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Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis

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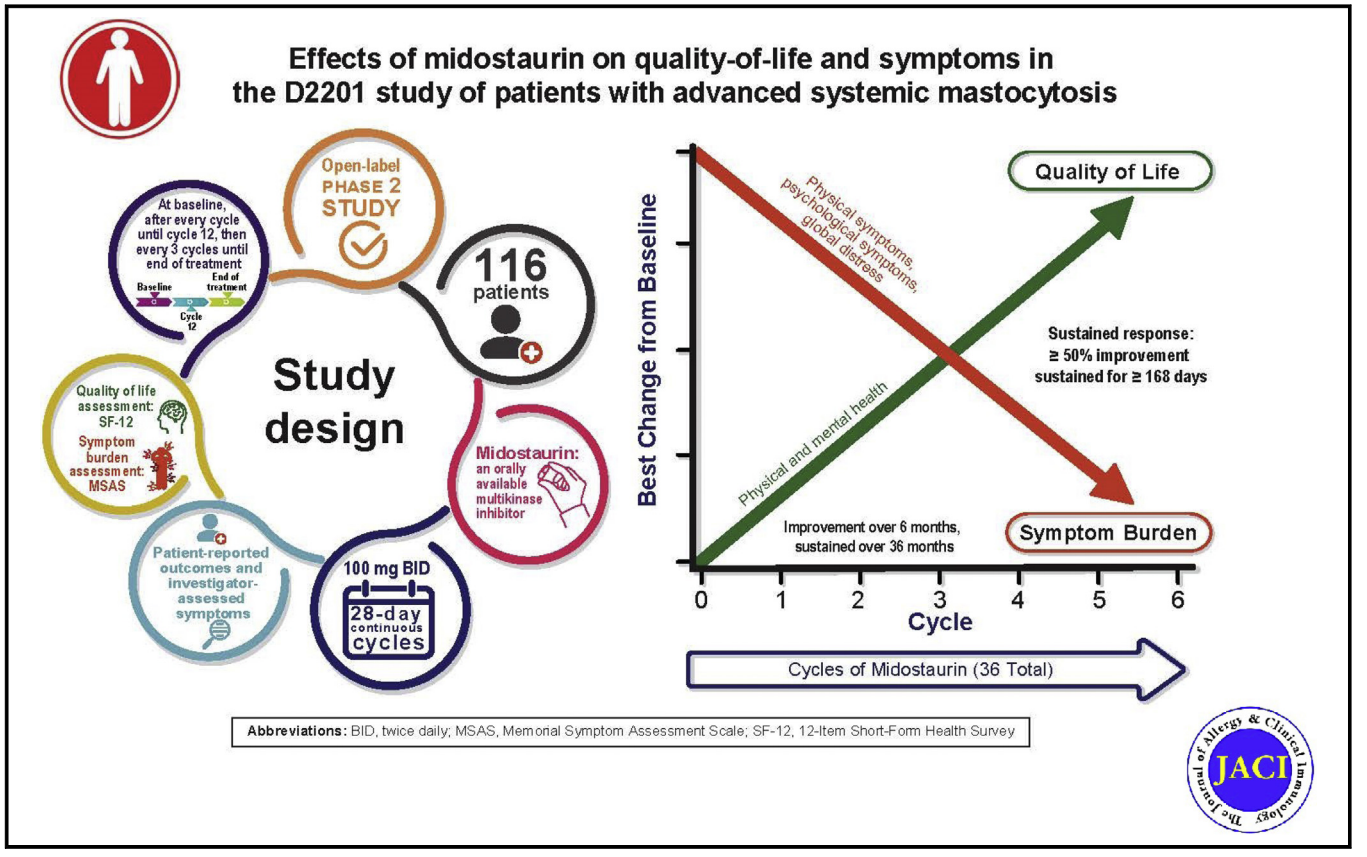
GRAPHICAL ABSTRACT



Background: Advanced systemic mastocytosis (advSM) is characterized by presence of the *KIT* D816V mutation and pathologic accumulation of neoplastic mast cells (MCs) in various tissues, leading to severe symptoms and organ damage (eg, cytopenias, liver dysfunction, portal hypertension, malabsorption, and weight loss). Treatment with midostaurin, an orally active multikinase/KIT inhibitor now approved for advSM in the United States and the European Union, resulted in

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a high rate of response accompanied by reduced MC infiltration of the bone marrow and lowered serum tryptase level.

Objective: We aimed to determine whether midostaurin improves health-related quality of life (QOL) and MC mediator–related symptoms in patients with advSM.

Methods: In 116 patients with systemic mastocytosis (89 patients with advSM fulfilling the strict inclusion criteria of the D2201 study [ClinicalTrials.gov identifier NCT00782067]), QOL and symptom burden were assessed during treatment with midostaurin by using the 12-Item Short-Form Health Survey (SF-12) and the Memorial Symptom Assessment Scale patient-reported questionnaires, respectively. MC mediator–related symptoms were evaluated by using a specific physician-reported questionnaire.

Results: Over the first 6 cycles of treatment with midostaurin (ie, 6 months), patients experienced significant improvements in total SF-12 and Memorial Symptom Assessment Scale scores, as well as in subscores of each instrument. These improvements were durable during 36 months of follow-up. Similarly, we found substantial improvements (67%-100%) in all MC mediator–related symptoms.

Conclusion: QOL and MC mediator–related symptoms significantly improve with midostaurin treatment in patients with advSM (ClinicalTrials.gov identifier, NCT00782067). (J Allergy Clin Immunol 2020;146:356-66.)

Key words: *Advanced systemic mastocytosis,* KIT *mutation, mastocytosis, mediator symptoms, midostaurin, quality of life, tryptase, skin lesions of mastocytosis*

Abbreviations used

AdvSM:	Advanced systemic mastocytosis
ASM:	Aggressive systemic mastocytosis
BM:	Bone marrow
ITT:	Intention-to-treat
MC:	Mast cell
MC-QoL:	Mastocytosis Quality of Life Questionnaire
MQLQ:	Mastocytosis Quality-of-Life Questionnaire
MSAS:	Memorial Symptom Assessment Scale
PEP:	Primary efficacy population
QOL:	Quality of life
SF-12:	12-Item Short-Form Health Survey
SM:	Systemic mastocytosis
SM-AHN:	Systemic mastocytosis with an associated hematologic neoplasm
SSC:	Study steering committee

Mastocytosis is characterized by symptoms due to the proliferation and accumulation of neoplastic mast cells (MCs) in 1 or more organs, most frequently the bone marrow (BM) and skin.[1,2] Mastocytosis categories encompass nonadvanced forms, including cutaneous mastocytosis, indolent systemic mastocytosis (SM), and smoldering SM, as well as advanced forms, including aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and MC leukemia.[2-4] Mutations in *KIT*, usually *KIT* D816V, are found in more than 80% of patients with SM and serve as primary drivers of disease pathogenesis.[5,6] Serum levels of tryptase, an enzyme mainly produced by MCs, correlate with total MC burden.[7-9] Advanced SM (advSM) has a poor prognosis, with limited treatment options.[6-8,10]

In addition to signs and symptoms related to MC infiltration in BM and other organs, patients with advSM also experience symptoms due to release of MC mediators.[11] These mediators include histamine, cytokines, and lipid mediators, and their release is associated with various symptoms affecting the skin (eg, pruritus, wheals, blisters), gastrointestinal tract (eg, abdominal pain, diarrhea, nausea and vomiting), and other organs, and it can also present as anaphylaxis, flushing, headache, and fatigue.[12] Furthermore, approximately half of all patients with advSM develop specific skin lesions of mastocytosis.[13] Together, these symptoms can substantially impair quality of life (QOL).

