ul style="list-style-type: none"> Interrupt midostaurin until ANC is $\geq 1 \times 10^9$, then resume midostaurin at 50 mg twice daily; if tolerated, increase to 100 mg twice daily Discontinue midostaurin if low ANC persists for >21 days and is suspected to be related to midostaurin
Thrombocytopenia	<ul style="list-style-type: none"> Patients rarely discontinued midostaurin therapy due to thrombocytopenia [15,16] 	<ul style="list-style-type: none"> Patients with thrombocytopenia should avoid anti-inflammatory pain medicines and activities that might lead to bleeding [46] If platelet count is $< 50 \times 10^9/L$ and is attributed to midostaurin in a patient without MCL or if platelet count is $< 25 \times 10^9/L$ and is attributed to midostaurin in patients with baseline platelet count of $25\text{--}75 \times 10^9/L$ [39,40]: <ul style="list-style-type: none"> Interrupt midostaurin until platelet count is $\geq 50 \times 10^9/L$, then resume midostaurin at 50 mg twice daily; if tolerated, increase to 100 mg twice daily Discontinue midostaurin if low platelet count persists for >21 days and is suspected to be related to midostaurin
Nonhematologic adverse events		
Gastrointestinal events (nausea, vomiting, diarrhea)	<ul style="list-style-type: none"> Despite being the 3 most common nonhematologic AEs experienced by patients in the D2201 study, only 4 patients (4%) discontinued therapy due to these events [15] 	<ul style="list-style-type: none"> Nausea and vomiting can generally be controlled with antiemetics; in some cases, dose adjustment or interruption might be needed A dose reduction or antidiarrheals are potential options for effectively targeting diarrhea Nondrug approaches, such as opening the midostaurin blister packaging 1 hour prior to dosing, taking midostaurin with food, eating small meals throughout the day, and avoiding strong odors, are recommended In patients with grade 3/4 nausea and/or vomiting despite optimal antiemetic therapy [39,40]: <ul style="list-style-type: none"> Interrupt midostaurin for 3 days (6 doses), then resume midostaurin at 50 mg twice daily; if tolerated, gradually increase back to 100 mg twice daily It is recommended to resume midostaurin with the evening dose rather than the morning dose In patients with grade 3/4 diarrhea [39,40]: <ul style="list-style-type: none"> Interrupt midostaurin until event has resolved to grade ≤ 2, then resume midostaurin at 50 mg twice daily; if tolerated, increase back to 100 mg twice daily^a
Hyperlipasemia	<ul style="list-style-type: none"> In the D2201 and A2213 studies, 37% of patients experienced new or worsening lipase elevations (18% were grade ≥ 3) [39] One patient in D2201 discontinued due to grade 3/4 hyperlipasemia [15] 	<ul style="list-style-type: none"> Instances of hyperlipasemia were asymptomatic Patients should be observed and told to avoid alcohol consumption

(Continued)

Table 4. (Continued).

Event	Trial Data	Management Recommendations
Hyperglycemia	<ul style="list-style-type: none"> In the D2201 and A2213 studies, 80% of patients experienced nonfasting hyperglycemia (18% were grade ≥ 3) [39] 	<ul style="list-style-type: none"> Evaluate patients for glucose intolerance (HbA1C) Evaluation by a diabetologist and/or an endocrinologist is recommended The need for oral hypoglycemic agents or insulin should be evaluated Provide patient education on the importance of optimizing cardiac risk factors
QT prolongation	<ul style="list-style-type: none"> In the D2201 and A2213 studies, 11% of patients experienced QT prolongation (<1% were grade ≥ 3) [39] 	<ul style="list-style-type: none"> Consider regularly scheduled electrocardiogram assessments in patients taking midostaurin concurrently with medications that can prolong the QT interval [39,40] In patients with grade 3/4 QT prolongation [39,40]: <ul style="list-style-type: none"> Interrupt midostaurin until resolved to grade ≤ 2, then resume midostaurin at 50 mg twice daily; if tolerated, increase back to 100 mg twice daily Discontinue midostaurin if toxicity is not resolved to grade ≤ 2 within 21 days or if severe toxicity recurs at a reduced dose of midostaurin [40]
Interstitial lung disease/ pneumonitis/ pulmonary toxicity	<ul style="list-style-type: none"> Rare but serious event in patients treated with midostaurin as monotherapy or with chemotherapy 	<ul style="list-style-type: none"> Monitor patients for pulmonary symptoms [39,40] Interrupt midostaurin in patients experiencing grade 3/4 pulmonary toxicity until the event has resolved to grade ≤ 2, then resume midostaurin at 50 mg twice daily, and, if tolerated, increase back to 100 mg twice daily^a Discontinue midostaurin in patients experiencing signs and/or symptoms indicative of interstitial lung disease or pneumonitis without an infectious etiology^b
Rash and photosensitivity	<ul style="list-style-type: none"> In the D2201 and A2213 studies, 14% of patients experienced rash (3% were grade ≥ 3) [39] In a French compassionate use program, 25% of patients developed photosensitivity [43] 	<ul style="list-style-type: none"> For rash, monitor and consider treatment with topical corticosteroids and H1 antihistamines as needed For photosensitivity, advise patients to protect themselves from the sun (e.g. avoidance of the sun during peak hours, wearing of sunprotective clothing [such as hats, sunglasses, long sleeves, and pants], use of sunscreen with broad-spectrum coverage with a sun protection factor ≥ 30, and reapplication of sunscreen every 2 hours)

