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Chapter 5

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MIDOSTAURIN IN INDOLENT SYSTEMIC MASTOCYTOSIS PATIENTS: AN OPEN-LABEL PHASE 2 TRIAL

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Abstract

Background: Indolent systemic mastocytosis (ISM) is the most prevalent primary mast cell disorder and is associated with a variety of mast cell activation symptoms refractory to anti-histamine therapy. Midostaurin, a protein kinase inhibitor of KIT-D816V, has been recently found to reduce symptoms in aggressive systemic mastocytosis.

Methods: We conducted an open-label, nonrandomized, single-center, phase 2 trial of oral midostaurin at a dose of 100 mg twice daily for 24 weeks in 20 ISM patients with severe mediator symptoms. The primary outcome was the symptomatic response rate according to the mastocytosis symptom assessment form (MSAF) sumscore after 12 weeks of treatment. Secondary endpoints included the persistence of symptoms after 24 weeks, disease specific quality of life (MQLQ) and the effects on serum tryptase, bone marrow and skin infiltration.

Findings: Symptom severity at week 12 showed a statistical significant median 35% (P< 0.001; IQR: 16% - 56%) reduction that lasted until week 24, with the strongest effects on fatigue and musculoskeletal pain. Disease specific quality of life improved significantly (P< 0.001, median improvement 29%, IQR 16% - 47%) after 24 weeks. These effects were accompanied by a sharp reduction in tryptase levels within 4 weeks of treatment (from 36.0 to 15.5 ug/l, P< 0.001), an improvement of skin infiltration in 80% and a modest decrease in bone marrow mast cell infiltration in 50% of patients after 24 weeks. The most common adverse events were grade 1-2 nausea (80%) resulting in 3 patients dropping out, headache (50%) and diarrhea (35%).

Conclusions: We find midostaurin to be effective, safe and reasonably well tolerated treatment for mediator release symptoms and skin infiltration in ISM patients

Introduction

Mastocytosis is a spectrum of diseases characterized by an increased number of mediator-releasing monoclonal mast cells infiltrating multiple organ systems. The treatment and management of mastocytosis patients is largely dependent on the classification of their disease.[1,2] Indolent systemic mastocytosis (ISM) is the most predominant category, with mast cell infiltration of - in particular - the bone marrow, gastrointestinal tract and skin, but – by definition - no resulting organ dysfunction.(3) For most ISM patients the mast cell burden will remain stable throughout a near-normal life expectancy. [4]

Unfortunately, the quality of life can be severely affected as many ISM patients suffer from debilitating mast cell activation symptoms. [5] Here, activated mast cells release mediators inducing a wide spectrum of chronic and paroxysmal symptoms, such as flushing, pruritus, anaphylaxis, fatigue, depression and osteoporosis.[6, 7] Anti-histaminic and mast cell stabilizing agents are effective in treating most of these symptoms. However, even with therapy over 70% ISM patients experience an impaired quality of life due to refractory symptoms such as fatigue, illustrating the large unmet therapeutic need.[5] Moreover, esthetically displeasing skin-infiltrates such as urticaria pigmentosa (UP) are present in approximately 45-70% of ISM patients[8,9] and are notoriously treatment resistant, often relapsing after psoralen and ultraviolet A therapy within 2 to 8 months.[10]

Key in the pathogenesis of mastocytosis are the activating mutations (typically *KIT* D816V) in the Kit receptor that lead to unrestricted activity of its intrinsic tyrosine kinase activity and subsequent autophosphorylation.[11] Kit receptor signaling facilitates mast cell proliferation and mediator release, including IgE-mediated degranulation.[12] Preclinical studies have shown that tyrosine kinase inhibitors targeting Kit can inhibit proliferation and induce apoptosis in mast cells.[13-15] The protein kinase inhibitor PKC412 (midostaurin) can inhibit the D816V mutated *KIT* kinase and additionally inhibit IgE-mediated degranulation through its action on protein kinase C.[15,16] Recently completed studies of midostaurin in the aggressive forms of SM resulted in an overall response rate of 60-71% and a major response rate of 45-57%, whereas adverse events related to midostaurin were mostly limited to nausea, vomiting and

diarrhea.[17,18] In particular, mast cell activation symptoms rapidly responded to treatment with midostaurin, often preceding the decrease in mast cell infiltration. These observations suggest that midostaurin has both mast cell depleting and mast cell stabilizing properties with manageable side effects, prompting speculation on its usefulness in ISM.[17,19]

We therefore conducted a phase 2 trial in ISM patients with severe mast cell activation symptoms refractory to anti-histaminic and mast cell stabilizing treatment to study the efficacy and safety of midostaurin. We will show that the drug is safe and effective in symptom-reduction with simultaneously fast and marked improved quality of life.