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Disclosure of potential conflicts of interest. K. Hartmann is member of study steering committees for studies in systemic mastocytosis (Novartis D2201 study and Blueprint Medicines study); she has received consulting fees, honoraria, and reimbursement of travel expenses from ALK-Abelló, Allergopharma, Blueprint Medicines, Deciphera, Menarini, Novartis Pharmaceuticals Corporation, and Takeda, as well as research grants from Euroimmun and ThermoFisher. J. Gotlib is chairman and cochairman of study steering committees for studies in systemic mastocytosis (Novartis D2201 study, Blueprint Medicines study, and Deciphera study) and has received consulting fees, honoraria, and reimbursement of travel expenses from Blueprint Medicines, Deciphera, and Novartis Pharmaceuticals Corporation. C. Akin is member of a study steering committee (Novartis D2201 study) and has received consulting fees from Blueprint Medicines. F.T. Awan has received consulting fees from Genentech, AstraZeneca, AbbVie, Janssen, Pharmacyclics, Gilead Sciences, Kite Pharma, Dava Oncology, Celgene, Blueprint Medicines, and Sunesis. E. Hexner has received research support from Novartis Oncology and Blueprint Medicines. M. J. Mauro has received consulting fees, honoraria, and reimbursement of travel expenses from Bristol-Myers Squibb, Takeda, Pfizer, and Novartis, as well as institutional research support from Novartis, Bristol-Myers Squibb, and SPARC/Sun Pharma. H. Menssen, S. Redhu, and S. Knoll are employed by Novartis Pharmaceuticals Corporation and may hold stock or stock options in the company. K. Sotlar has received consulting fees, honoraria, and reimbursement of travel expenses from Novartis. T. George is member of study steering committees for studies in systemic mastocytosis (Novartis D2201 study and Blueprint Medicines study) and has received consulting fees from Blueprint Medicines, Deciphera, and Novartis Pharmaceuticals Corporation. P. Valent is member of a study steering committee in systemic mastocytosis (Novartis D2201 study) and has received consulting fees and honoraria from Novartis Pharmaceuticals Corporation, Deciphera, and Blueprint Medicines. A. Reiter is member of study steering committees for studies in systemic mastocytosis (Novartis D2201 study and Blueprint Medicines study) and has received consulting fees, honoraria, and reimbursement of travel expenses from Blueprint Medicines, Deciphera, and Novartis Pharmaceuticals Corporation, as well as research funding from Novartis Pharmaceuticals Corporation. H. C. Kluin-Nelemans has received financial support (to her department) from Novartis Pharmaceuticals Corporation. The rest of the authors declare that they have no relevant conflicts of interest.

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Midostaurin is an orally active multikinase inhibitor that targets KIT and also blocks immunoglobulin E (IgE)–dependent secretion of mediators *in vitro*.[14,15] Previously, we reported primary results of the D2201 study—a global, phase 2, single-arm, open-label study of midostaurin that demonstrated a 60% response rate using modified Valent response criteria and modified Cheson criteria to adjudicate advSM-related organ damage and measures of MC burden, including BM MC infiltration, serum tryptase levels, and splenomegaly.[16] In the present analysis, we sought to describe in more detail the effect of midostaurin on QOL and MC mediator–related symptoms in patients enrolled in the D2201 study.

METHODS

Study design

The patient population, eligibility criteria, and study design have been previously described; the baseline characteristics of the study population are summarized in Table E1 in the Online Repository (at www.jacionline.org)[16] The study (ClinicalTrials.gov identifier NCT00782067) was designed and reported in accordance with the provisions of the Declaration of Helsinki and approved by the institutional review board at each participating institution. All patients provided written informed consent. Briefly, adult patients (aged ≥18 years) with histologically documented ASM, SM-AHN, or MC leukemia per World Health Organization criteria[17] were enrolled in this study and received oral midostaurin, 100 mg twice daily in 28-day continuous cycles. Eligibility and response were adjudicated by a study steering committee (SSC).[16]

Role of the funding source

The study was designed by Novartis Pharmaceuticals Corporation and by the SSC members. The study was sponsored and funded by Novartis Pharmaceuticals Corporation. Data were collected and analyzed by the sponsor in conjunction with the authors, who had full access to the data. The article was written by the authors with the support of ArticulateScience LLC, which was funded by the sponsor.

Patient population

QOL analyses were performed on the intention-to-treat (ITT) population to include all available data in the statistical analyses. The ITT population comprised all patients in the study (N = 116), including all patients without measurable C-findings at baseline or with C-findings at baseline that were considered by the SSC to be probably unrelated to mastocytosis (n = 27).[16] C-findings included cytopenias and liver function abnormalities such as portal hypertension and ascites, malabsorption, hypoalbuminemia, weight loss of at least 10% in the prior 6 months, and large osteolytic bone lesions or pathologic fractures; the latter 2 were considered not measurable and could not be the sole C-finding present to be evaluable. Patients were enrolled at 29 centers worldwide from July 2009 to July 2012.[16] Detailed demographics for the study population have been previously reported and are summarized in Table E1 in the Online Repository.[16] The primary efficacy population (PEP [defined as patients with ≥1 measurable C-finding considered related to SM as adjudicated by the SSC]) included 89 patients: 53 responders (60%) and 36 nonresponders (40%). Response was defined as major (complete resolution of ≥1 C-finding) or partial (>50% improvement in ≥1 C-finding or a >20% to ≤50% improvement in ≥1 C-finding).

Data collection of patient-reported outcomes

Patient-reported QOL and symptom burden were assessed by using the 12-Item Short-Form Health Survey (SF-12)[18] and the Memorial Symptom Assessment Scale (MSAS)[19] questionnaires, respectively. Questionnaires were administered before each visit to avoid biasing patients following their disease status update. Scores were collected at baseline, every 4 weeks until the end of cycle 12, every 3 cycles thereafter, and at the end of treatment.

The SF-12 evaluated 2 overarching health summary measures indicative of patient health-related QOL.[18,20] Patients answered 12 health-related questions using a 5-point scale to record their perceived level of functioning.[18] Each SF-12 scale ranged from 0 to 100. On the basis of the responses to individual symptoms, a physical composite score and a mental composite score were derived. An increase relative to baseline in the SF-12 score indicated improved QOL. The minimally important difference was 4 points for the physical component score and 2 points for the mental component score.[20]

In the MSAS questionnaire, patients rated the severity and distress of 32 symptoms and the frequency of 24 of the 32 symptoms.[19] Patients rated symptom severity and frequency on a 4-point Likert scale and symptom distress on a 5-point scale. The MSAS included 4 subscales (total MSAS, physical symptom score, psychological symptom score, and global distress index).[21] A decrease in MSAS scores over time indicated symptom improvement.[21,22] Minimal important differences were determined for the total MSAS subscore (0.20-0.45), physical symptom score (0.31-0.42), psychological symptom score (0.45-0.66), and global distress index (0.36-0.59).[21,22]

Data collection of MC mediator–related symptoms

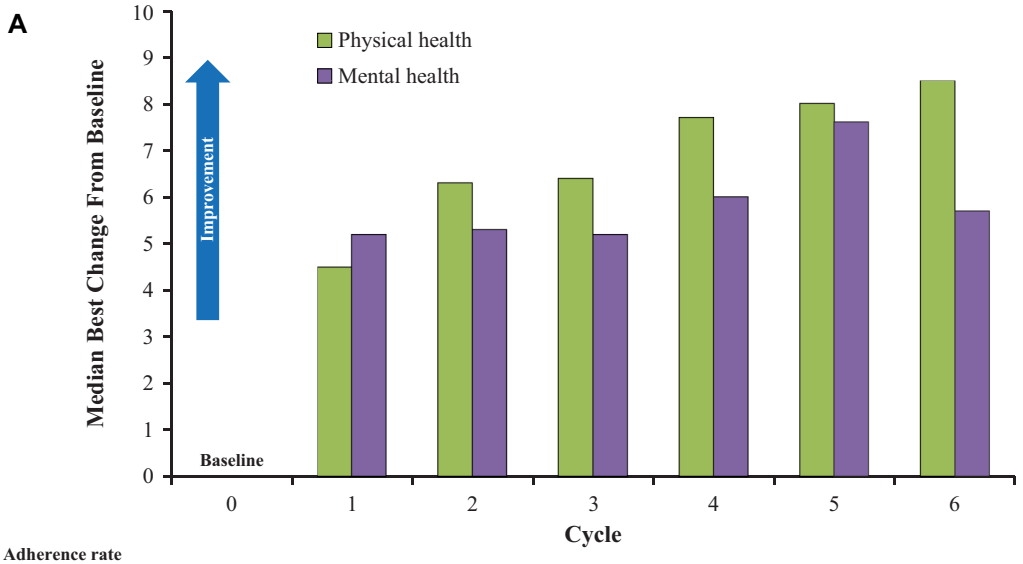
MC mediator–related symptoms were assessed by the investigator at baseline (month 0, the last nonmissing value before the first dose) and at each visit (every 4 weeks until the end of cycle 12, every 3 cycles thereafter, and at the end of treatment). Signs and symptoms included skin symptoms (skin lesions of mastocytosis, pruritus/whealing, flushing), circulatory symptoms (anaphylaxis/syncope), gastrointestinal symptoms (diarrhea, abdominal cramping, nausea, vomiting), and other symptoms possibly related to mastocytosis (musculoskeletal pain, neurologic symptoms, and psychiatric/psychological symptoms).