ANC, absolute neutrophil count; HbA1C, glycated hemoglobin A1C.

^aIn the European Union, per the summary of product characteristics, discontinue midostaurin if toxicity is not resolved to grade ≤ 2 within 21 days or if severe toxicity recurs at a reduced dose of midostaurin [40].

^bIn the European Union, per the summary of product characteristics, discontinue midostaurin if grade ≥ 3 pulmonary symptoms indicative of interstitial lung disease or pneumonitis [40] are observed.

to distinguish symptoms related to systemic mastocytosis and treatment-related AEs (Table 3).

4.1. Gastrointestinal adverse events

The most common AEs associated with midostaurin are GI related (i.e., nausea, vomiting, and diarrhea) [39]. In a survey of patients with advSM, 45% of patients reported moderate to severe symptoms associated with diarrhea in the previous year [34]. Therefore, it may be challenging to distinguish between disease- and midostaurin-related diarrhea (Table 4) [44]. First, it is important to determine whether appropriate doses of histamine H2 receptor blockers or cromolyn sodium are being administered, which can help disease-related diarrhea. If the patient does not respond to these medications, it is then more probable that the diarrhea is related to midostaurin therapy. A dose reduction of midostaurin or concomitant use of antidiarrheal agents (e.g. diphenoxylate/atropine, loperamide) are potential options for managing diarrhea, but neither may be helpful to distinguish between disease- and midostaurin-related diarrhea. Bowel involvement by MCs and/or MC

mediator release can lead to diarrhea [45]. Endoscopy and/or colonoscopy with random biopsies and staining for CD117, tryptase, and especially CD25 (to evaluate for neoplastic mast cells) can help determine whether the bowel is involved by mastocytosis. A temporal increase in the frequency and/or severity of diarrhea above baseline or disease-related diarrhea with initiation of midostaurin may help to determine how much of this symptom is related to the initiation of this agent. It may also be beneficial to reevaluate potential food intolerances during the process of investigating the source of the GI symptoms. The incidence of diarrhea in D2201 was reported as 54% of patients, with 8% of patients experiencing grade 3/4 diarrhea (Table 2) [15].

In our experience, nausea may occur daily after taking midostaurin, usually more profoundly after the morning dose and immediately after the initiation of treatment, but symptoms generally improve over time. Vomiting is a less frequent complication in our practice but is second only to nausea in terms of its observed frequency in clinical studies. Respective rates of nausea and vomiting were 79% and 66% in D2201 and 88% and 69% in A2213 (Table 2) [15,16,44]. These findings are

consistent with the rates of nausea (83%) and vomiting (61%) observed in the phase 3 trial of midostaurin + chemotherapy for the treatment of *FLT3* mutation-positive AML; however, note that instances of grade 3/4 nausea and vomiting were less frequent with midostaurin, which was given at a dosage of 50 mg twice daily rather than the 100 mg twice daily for advSM, than they were in the comparator placebo + chemotherapy arm in that study [39].

In a pooled analysis of patients enrolled in the D2201 and A2213 studies, most patients who experienced nausea, vomiting, and diarrhea had ≤ 2 episodes (Figure 1(a)). Nausea, vomiting, and diarrhea episodes were mitigated by using concomitant supportive care medications, such as a highly effective antiemetic (e.g. ondansetron or granisetron) 30 minutes to 1 hour before each dose, by administering the dose with food, and by taking the evening dose just before going to bed (to avoid being awakened by nausea), but in some cases, dose adjustment or midostaurin discontinuation was required (Figure 1(b)).