Frequency of MC mediator–related symptoms was rated by using a 5-category scale (no symptoms; mild, infrequent; moderate; severe; and very severe). Severity of symptoms was recorded by using a shift table (ie, mild to very severe symptoms). Furthermore, photographs were taken of some patients to illustrate changes in cutaneous lesions (the taking of photographs was not protocol-defined).

Statistical methods

Patient responses on the SF-12 and MSAS were summarized by using descriptive summary statistics. SF-12 domain and summary scores[20] and MSAS subscale summary scores[19] were calculated according to standard scoring guidelines. Summary statistics included changes from baseline to the end of each cycle in all SF-12 and MSAS scores and subscores. The baseline and best postbaseline values for summary scores (the SF-12 physical component score and mental component score and the total MSAS score) were compared with the minimally important difference for each metric, which indicated the minimum score improvement shown to be clinically meaningful.[18,22] A Wilcoxon signed rank test was used to calculate the *P* value comparing baseline and best postbaseline scores. A Pearson correlation coefficient was used to measure correlation between symptom improvement (SF-12 and MSAS scores) and duration of response. The numbers of patients with a 50% or greater improvement in SF-12 physical and mental component scores and total MSAS score were also calculated for patients who received up to 36 cycles of midostaurin therapy. The results are reported for patients in the ITT population to ensure inclusion of the largest QOL data set available. Analyses were repeated on the smaller PEP for confirmation; similar trends were observed across the ITT population and PEP for all measures.

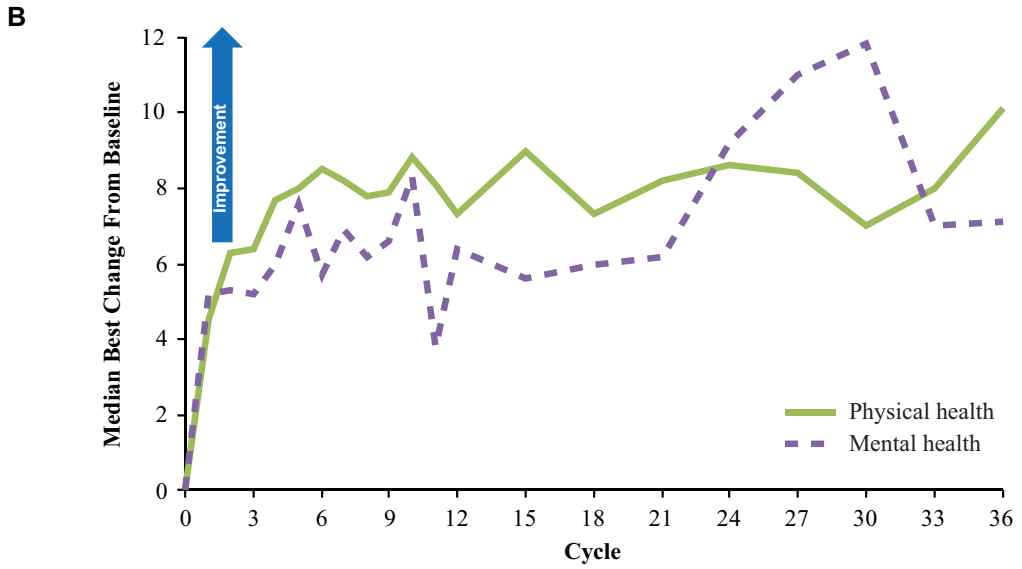
For mediator symptoms, baseline was defined as the last nonmissing value before the first dose. At baseline, percentages were based on the number of patients evaluable at that time point for a given symptom. At other time points, values were reported for patients with a symptom at baseline and 1 or more evaluations during treatment, either overall or at specific time points.



Adherence rate

Survey time point, cycle	0	1	2	3	4	5	6
Eligible patients, n	110	107	100	87	83	80	74
Full adherence, %	91	93	94	95	99	96	93
Partial adherence, %	9	7	6	5	1	4	7
Full/partial adherence	100	100	100	100	100	100	100

Symptoms were evaluated on day 1 of cycle 1, day 28 of cycle 1, and day 28 of cycles 2 to 6.



Adherence rate

Survey time point, cycle	0	3	6	9	12	15	18	21	24	27	30	33	36
Eligible patients, n	110	87	74	64	59	43	35	32	21	18	16	16	11
Full adherence, %	91	95	93	94	92	95	97	91	100	83	88	100	100
Partial adherence, %	9	5	7	6	8	5	3	9	0	17	12	0	0
Full/partial adherence, %	100	100	100	100	100	100	100	100	100	100	100	100	100

Symptoms were evaluated at baseline (day 1 of cycle 1), day 28 of cycle 1, and day 28 of cycles 2 to 12 and every 3 cycles thereafter.

FIG 1. Improvements in health-related QOL (according to SF-12 scores) in response to midostaurin. Median changes in SF-12 scores from baseline over the first 6 cycles of treatment in patient-reported health-related QOL measures (SF-12). **A,** Median changes in the combined physical health and mental health scores. **B,** Median change over baseline in QOL with up to 36 cycles of midostaurin.

TABLE I. QOL in the study population: numbers of patients with and without sustained improvement in SF-12 and MSAS scores and correlation between response duration and improvement in QOL (N = 116)

		Patients without sustained improvement*		Correlation between DOR and QOL summary scores		Patients with sustained improvement†		Correlation between DOR and QOL summary scores	
SF-12 or MSAS summary score	Median baseline score (range)	n (%)	Median DOR (range), d	Pearson correlation coefficient	*P* value	n (%)	Median DOR (range), d	Pearson correlation coefficient	*P* value
QOL (SF-12 subscores)									
Physical component score	36.5 (12.6-57.8)	9 (7.8)	31 (28-141)	0.126	.42	10 (8.6)	356 (281-1064)	0.596	<.001
Physical functioning	25.0 (0.0-100.0)	9 (7.8)	58 (29-141)	0.226	.20	11 (9.5)	476 (244-1485)	0.706	<.001
Role-limiting physical problems	25.0 (0.0-100.0)	15 (12.9)	57 (29-162)	0.329	.06	17 (14.7)	449 (169-1485)	0.603	<.001
Bodily pain	75.0 (0.0-100.0)	16 (13.8)	82.5 (28-142)	0.049	.78	12 (10.3)	487 (169-846)	0.534	<.001
General health	25.0 (0.0-100.0)	12 (10.3)	44.5 (24-162)	0.307	.10	15 (12.9)	392 (190-1512)	0.746	<.001
Mental component score	45.3 (21.6-68.1)	6 (5.2)	29 (29-143)	0.347	.03	5 (4.3)	252 (183-400)	0.523	<.001
Social functioning	50.0 (0.0-100.0)	14 (12.1)	57 (15-140)	0.200	.29	30 (25.9)	337 (168-1415)	0.592	<.001
Vitality	25.0 (0.0-100.0)	15 (12.9)	62 (29-140)	0.637	<.001	18 (15.5)	379 (172-1512)	0.694	<.001
Role-limiting mental problems	58.9 (0.0-100.0)	17 (14.7)	54 (22-148)	0.034	.85	16 (13.8)	494 (225-1070)	0.595	<.001
Mental health	62.5 (12.5-100.0)	13 (11.2)	57 (28-162)	0.286	.08	14 (12.1)	341 (168-1070)	0.695	<.001
Symptom burden (MSAS subscores)									
Total symptom burden	1.0 (0.0-2.5)	21 (18.1)	85 (8-143)	–0.179	.39	27 (23.3)	290 (169-1064)	0.666	<.001
Symptom distress	1.1 (0.0-2.8)	19 (16.4)	60 (8-143)	–0.032	.87	31 (26.7)	358 (168-1373)	0.561	<.001
Physical symptoms	1.2 (0.0-2.9)	22 (19.0)	69.5 (8-148)	0.134	.53	23 (19.8)	267 (169-1380)	0.649	<.001
Psychological symptoms	1.0 (0.0-2.8)	18 (15.5)	72 (8-162)	0.179	.37	29 (25.0)	330 (168-1260)	0.614	<.001