4.2. Cytopenias

Cytopenias are common in patients with advSM [9], and understanding the etiology of low blood counts in these individuals can be challenging. Sometimes the extent of MC infiltration in the bone marrow and the serum tryptase level correlate reasonably well with the degree of cytopenia(s). In such cases, the decreased blood counts are considered a *bona fide* C-finding, i.e. related to the SM component. However, in some cases, the degree of bone marrow MC infiltration is considered too low (e.g. 5%-10%) to account for the degree of cytopenia(s); in such cases, an AHN (i.e. MDS, MPN, MDS/MPN, CMMML, CEL, AML, or lymphoid disorders) may account for the cytopenias. AHNs and SM are often derived from the same multipotent hematopoietic progenitors in cases of a myeloid AHN; in these cases, the *KIT* D816V allele burden may reflect the total disease burden (e.g. both SM and AHN components), and the AHN component may primarily account for the cytopenia(s) [5,6,47]. Cytopenia(s) can also result from hypersplenism related to the SM and/or AHN component(s) as well as myelosuppression from prior therapies [9], as many patients with advSM are heavily pretreated [15,48,49]. Finally, one must also rule out coexisting comorbidities or medications that can contribute to cytopenias.

In the D2201 study, any-grade neutropenia, anemia, and thrombocytopenia were reported in 48%, 63%, and 52% of patients, respectively; grade 3/4 abnormalities were reported in 24%, 41%, and 29% of patients, respectively (Table 2). Midostaurin was discontinued in 4% of patients due to cytopenia(s) (including individual reports of neutropenia and thrombocytopenia) (Table 4) [15]. In A2213, any-grade neutropenia, anemia, and thrombocytopenia were reported in 12%, 27%, and 23% of patients, respectively; grade 3/4 abnormalities were reported in 8%, 12%, and 8% of patients, respectively (Table 2) [16]. The role of erythropoiesis-stimulating agents was not assessed in the midostaurin studies.

Among the 142 patients who received midostaurin therapy in clinical studies (D2201 and A2213), 41 patients (28.9%) had at least one grade ≥ 3 infection; of these, the majority had only 1 event [50]. The use of granulocyte-colony stimulating factor (G-CSF) might be appropriate in some patients with neutropenia and febrile neutropenia, although use of this drug was not formally assessed in the clinical studies.

Routine blood count monitoring should be undertaken in all patients receiving midostaurin. We generally recommend monitoring the complete blood count with differential every 1 to 2 weeks (depending on baseline severity of blood counts) during the first 8 weeks of therapy, with monitoring intervals extended thereafter based on the degree of emergent cytopenias. Red blood cell and platelet transfusions should be provided as needed following local guidelines. In the absence of clear signs of an infection, midostaurin should be continued in neutropenic patients, even if neutrophils are low and the bulk of SM could not be reduced. When febrile neutropenia occurs or other signs of an infection are seen, therapy with midostaurin is usually interrupted, and G-CSF and antibiotics should be administered following local guidelines. After recovery, midostaurin can be continued in most cases, but the timing and dosing has to be adjusted to the individual situation in each case. A summary of measures and specific actions required in the clinical studies mentioned above in cytopenic patients with advSM treated with midostaurin is shown in Table 4.

4.3. Hyperlipasemia

In the D2201 and A2213 studies, 37% of patients experienced new or worsening hyperlipasemia, including 18% with grade 3/4 elevations (Table 4) [39]. Hyperlipasemia is often a symptom of pancreatitis; however, in these studies, the laboratory abnormalities were asymptomatic. Asymptomatic hyperlipasemia without clinical pancreatitis has been reported with other tyrosine kinase inhibitors, such as nilotinib, sorafenib, and sunitinib [51,52]. Patients with this laboratory finding should be observed and given supportive care as indicated, and alcohol should be prohibited until values normalize [52]. No midostaurin dose adjustments have been required for patients experiencing hyperlipasemia [39,40].

4.4. Hyperglycemia

In the D2201 and A2213 studies, 80% of patients experienced nonfasting hyperglycemia, including 18% with grade 3/4 elevations (Table 4) [39]. Nonfasting hyperglycemia can be a risk factor for cardiovascular disease and can limit optimal glycemic control [53,54]. Patients experiencing hyperglycemia should receive a formal evaluation for glucose intolerance and should be evaluated by a diabetologist or endocrinologist. Patients should be educated about optimizing cardiac risk factors, and the need for oral hypoglycemic agents or insulin should be evaluated. No midostaurin dose adjustments have been required for patients experiencing hyperglycemia [39,40].

Figure 1. Frequency of gastrointestinal events and actions taken following gastrointestinal events in studies evaluating midostaurin in patients with advSM (N = 142) [50]. (a) Frequency of gastrointestinal events in patients who reported ≥ 1 episode. (b) Action taken following gastrointestinal events as a percentage of the total actions taken for each adverse event.

4.5. QT prolongation

QT prolongation was observed in 11% of patients enrolled in the D2201 and A2213 clinical studies and was among the most common AEs ($>5\%$) that led to dose adjustments of midostaurin. QT prolongation was also among the most frequent causes of AE-related treatment discontinuations. If a patient is taking midostaurin concurrently with other medications that can prolong the QT interval, physicians should consider regularly scheduled assessments by electrocardiogram [39,40].

4.6. Interstitial lung disease, pneumonitis, or other pulmonary toxicities

Interstitial lung disease or pneumonitis has been reported in patients receiving midostaurin as a single agent or in combination with chemotherapy (Table 4) [39]; however, no cases of pulmonary hemorrhage were reported in clinical studies in mastocytosis [15,16]. Nevertheless, given that 2% of patients with advSM did experience interstitial lung disease or pneumonitis with midostaurin, monitoring for pulmonary symptoms indicative of interstitial lung disease or pneumonitis is recommended [39]. In patients in whom diagnostic testing suggests interstitial lung disease or pneumonitis without a clear infectious etiology, midostaurin therapy should be discontinued [39]; for patients in the European Union, the prescribing label indicates that those with grade ≥ 3 interstitial lung disease or pneumonitis should discontinue

midostaurin [40]. For other grade 3/4 pulmonary toxicities, midostaurin should be interrupted until the event has resolved to grade ≤ 2 , then resumed at half dose (50 mg twice daily) and, if tolerated, subsequently increased to the full dose (100 mg twice daily) [39,40]. For patients in the European Union, the prescribing label indicates that if the toxicity is not resolved to grade ≤ 2 within 21 days or if severe toxicity recurs at a reduced dose, midostaurin should be discontinued [40].

4.7. Use of CYP3A4 inhibitors and inducers with midostaurin

Midostaurin is metabolized by cytochrome P450 3A4 (CYP3A4); the coadministration of strong CYP3A4 inhibitors may increase exposure to midostaurin and thereby increase the risk of AEs [39,40]. The coadministration of strong CYP3A4 inducers may decrease exposure to midostaurin and thereby reduce efficacy. In patients receiving midostaurin, consider avoiding the coadministration of strong CYP3A4 inhibitors or inducers; if the coadministration of strong CYP3A4 inhibitors cannot be avoided, monitor for increased risk of AEs.

4.8. Rash and photosensitivity

Among 2 studies in advSM comprising 142 patients, the frequency of all grade rash was 14% and grade ≥ 3 rash was 3%

[39]. Administration of topical corticosteroids and H1 antihistamines may help in relieving the symptoms of the rash. In a French prospective survey of 28 patients with mastocytosis who were treated with midostaurin under a transitory-use authorization program, photosensitivity was reported in 25% of individuals [43]. Although this was not reported as a common AE in the other studies of advSM, prophylactic measures such as wearing suitable clothing and using sunscreen could be considered for patients taking midostaurin.

5. Return to the cases

5.1. Case 1

As mentioned above, despite nausea and vomiting being the most common nonhematologic AEs with midostaurin therapy, several steps can be taken to manage these AEs. Following the first report of nausea and vomiting, the patient indicated that he had been taking his dose on an empty stomach. He was advised to instead take the medication with food and was prescribed ondansetron 8 mg to be taken 1 hour prior to midostaurin. Follow-up showed that while the nausea was not completely resolved, it had improved. Prochlorperazine 10 mg was added, to be taken after the morning dose of midostaurin on an as-needed basis for persistent nausea. He responded well, without the need for midostaurin dose reduction. Over time, he was able to discontinue the supplemental prochlorperazine and maintained full adherence to the midostaurin regimen. The patient responded to therapy with resolution of ascites and diarrhea plus a weight gain of 8 kg.