DOR, Duration of response.

*Patients with a 50% or greater decrease in MSAS score relative to baseline or patients with a 50% or greater increase in SF-12 summary score relative to baseline sustained for less than 168 days.

†Patients with a 50% or more decrease in MSAS score relative to baseline or patients with a 50% or greater increase in SF-12 summary score relative to baseline sustained for at least 168 days.

RESULTS

Overall health status and QOL

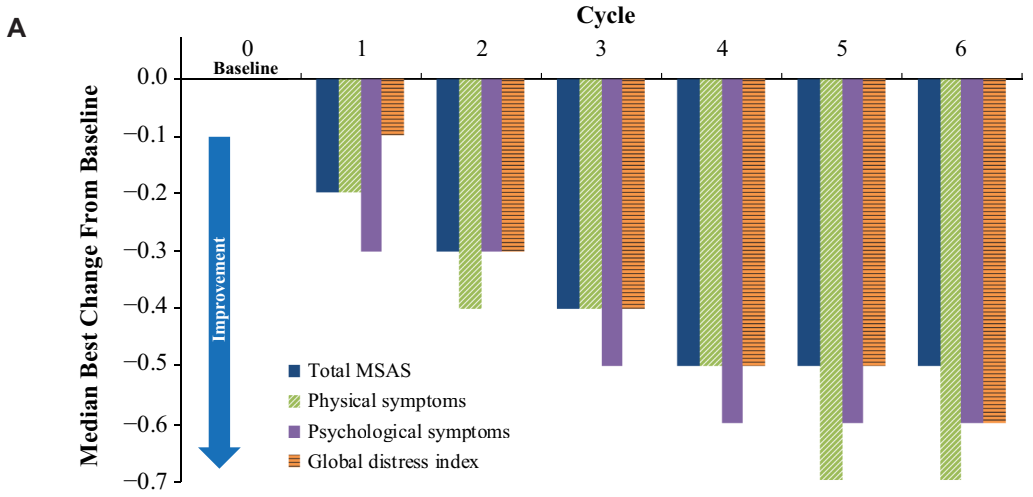
Overall health status and QOL were assessed during treatment with midostaurin by using the SF-12 score at baseline and during treatment (Fig 1). All patients either fully or partially completed the SF-12 form at every time point assessed; at least 50% of patients fully completed the form at each time point, and the mean rate of full completion across time points was approximately 68% (see Fig E1 in the Online Repository at www.jacionline.org). SF-12 scores, particularly the physical health scores, rapidly improved over the first 6 cycles (Fig 1, *A*). The median best change from baseline was more than 4 points in both physical and mental health subscores after only 1 cycle of treatment. Improvements in physical health stabilized after 6 cycles, whereas mental health showed some fluctuation after that time point (Fig 1, *B*). Overall, however, sustained improvements were noted (ie, a ≥50% increase relative to baseline in SF-12 subscore for ≥168 days) in both mental and physical health scores with up to 36 cycles of midostaurin therapy (Fig 1, *B* and Table I).

For those patients with sustained responses, Pearson correlation coefficients (range, 0.592-0.746) and *P* values less than .001 with all SF-12 subscores indicated a high correlation with duration of response. However, for those patients whose responses were not sustained (ie, a ≥50% increase relative to baseline in SF-12 subscore for <168 days), the majority of subscores showed no correlation with duration of response (Pearson correlation coefficient range, 0.034-0.637; $P > .05$); the sole exceptions were the overall mental component score (Pearson correlation coefficient, 0.347; $P = .03$) and vitality subscore (Pearson correlation coefficient, 0.637; $P < .001$). The median duration of response in patients with sustained improvements in SF-12 subscores ranged from 252 days to 494 days, whereas the median duration of response in patients without sustained improvements ranged from 29 days to 82.5 days (Table I). Notably, similar trends were observed if the analysis was restricted to the PEP, with responders showing a greater improvement than nonresponders (data not shown).

Of note, the baseline SF-12 summary scores were worse than those in published reports of patients with colorectal or lung cancer at baseline[23]; however, after treatment with midostaurin, the subscores increased significantly ($P < .0001$), with mental component scores improving to reach scores similar to those reported in healthy individuals (see Fig E2 in the Online Repository at www.jacionline.org).

Symptom burden

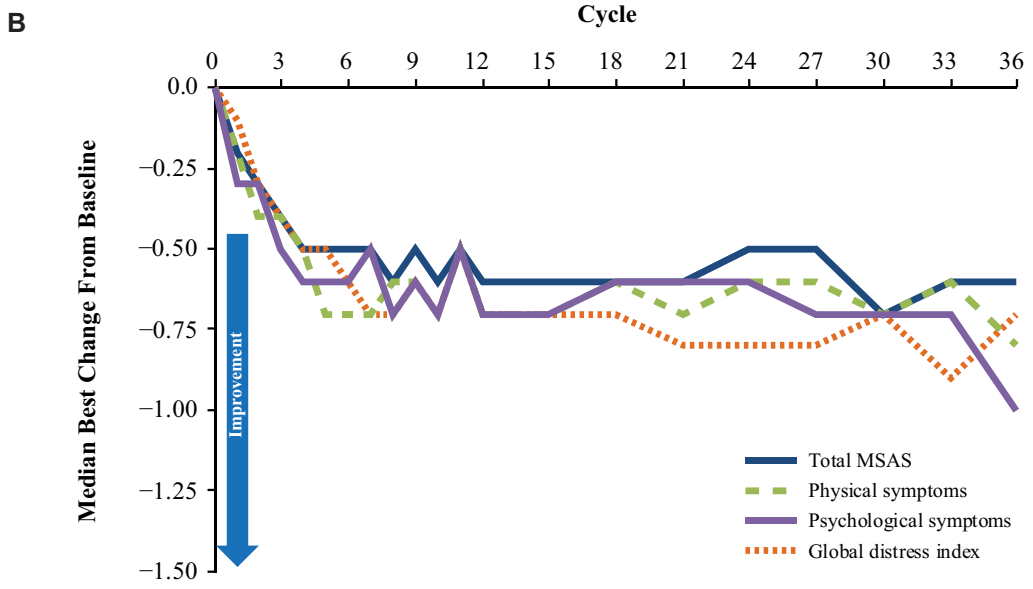
In addition to QOL, symptom burden during treatment was assessed by using the MSAS questionnaire (Fig 2). All patients completed the questionnaire either fully or partially at every time point assessed; at least 75% of patients fully completed the form at each time point, and the mean rate of full completion across time points was approximately 94% (see Fig E1 in the Online Repository). Symptom burden substantially improved over the first 6 months, with marked improvements in all MSAS scores relative to baseline (Fig 2, *A*). Moreover, MSAS total and summary scores also showed continual and sustained improvement with up to 36 cycles of midostaurin therapy (Fig 2, *B* and Table I). Similar to the SF-12 subscore observations, the MSAS summary score improvements correlated with duration of response for patients with sustained responses (Pearson



Adherence rate

Survey time point, cycle	0	1	2	3	4	5	6
Eligible patients, n	107	101	98	85	82	78	74
Full adherence, %	59	55	60	58	60	72	70
Partial adherence, %	41	45	40	42	40	28	30
Full/partial adherence	100	100	100	100	100	100	100

Symptoms were evaluated at baseline (day 1 of cycle 1), on day 28 of cycle 1, and on day 28 of cycles 1 to 6.