As exemplified by the case above, in order to mitigate midostaurin-related nausea and vomiting, patients should receive prophylactic antiemetics (preferably the aforementioned effective antiemetics) twice daily ≥ 30 minutes prior to each dose of midostaurin [39]. Patients often experience nausea 1 hour after receiving the first dose of midostaurin of the day (i.e. morning dose) that lasts for 1 hour (the so-called 'after 1 hour for 1 hour' rule); but, for yet-unknown reasons, patients typically experience nausea to a far lesser extent after the evening dose. Nevertheless, prophylactic antiemetics are recommended for all doses of midostaurin. For patients with breakthrough nausea, additional antiemetics (e.g. prochlorperazine maleate, promethazine hydrochloride, or lorazepam) can be administered with or shortly after the dose of midostaurin. If none of the aforementioned antiemetics improve symptoms, corticosteroids could be considered to treat nausea; however, one needs to consider that corticosteroids could increase the metabolism of midostaurin, thereby reducing its levels. Patients should also take midostaurin with a meal, as this increases exposure by 1.2-fold [39]. The American Cancer Society offers additional recommendations on the nonpharmacologic management of nausea and vomiting [55]. Some patients may find it helpful to apply a small amount of a strong, pleasant-smelling ointment (e.g. mentholated petroleum jelly) to the nose prior to opening the blister that contains the midostaurin pills to mask the odor in the preservative. An additional option is to open the blisters 1 hour before dosing, exposing them to free air before swallowing.

5.2. Case 2

When assessing whether a patient should discontinue midostaurin therapy due to a cytopenia, it is important to consider changes in other signs and/or symptoms of disease. Because of improvement in symptoms, serum tryptase level, splenomegaly, and eosinophilia, the patient's anemia and thrombocytopenia were felt not to be disease related, but instead determined to be drug-related cytopenias. Between 1 and 2 months after initiating midostaurin treatment, the patient's hemoglobin and platelet levels started to improve. By the end of 2 months of therapy, the eosinophilia resolved, his hemoglobin level was 11.5 g/dL, and his platelet count normalized to $160 \times 10^9/L$. No palpable splenomegaly was noted. Furthermore, the bone marrow MC burden decreased to 5%, which was accompanied by a decrease in the serum tryptase level to 15 ng/mL.

6. Conclusions

The management of AEs during treatment is a necessary element in the care of patients with advSM receiving midostaurin therapy. AE management is an added challenge when treating advSM, which is itself a heterogeneous condition whose symptoms can be difficult to distinguish, because disease-related signs and symptoms must be differentiated from AEs associated with midostaurin therapy. In this review, we have provided strategies to help distinguish drug-related from disease-related manifestations, which in turn will help optimize management of hematologic and nonhematologic AEs. In turn, the goal of these strategies is to avoid unnecessary dose reduction, interruption, or discontinuation of midostaurin in patients who might otherwise benefit from therapy. It is expected that patients taking midostaurin will experience nausea, although symptoms may improve over time, particularly when managed correctly. Although the landscape for the handling of midostaurin-related AEs is complex, these recommendations should allow patients and prescribing physicians to optimize the potential benefits of midostaurin in advSM.

7. Expert opinion

Other than allogeneic hematopoietic stem cell transplantation, no curative therapies are currently available for patients with advSM. Until such a therapy is developed, clinicians must work with available therapies and strive to optimally balance the risk-benefit profiles of those treatments for their patients. AdvSM is relatively rare and requires the expertise of a team of specialists (e.g. hematologists, allergists/immunologists, gastroenterologists, and dermatologists) for proper control of symptoms. Options for the symptomatic management of SM have long been available, but midostaurin, a targeted therapy with activity against D816V-mutated KIT, is now available for patients with advSM.

The management of AEs occurring in patients with advSM treated with midostaurin can be difficult. Here we discuss strategies that can be employed to help optimally control common AEs experienced in this heterogeneous and complex

patient population. We also incorporate our experiences with patients treated outside clinical trials, who reflect real-world practice where optimal use of midostaurin in this rare group of diseases requires a nuanced approach.

The incorporation of midostaurin into the care of patients with advSM may result in AEs that overlap with and are difficult to distinguish from symptoms associated with advSM itself; thus, it is important to untangle the AEs associated with midostaurin use from those that are disease-related. The inability to do so could result in patients prematurely interrupting or reducing doses of midostaurin, thus decreasing the potential benefit associated with the drug. Tracking measures of mast cell burden, such as serum tryptase level, bone marrow mast cell burden, as well as changes in organ damage induced by neoplastic mast cells can help the treating physician adjudicate whether emergent cytopenias or nonhematologic adverse events are related to disease progression or midostaurin therapy. For example, in a patient with a marked reduction in bone marrow mast cell burden and serum tryptase level, worsening anemia or thrombocytopenia should be suspected as related to midostaurin treatment. Conversely, worsening of organ damage in concert with an increase in measures of mast cell burden, and/or disease-related symptoms suggests that a worsening in the severity and/or frequency of hematologic or nonhematologic adverse events more likely reflects disease progression. As clinical presentations of advSM are heterogeneous and individual tolerability of drug therapy varies considerably, increasing experience with mast cell disorders and midostaurin will enhance decision-making. Because of these individual responses, the authors recommend that (1) physicians adhere to the US Food and Drug Administration or European Medicines Agency prescribing information which also includes patient information pages, (2) physicians refer patients to the National Comprehensive Cancer Network patient and caregiver resources, (3) physicians consult as needed with advSM experts, (4) patients seek the guidance of The Mast Cell Disease Society (TMS), and (5), most importantly, patients discuss safety issues with their prescribing physician. It is our hope that by increasing the familiarity with the clinical experiences discussed here, more patients will be able to optimize midostaurin treatment.

For patients with advSM who respond well to midostaurin treatment, the course of treatment is indefinite so long as an adequate response is maintained with good tolerance and without unacceptable toxicity. Ongoing clinical trials of new targeted agents (e.g. the selective KIT D816V inhibitor avapritinib (BLU-285; Blueprint Medicines; Cambridge, MA), ripretinib (Deciphera Pharmaceuticals, Inc.; Waltham, MA) and the combination of KIT-targeting agents with AHN-directed agents are a focus of ongoing and future clinical research investigations in advSM. Balancing attempts to extend survival, protect patients (i.e. by avoiding AEs), and maximize quality of life are the goals of personalized medicine in advSM.

Abbreviation

AdvSM: advanced systemic mastocytosis; AE: adverse event; AHN: associated hematologic neoplasm; AML: acute myeloid leukemia; ANC: absolute neutrophil count; AP: alkaline phosphatase; ASM: aggressive systemic

mastocytosis; CEL: chronic eosinophilic leukemia; CMML: chronic myelomonocytic leukemia; CYP3A4: cytochrome P450 3A4; FLT3: FMS-like tyrosine kinase 3; GGT: gamma-glutamyl transferase; GI: gastrointestinal; HbA1C: glycated hemoglobin A1C; ISM: indolent systemic mastocytosis; KIT: KIT proto-oncogene, receptor tyrosine kinase; MC: mast cell; MCL: mast cell leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; NOS: not otherwise specified; SM: systemic mastocytosis; URI: upper respiratory tract infection; UTI: urinary tract infection

Acknowledgments

Editorial assistance for this manuscript was provided by JoAnna Anderson, PhD, of ArticulateScience LLC.

Funding

This paper was funded by Novartis Pharmaceuticals Corporation. J Gotlib is supported by the Charles and Ann Johnson Foundation. P Valent was supported by the Austrian Science Fund (FWF) under Grant F4704-B20.

Declaration of interest

J Gotlib was the Chairman of the Study Steering Committee for the global trial of midostaurin and received funding to conduct trials of midostaurin. He also served on an advisory board for Novartis and received honoraria and reimbursement of travel expenses. J Gotlib has also served as Chair or Co-Chair of Study Steering Committees for avapritinib and ripretinib. HC Kluin-Nelemans was a non-paid member of the Study Steering Committee for the global trial of midostaurin and the Department of Hematology Groningen received funding to conduct a phase II trial of midostaurin for patients with ISM. C Akin provided consulting work and served on a scientific advisory board for a mastocytosis study with midostaurin for Novartis. He also provided consulting work and research support for Blueprint. K Hartmann was a member of the Study Steering Committee for the global Novartis trial of midostaurin. She also served on advisory boards for Novartis and received honoraria and reimbursement of travel expenses. P Valent was a member of the Study Steering Committee for the global Novartis trial of midostaurin and received honoraria and a research grant from Novartis. He also received personal fees from Accord, Astellas, Blueprint, Celgene, Daiichi Sankyo, Deciphera, Pfizer, and ThermoFisher. A Reiter was a member of the Study Steering Committee for the global trial of midostaurin and received funding to conduct trials of midostaurin. He also served on an advisory board for Novartis and received honoraria and reimbursement of travel expenses. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