Adherence rate

Survey time point, cycle	0	3	6	9	12	15	18	21	24	27	30	33	36
Eligible patients, n	107	85	74	63	59	43	35	32	21	18	17	16	11
Full adherence, %	59	58	70	68	64	65	69	78	52	61	71	56	64
Partial adherence, %	41	42	30	32	36	35	31	22	48	39	29	44	36
Full/partial adherence, %	100	100	100	100	100	100	100	100	100	100	100	100	100

Symptoms were evaluated at baseline (day 1 of cycle 1), day 28 of cycle 1, and day 28 of cycles 2 to 12 and every 3 cycles thereafter.

FIG 2. Improvement in symptom burden (MSAS score) in response to midostaurin. Median changes from baseline over the first 6 cycles during treatment in patient-reported symptom burden measures (using the MSAS tool), including total MSAS, physical symptom burden, psychological symptom burden, and global distress caused by physical and psychological symptom burden (**A**). Median change over baseline in patient-reported symptom burden (MSAS) with up to 36 cycles of midostaurin (**B**).

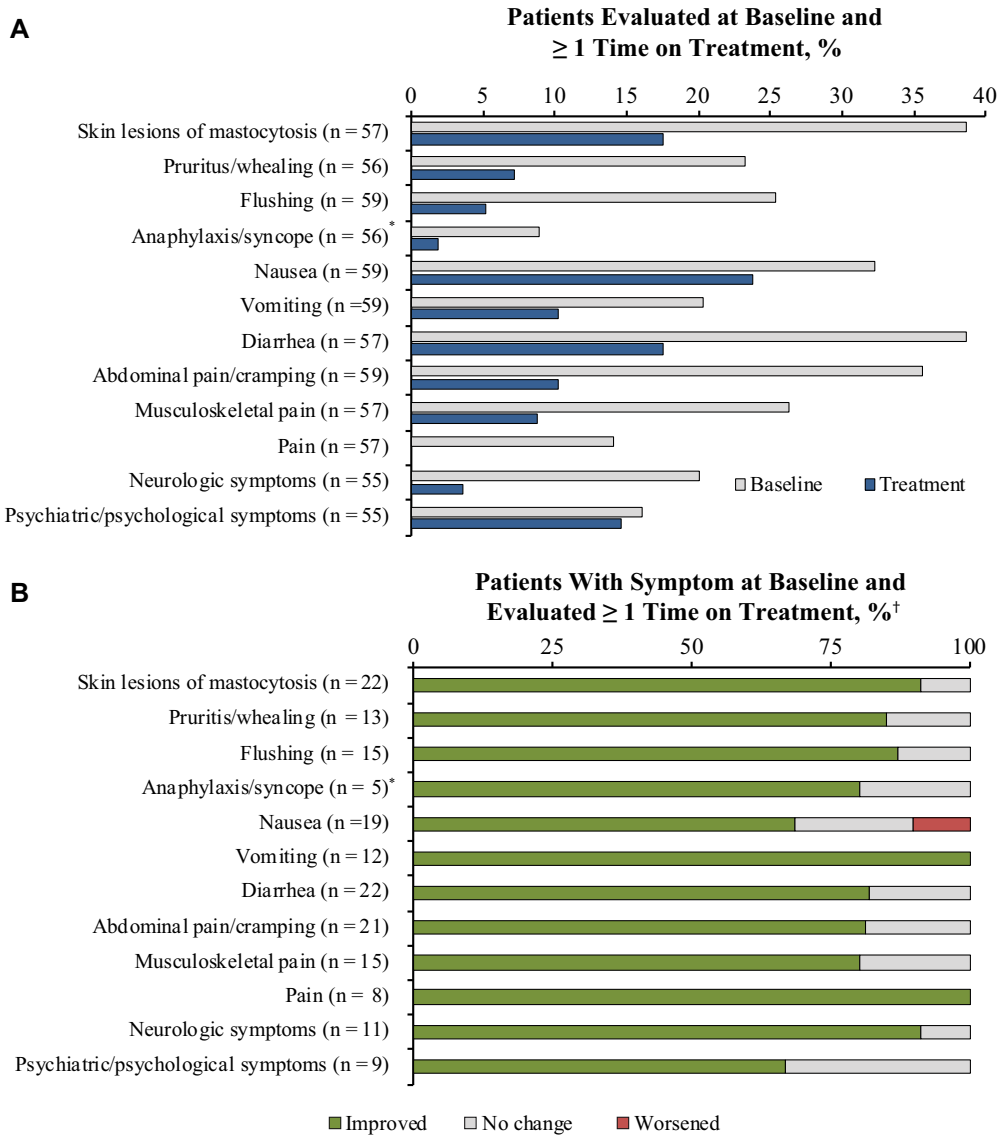


FIG 3. Improvement in MC mediator–related symptoms in response to midostaurin. The frequency of different mediator-related symptoms at baseline (*gray*) and during treatment (*blue*) per investigator assessment in members of the study population who were evaluated at baseline and at any point while receiving treatment **(A)**. Summary of shift in mediator-related symptoms from baseline to best value during treatment in all patients with the specific symptom evaluated at baseline and at least once during treatment **(B)**. *Anaphylaxis/syncope includes near-syncope and syncope associated with flushing and tachycardia. †Because of the small numbers of patients in some of the symptom groups, caution should be used when interpreting the data.

correlation coefficient range, 0.561-0.666; $P < .001$), but not for those without sustained responses (Pearson correlation coefficient range, –0.179 to 0.179; $P > .05$). The median duration of response in patients with sustained improvements in MSAS summary scores ranged from 267 days to 358 days, whereas the median duration of response in patients without sustained improvements ranged from 60 days to 85 days (Table I). The trends in improvement in symptom burden remained consistent if the analysis was restricted to the PEP, with responders again showing a greater improvement than nonresponders (data not shown).

As noted in the primary analysis of this study,[16] the prevalence of 30 of 32 symptoms decreased with midostaurin treatment (from baseline to best total MSAS score), except for nausea and vomiting. Additionally, all MSAS subscores were worse than those reported in patients with breast, colorectal, gynecologic, lung, or prostate cancer[24,25]; with midostaurin treatment, all of these subscores improved significantly ($P < .0001$) (see Fig E2 in the Online Repository).