ORCID

Hanneke C. Kluin-Nelemans <http://orcid.org/0000-0003-2617-9427>

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

- Arock M, Akin C, Hermine O, et al. Current treatment options in patients with mastocytosis: status in 2015 and future perspectives. *Eur J Haematol*. 2015 Jun;94(6):474–490.
- Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. *Am J Hematol*. 2019 Mar;94(3):363–377.
- Valent P, Akin C, Hartmann K, et al. Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. *Cancer Res*. 2017 Mar 15;77(6):1261–1270.
- Valent P, Horny H-P, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leukemia Res*. 2001 Jul;25(7):603–625.
- Garcia-Montero AC, Jara-Acevedo M, Teodosio C, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood*. 2006;108(7):2366–2372.
- Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. *J Mol Diagn*. 2011 Mar;13(2):180–188.
- Verstovsek S. Advanced systemic mastocytosis: the impact of KIT mutations in diagnosis, treatment, and progression. *Eur J Haematol*. 2013 Feb;90(2):89–98.
- Chatterjee A, Ghosh J, Kapur R. Mastocytosis: a mutated KIT receptor induced myeloproliferative disorder. *Oncotarget*. 2015;6(21):18250–18264.
- Gotlib J, Pardanani A, Akin C, et al. 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(13):2393–2401.
- Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405.
- Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest*. 2007 Jun;37(6):435–453.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Systemic Mastocytosis. V2.2019. 2018.
- Valent P, Sotlar K, Sperr WR, et al. Refined diagnostic criteria and classification of mast cell leukemia (MCL) and myelomastocytic leukemia (MML): a consensus proposal. *Ann Oncol*. 2014 Sep;25(9):1691–1700.
- Valent P, Sotlar K, Sperr WR, et al. Chronic mast cell leukemia: a novel leukemia-variant with distinct morphological and clinical features. *Leuk Res*. 2015;39(1):1–5.
- Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med*. 2016 Jun 30;374(26):2530–2541. .
 • **Results of the D2201 pivotal phase 2 trial of midostaurin in advanced systemic mastocytosis.**
- DeAngelo DJ, George TI, Linder A, et al., Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia*. 2018;32(2):470–478. .
 • **Results of the A2213 pivotal phase 2 trial of midostaurin in advanced systemic mastocytosis.**
- Elena C, Merante S, Ferretti VV, et al. Selection and efficacy of cytoreductive agents in patients with mastocytosis included in the registry of the European Competence Network on Mastocytosis (ECNM).. *Blood*. 2017;130(suppl 1). [abstract 1650].
- Muñoz-González JI, Jara-Acevedo M, Alvarez-Twose I, et al. Impact of somatic and germline mutations on the outcome of systemic mastocytosis. *Blood Adv*. 2018;2(21):2814–2828.
- Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. *Blood*. 2013;122(14):2460–2466.
- Jawhar M, Schwaab J, Meggendorfer M, et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. *Haematologica*. 2017;102(6):1035–1043.
- Stoecker MM, Wang E. Systemic mastocytosis with associated clonal hematologic nonmast cell lineage disease. *Arch Pathol Lab Med*. 2012;136:832–838.
- Horny HP, Sotlar K, Sperr WR, et al. Systemic mastocytosis with associated clonal haematological non-mast cell lineage diseases: a histopathological challenge. *J Clin Pathol*. 2004;57(6):604–608.
- Richardson A, Butterfield JH. Concurrent mastocytosis and monoclonal gammopathy of undetermined significance, a case series. *J Allergy Clin Immunol*. 2019;143(2):AB180.
- Gasljevic G, Grcar-Kuzmanov B, Grosel A, et al. Hodgkin's lymphoma is a rare form of clonal haematological non-mast cell disease in systemic mastocytosis. *Diagn Pathol*. 2015 Mar 14;10(1):5.
- Valent P, Akin C, Sperr WR, et al. Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. *Leuk Res*. 2003 Jul 01;27(7):635–641.
- Erben P, Schwaab J, Metzgeroth G, et al. The KIT D816V expressed allele burden for diagnosis and disease monitoring of systemic mastocytosis. *Ann Hematol*. 2014 Jan 01;93(1):81–88.
- Shomali W, Gotlib J. The new tool “KIT” in advanced systemic mastocytosis. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):127–136.
- Siebenhaar F, Akin C, Bindslev-Jensen C, et al. Treatment strategies in mastocytosis. *Immunol Allergy Clin North Am*. 2014 May;34(2):433–447.
- Sokol H, Georgin-Lavialle S, Canioni D, et al. Gastrointestinal manifestations in mastocytosis: A study of 83 patients. *J Allergy Clin Immunol*. 2013;132(4):866–873.e3.
- Fuller SJ. New insights into the pathogenesis, diagnosis, and management of mastocytosis. *Hematol Oncol Clin North Am*. 2012 Dec;26(6):1143–1168.
- Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113(23):5727–5736.
- Hermine O, Lortholary O, Leventhal PS, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PloS One*. 2008;3(5):e2266.
- Jennings S, Russell N, Jennings B, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. *J Allergy Clin Immunol Pract*. 2014 Jan-Feb;2(1):70–76.
- 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].
- Metcalfe DD, Mekori YA. Pathogenesis and pathology of mastocytosis. *Annu Rev Pathol*. 2017 Jan 24;12:487–514.
- Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. *Blood*. 2015 Aug 20;126(8):1009–1016. quiz 1050.
- Reiter A, Kluin-Nelemans HC, George T, et al. Pooled survival analysis of midostaurin clinical study data (D2201 + A2213) in patients with advanced systemic mastocytosis compared with historical controls. *EHA*. 2017;102(s2). [abstract S788].
- Valent P, Akin C, Hartmann K, et al. Midostaurin: a magic bullet that blocks mast cell expansion and activation. *Ann Oncol*. 2017;28(10):2367–2376.
- Novartis Pharmaceuticals Corporation. Rydapt (midostaurin) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020. English.

40. Novartis Europharm Ltd. Rydapt (midostaurin) summary of product information. Camberley, UK: Novartis Europharm Ltd; 2018. English.
41. Krauth M-T, Mirkina I, Herrmann H, et al. Midostaurin (PKC412) inhibits immunoglobulin E-dependent activation and mediator release in human blood basophils and mast cells. *Clin Exp Allergy*. 2009;39(11):1711–1720.
42. Peter B, Winter GE, Blatt K, et al. Target interaction profiling of midostaurin and its metabolites in neoplastic mast cells predicts distinct effects on activation and growth. *Leukemia*. 2016 Feb 01;30(2):464–472.
43. Chandesris MO, Damaj G, Canioni D, et al. Midostaurin in advanced systemic mastocytosis. *N Engl J Med*. 2016;374(26):2605–2607.
44. Hartmann K, Gotlib J, Akin C, et al. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis. *J Allergy Clin Immunol*. 2020;146(2):356–366.e4.
45. Philpott H, Gow P, Crowley P, et al. Systemic mastocytosis: a gastroenterological perspective. *Frontline Gastroenterol*. 2012 Jan;3(1):5–9.
46. Low platelet count (bleeding): American Cancer Society. [cited 2020 Jun 10]. Available from: <https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/bleeding.html>
47. Yavuz AS, Lipsky PE, Yavuz S, et al. Evidence for the involvement of a hematopoietic progenitor cell in systemic mastocytosis from single-cell analysis of mutations in the c-kit gene. *Blood*. 2002 Jul 15;100(2):661–665.
48. Lim KH, Pardanani A, Butterfield JH, et al. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. *Am J Hematol*. 2009;84(12):790–794.
49. Casassus P, Caillat-Vigneron N, Martin A, et al. Treatment of adult systemic mastocytosis with interferon- α : results of a multicentre phase II trial on 20 patients. *Br J Haematol*. 2002;119(4):1090–1097.
50. Novartis Pharmaceuticals Corporation. Response to FDA Information Request (personal communication). 2016 Dec 23.
51. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010 Jun 17;362(24):2251–2259.
52. Guevremont C, Alasker A, Karakiewicz PI. Management of sorafenib, sunitinib, and temsirolimus toxicity in metastatic renal cell carcinoma. *Curr Opin Support Palliat Care*. 2009 Sep;3(3):170–179.
53. Woerle HJ, Neumann C, Zschau S, et al. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes Importance of postprandial glycemia to achieve target HbA1c levels. *Diabetes Res Clin Pract*. 2007 Aug;77(2):280–285.
54. Lin HJ, Lee BC, Ho YL, et al. Postprandial glucose improves the risk prediction of cardiovascular death beyond the metabolic syndrome in the nondiabetic population. *Diabetes Care*. 2009 Sep;32(9):1721–1726.
55. Managing Nausea and Vomiting at Home: American Cancer Society. [cited 2020 Jun 10]. Available from: <https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/nausea-and-vomiting/nausea-and-vomiting>