Mediator-related symptoms

Furthermore, physician-assessed MC mediator–related symptoms were analyzed during treatment with midostaurin (Fig 3). Data were available for 47% to 51% of patients at baseline

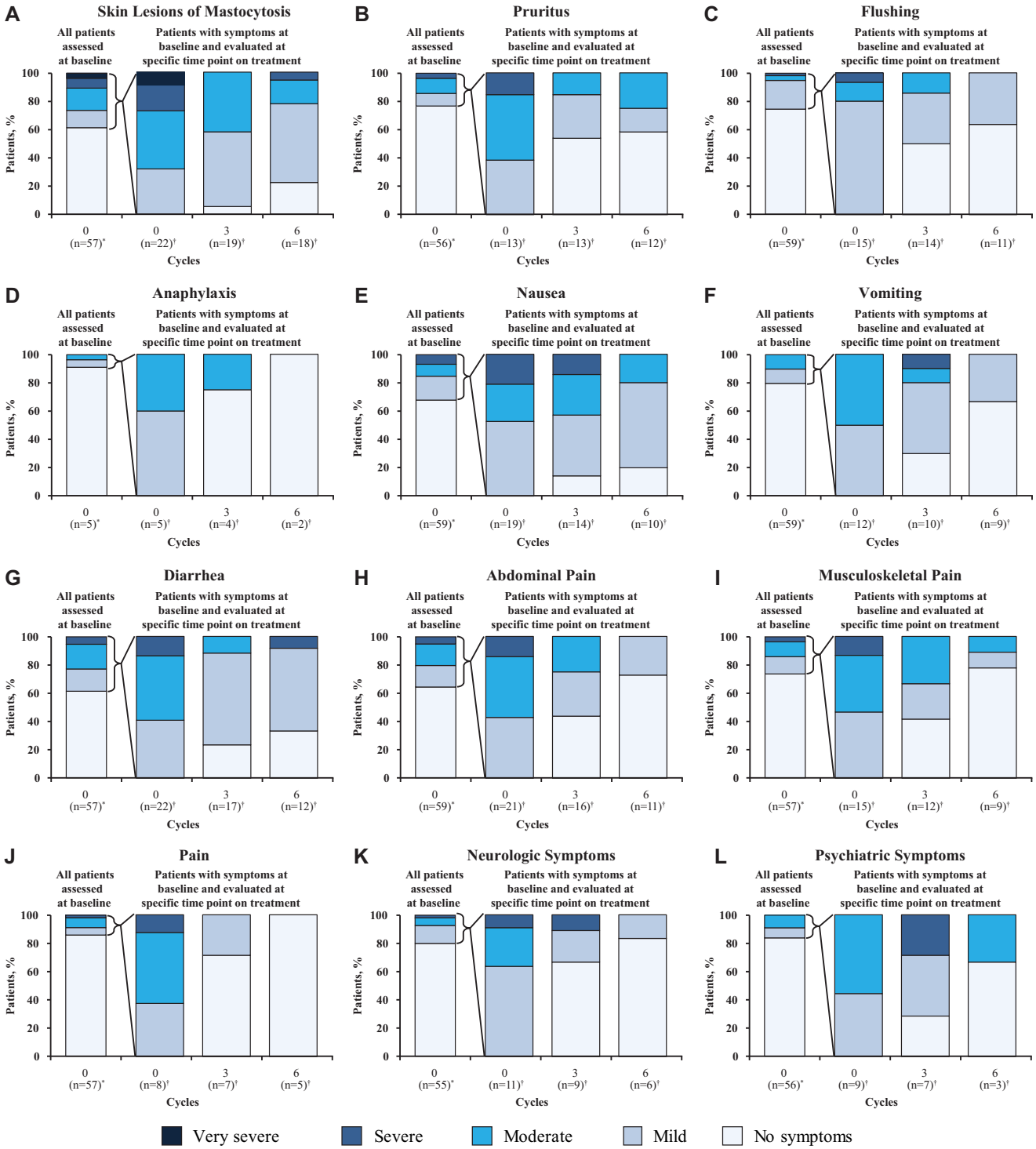


FIG 4. Improvements in the severity of MC mediator–related symptoms over 6 cycles of treatment with midostaurin. The frequency of mediator-related symptoms is differentiated according to severity at 0, 3, and 6 cycles of treatment per investigator assessment for skin lesions of mastocytosis (**A**), pruritus/whealing (**B**), flushing (**C**), anaphylaxis/syncope (**D**), nausea (**E**), vomiting (**F**), diarrhea (**G**), abdominal pain/cramping (**H**), musculoskeletal pain (**I**), pain (**J**), neurologic symptoms **(K)** and psychiatric/psychological symptoms (**L**). The leftmost column of each panel denotes the symptom severity at baseline (0 months). Columns to the right denote symptom severity only in those patients reporting that symptom at baseline. Patients with no symptoms are represented in white, those who reported mild symptoms are represented in light gray, those who reported moderate symptoms are represented in medium gray, those who reported severe symptoms are represented in dark gray symptoms, and those who reported very severe symptoms are represented in black. Because of the small numbers of patients in some symptom groups, caution should be used when interpreting the data. *Patients assessed for symptom at baseline. †Patients with symptoms present at baseline.

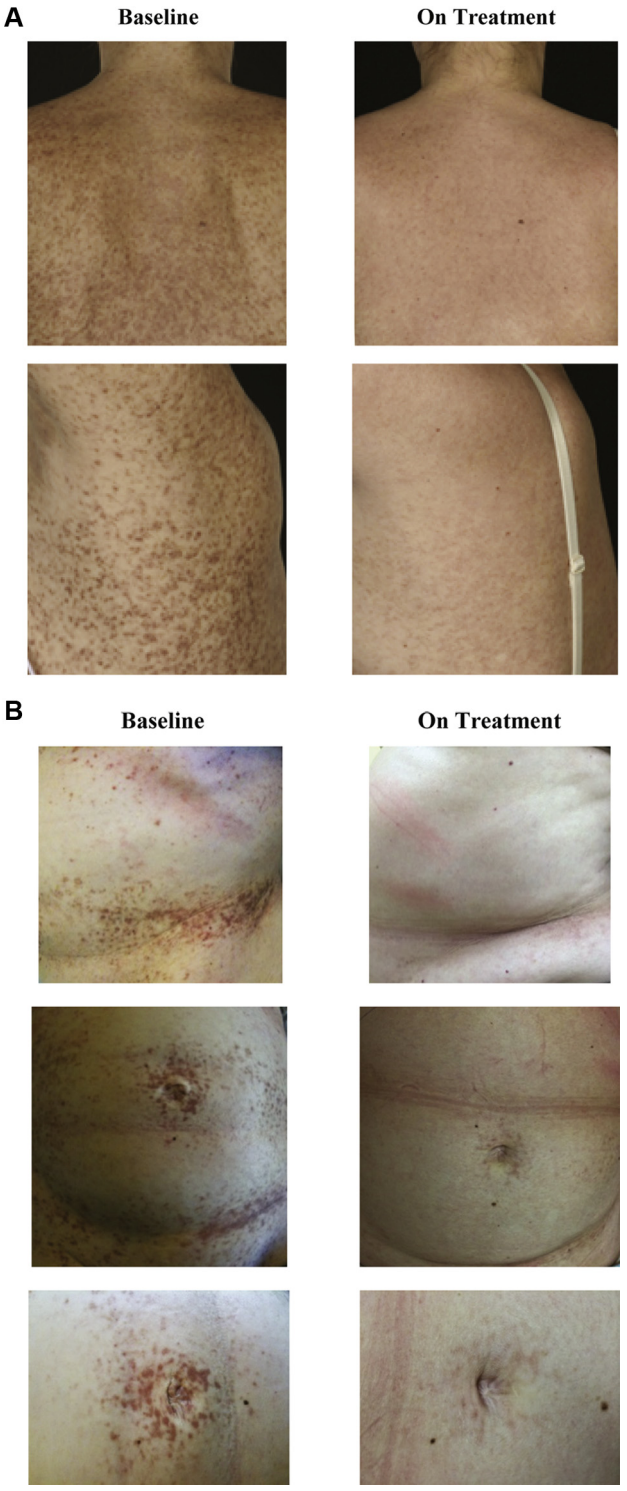


FIG 5. Improvement in cutaneous lesions in patients with positive response to midostaurin treatment. Skin lesions at baseline (*photographs on the left*) and after several weeks of treatment (*photographs on the right*) in a patient with aggressive SM (**A**) and a patient with SM-AHN (**B**).

(percentage varied among the different items scored) and for 72% to 73% of patients at least once during treatment. At baseline, 9% to 39% of patients had every mediator-related symptom, ranging from mild to severe.

The rates of mediator-related symptoms dramatically decreased during treatment (Fig 3, *A*). In patients with a baseline assessment and at least 1 assessment during treatment, the most common symptoms at baseline were skin lesions of mastocytosis and diarrhea (22 of 57 patients [39%] for each); during treatment, the frequency of both symptoms decreased to 10 of 57 patients (18%). Most other symptoms showed a similar reduction during treatment. The exception was psychiatric/psychological symptoms, which were present in 9 of 55 patients (16%) at baseline and 8 of 55 patients (15%) during treatment.

Improvements occurred in 67% to 100% of patients who had a specific symptom at baseline and at least 1 postbaseline assessment (Fig 3, *B*). In fact, at least 80% of patients showed improvements across all symptoms except psychiatric/psychological symptoms, which improved in 67% of patients. Most other patients experienced no change in each symptom present at baseline (except nausea, which showed worsening in a few patients, which is consistent with the known tolerability profile of midostaurin). Most patients who did not have a specific symptom at baseline did not develop that symptom while receiving treatment. Most new symptoms were gastrointestinal: nausea (mild and infrequent) in 5 of 40 patients (13%), vomiting (mild and infrequent) in 4 of 47 patients (9%), vomiting (moderate) in 1 of 47 patients (2%), and diarrhea (mild and infrequent) in 2 of 35 patients (6%).

Fig 4 shows all symptom improvements in patients with baseline symptoms who were evaluable at cycles 3 and 6. Per symptom, a wide range of improvement was seen, varying from improvement in 5% to 75% of patients after 3 cycles and improvement in 22% to 100% of patients after 6 cycles (Fig 4). The symptoms with the highest rate of complete resolution were anaphylaxis/syncope (3 of 4 patients [75%] at 3 months and 2 of 2 patients [100%] at 6 months), as well as neurologic symptoms (6 of 9 patients [67%] at 3 months and 5 of 6 patients [83%] at 6 months). Furthermore, in most patients who did not show complete resolution of symptoms, we observed substantial improvement in the severity of symptoms. Moreover, despite the association of midostaurin treatment with the development of gastrointestinal symptoms (ie, nausea and vomiting), the number of patients with these symptoms reported at baseline decreased at 3 and 6 months. By 6 months, the number of reported patients with nausea decreased from 19 to 10 and the number of those with vomiting decreased from 12 to 9; the severity of these symptoms improved over this time as well, with most patients shifting from moderate or severe to no or mild nausea and/or vomiting (Fig 4). Similar improvements in symptom severity were observed if the analysis was restricted to the PEP, regardless of whether patients achieved a response (data not shown).

In many centers, improvements in skin lesions during treatment with midostaurin were also captured photographically, documenting substantial improvement in cutaneous lesions (Fig 5). Fig 5, *A*, for example, depicts a patient with ASM and skin lesions on her back and shoulders, which decreased significantly during treatment. Fig 5, *B* shows a patient with SM-AHN (SM with chronic eosinophilic leukemia) who experienced marked improvement of truncal skin lesions. In this patient, improvement of skin lesions was also accompanied by a decrease in BM MC burden, reduction of serum tryptase levels, and normalization of eosinophils and albumin, as well as weight gain of 25 kg (which equaled the amount of disease-related weight loss before initiation of midostaurin therapy).

DISCUSSION

In the present study, we have reported on significant improvements of QOL, MC mediator–related symptoms and skin lesions in patients with advSM treated with the multikinase/KIT inhibitor midostaurin. This report is the first to assess the improvement in QOL and mediator symptoms in a large cohort of patients with advSM through use of assessments by both physicians and the patients themselves. In addition, thanks to careful collection of these data, the baseline QOL assessments from this study may also serve as a reference for future evaluations in patients with advSM. Prior case reports and case series showed that treatment with IFNα-2b or cladribine reduced skin lesions and other symptoms; however, the effects of these drugs on other aspects of QOL have not been fully evaluated.[26,27]

No standard or validated assessment tool currently exists for measuring QOL in patients with advSM.[28,29] In addition to the SF-12 and MSAS, the cancer-specific tool of the European Organisation for Research and Treatment of Cancer, the QOL Questionnaire Core 30 has been used to assess symptoms in patients with SM.[28,30] The MSAS, however, is among the few existing tools created to assess the severity, frequency, and impact of a given symptom, although it is not specific to SM.[19] Another tool is the consensus scoring system with consensus response criteria that was proposed in 2007.[31] However, this objective, symptom-based scoring system does not address QOL. Recently, 2 mastocytosis QOL questionnaires (MC-QoL and MQLQ) were developed for nonadvanced categories of mastocytosis.[12,32] The MC-QoL evaluates the impact of 4 domains (symptoms, emotions, social/life functioning, and skin) on health-related QOL.[32] The MQLQ includes 8 SM-specific QOL domains: fatigue and mental health, anaphylaxis, skin symptoms, bone symptoms, unfamiliarity (ie, the burden related to ignorance of caretakers and the social environment concerning mastocytosis), flushing, general symptoms, and triggers.[12] Although the MC-QoL and MQLQ scores have been tested, they have not been validated in advSM. In the future, it will thus be important to validate a patient-reported outcome instrument for evaluating symptoms and QOL in advSM. Moreover, to fully understand the critical mechanism of midostaurin-mediated improvements in QOL and MC mediator-related symptoms, allergic and immunologic biomarkers would be helpful. Unfortunately, such markers have not yet been definitively identified and—awaiting further validation—were not collected before and during the current study.

Patients with advSM present with an array of symptoms that can dramatically affect their QOL; thus, improvements in these symptoms are of significant clinical value. In acknowledgment of this issue, novel response criteria incorporating symptom improvement as part of a comprehensive assessment of response have been proposed by several groups, including the European Competence Network on Mastocytosis, International Working Group on Myeloproliferative Neoplasms Research and Treatment,[33] and Mayo Clinic.[34] To date, however, large clinical studies using these criteria in patients with advSM have not been performed. Also, evaluation of the health-related QOL in patients with advSM faces many challenges, including the large heterogeneity of patient populations.[29] Interestingly, in our study, even patients who did not achieve a reduction in measures of MC burden showed an improvement in a variety of symptoms following treatment with midostaurin. This improvement may be related to the ability of midostaurin to inhibit the release of IgE-dependent histamine from MCs.[15,35] In this regard, it is worth noting that midostaurin treatment in patients with SM has also been observed to result in a markedly reduced IgE-mediated histamine release in blood basophils obtained *ex vivo*.[35]

Some mediator-related symptoms might be difficult to interpret given the overlap with adverse events associated with midostaurin, which include nausea, vomiting, and diarrhea. Although the overall frequency of nausea and vomiting increased during treatment, some patients with these symptoms at baseline experienced improvement while receiving midostaurin. The patient-reported SF-12 and MSAS questionnaires demonstrated significant improvements in mental health during the study. In contrast, per the physician-reported questionnaire, fewer improvements with midostaurin treatment were observed in psychiatric and/or psychological symptoms than in other symptoms. One interpretation of the lack of concordance could be that these symptoms might not have been directly related to the underlying mastocytosis or may have been overestimated in prior studies of mastocytosis. Another factor to consider is that patients and physicians may have reported these symptoms differently.

One limitation of the present study is that these QOL analyses do not account for patient withdrawals that led to the accumulation of missing data over time. Although this is compensated for in part by higher compliance rates during the first 6 cycles—when most patients continued to receive treatment and when symptoms could be expected to be most severe—the impact of missing data on later cycles, which represent a select population of patients who continued to receive treatment long-term, is less clear. An additional limitation is the study's sample size, which led to only a small fraction of patients who appeared resistant to midostaurin (ie, showed no change with treatment) for each symptom evaluated. As this fraction did not necessarily include the same patients from symptom to symptom, identification of a population that exhibited consistent resistance to midostaurin across all symptom domains was not possible. The size of this study also precluded assessment of the impact of features such as the following on response to midostaurin: patient age, sex, and performance status; degree of organ damage; and SM subtype. Further characterization of an apparent midostaurin-resistant population and identification of the features of such a population would be of clinical interest and await larger-scale studies powered for these types of analyses.

Our data demonstrated a considerable improvement in skin lesions of mastocytosis with midostaurin treatment based on both physician-assessed questionnaires and photographic documentation. These improvements were clearly evident during treatment (20 of 22 patients [91%] experienced symptom improvement from baseline), but skin lesions of mastocytosis did take more time to demonstrate clear responses than did other symptoms. In the recently performed study of midostaurin in patients with indolent SM, an identical level of improvement was seen.[36]

Our data, in combination with the previously reported efficacy and safety data reported for the D2201 and A2213 studies,[16,37] demonstrated that midostaurin had significant QOL benefits and was an effective treatment option for patients with advSM, with a manageable safety profile. These data provide a rationale to explore midostaurin in nonadvanced forms of mastocytosis, in which mediator symptoms are the main manifestation.

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Key messages

- **Midostaurin has been previously reported to normalize organ function in patients with advSM by reducing MC burden in bone marrow and other organs; the current analysis demonstrates that midostaurin also improves QOL and MC mediator–related symptoms in these patients.**
- **These results may also provide a rationale to explore midostaurin in nonadvanced forms of mastocytosis, in which mediator symptoms are the primary manifestation.**

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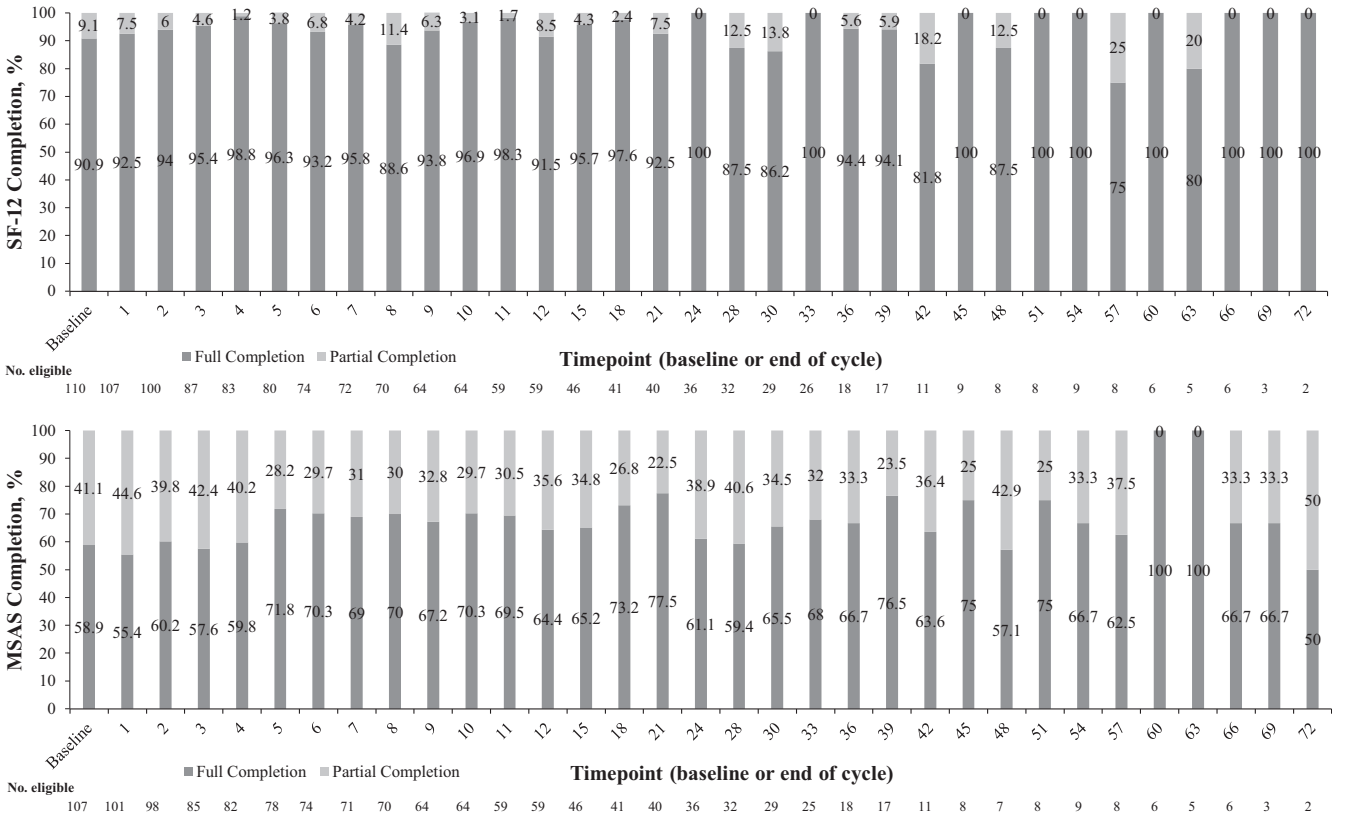

FIG E1. Completion rate over time for the SF-12 and MSAS surveys in the study population.

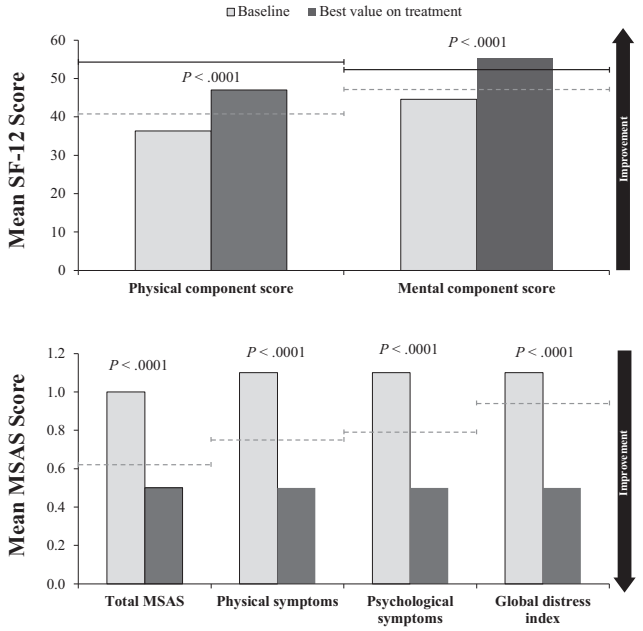

FIG E2. QOL (SF-12) and symptom burden (MSAS) in this study's population versus published scores for patients with cancer (MSAS and SF-12 [*gray dashed lines*]) and healthy individuals (SF-12 only [*solid black lines*]).[E2-E5]

TABLE E1. Baseline characteristics of the study population

Characteristics	Study population (N = 116)
Median age, y (range)	63 (25-82)
Male, n (%)	76 (66)
ECOG PS, n (%)	
0-1	77 (66)
2-3	39 (34)
No. of prior therapies, n (%)	
0	64 (55)
1	29 (25)
2	15 (13)
3	8 (7)
SM subtype, n (%)	
Non-MCL	95 (82)
ASM	ND*
SM-AHN	ND*
MCL	21 (18)
Measurable C-findings, n (%)	
Anemia	28 (24)
Thrombocytopenia	55 (47)
Neutropenia	7 (6)
Hypoalbuminemia	48 (41)
Increased total bilirubin level	25 (22)
Weight loss	12 (10)
Increased ALT level	6 (5)
Increased AST level	2 (2)
No. of C-findings per patient, n (%)	
1	31 (27)
2	20 (17)
≥3	38 (33)

The data presented in this table were originally published in Gotlib et al.[E1]

AHN, Associated hematologic neoplasm; *ALT*, alanine aminotransferase; *ASM*, aggressive systemic mastocytosis; *AST*, aspartate aminotransferase; *C*, clinical; *ECOG PS*, Eastern Cooperative Oncology Group performance status; *MCL*, mast cell leukemia; *ND*, not determined.

*Data on non-MCL SM subtype were available only for patients within the primary efficacy population. Among those 89 patients, 16 (14% of the overall study population) had ASM and 57 (49% of the overall study population) had SM-AHN; the SM subtype for the remaining 22 patients (19%) with non-MCL SM in the overall study population was not determined.