Methods

Patients

This is an open-label, nonrandomized, single-centre, phase 2 trial. Eligible patients were contacted and included based on their geographic proximity to the University Medical Centre Groningen. Patients at least 18 years of age were eligible if a diagnosis of *KIT* D816V+ indolent or smoldering systemic mastocytosis according to the World Health Organization criteria was present. [3] In addition, a serum tryptase ≥20 µg/l was required, and severe mediator-related symptoms refractory to H1 and H2 blocking drugs defined as a pre-study mastocytosis symptom assessment form (MSAF) score of 4 or more on 3 non-related items, or a pre-study score of 5 or more on 2 non-related items (one item from the scoring list can be replaced by flushes 7 or more per week or anaphylactic attacks 1 or more per month). In addition, all men of reproductive potential and women of child-bearing potential had to practice effective contraception. Excluded from the study were pregnant or nursing women, patients diagnosed with advanced aggressive mastocytosis, another malignancy unless they were disease-free for at least 5 years, or had a diagnosis of non-melanoma skin cancer. Finally patients were excluded who were suffering serious comorbidity interfering with therapy compliance and follow-up compliance. The patient accrual process is demonstrated in Figure 1. This study was approved by the University Medical Centre Groningen Institutional Review Board and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave written informed consent before study entry. The study is registered with Clinical Trials.gov, NCT01920204.

Intervention

All anti-histamine and mast cell stabilizing drugs that the patients were taking were continued. Midostaurin was supplied by Novartis (Basel, Switzerland) as capsules of 25 mg, and had to be taken orally at the dose of 100 mg twice a day. Patients received midostaurin continuously from day 1. Premedication with anti-emetic 5-HT3 receptor antagonists was started for all patients two hours before midostaurin intake and adjusted after two weeks according to symptoms of nausea and vomiting. After 24 weeks of treatment, a 2 month drug free wash-out period was introduced. Patients with a relapse of symptoms and an increase in tryptase levels were allowed to restart the drug during a follow-up phase. Toxicities and adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTC) Version 4.03. During the entire trial dose modifications were allowed in case of toxicity. Patients who developed grade 3 or 4 toxicity had to discontinue therapy with midostaurin until the adverse event recovered to grade less than or equal to 2. If toxicity did not resolve within 3 weeks, therapy was discontinued.

Assessments and measurement tools

Baseline studies included a complete physical examination, complete blood count, a comprehensive biochemistry panel (including liver function tests), and measurements of mast cell load. Serum tryptase levels were determined using the B12 assay (ImmunoCAP Tryptase, Thermo Fisher Scientific, Uppsala, Sweden). Urinary excretion of methylhistamine (MH) and methylimidazole acedic acid (MIMA) were determined as described previously.[20,21] Urine samples were collected after an overnight fast, discarding the first voiding after wakening. During the 24h before urine collection, patients were asked to refrain from histamine-rich foods and drinks. Hepatosplenomegaly and lymphadenopathy were documented by ultrasound. Skin involvement was documented using the Scoring Mastocytosis (SCORMA) scoring system.[22)]The SCORMA system was adapted by using only the skin-related measurement tools, parts A and B, preventing interference of mast cell release symptoms on the scoring of skin involvement.[22] Bone marrow mast cell infiltration together with immunophenotyping and molecular analysis was measured in biopsies and aspirates. Flow cytometric mast cell

immunophenotyping and *KIT* D816V mutation analysis were performed as described previously.[23]

Patients were seen at week 1, 2 and 4 and subsequently monthly unless earlier visits were deemed necessary. A complete blood count and comprehensive biochemistry panel were obtained at least every 4 weeks. Symptom severity was self-monitored weekly using the mastocytosis symptoms assessment form (MSAF).[(5)] Quality of life was measured at baseline and at weeks 12 and 24 using the general SF36 general health questionnaire, and the mastocytosis quality of life questionnaire (MQLQ).[5,24] The extent of bone marrow mast cell infiltration was quantified in biopsies and aspirates, prior to and 24 weeks after treatment.

Endpoints and safety

The primary objective of the study was to assess symptomatic response rate according to the MSAF sumscore after 12 weeks of midostaurin treatment. Secondary endpoints were the persistence of symptoms after 24 weeks of midostaurin treatment, changes in quality of life at weeks 12 and 24 in combination with the changes in mast cell load as assessed by the percentage change in bone marrow mast cell infiltration, serum tryptase, skin infiltration, lymphadenopathy and hepatosplenomegaly.

To ensure safety, an interim analysis focussing on adverse events, especially hematologic toxicity, was performed by the principal investigator after the first 10 patients had a follow-up of at least 12 weeks. Although no formal stopping rule was designed, standard good quality clinical practice allowed for early termination of the study in case of excess toxicity or unsatisfactory risk/benefit ratio of the therapy, as judged by study staff and involved treating physicians.

Statistical analysis

This is a phase 2 proof-of-concept study and therefore a formal sample size calculation was not performed. MQLQ scores were transformed to a 0 (worst) to 100 (best)scale to facilitate comparison with SF36 scores. In order to calculate aggregate scores for the SF36, MSAF and MQLQ missing data on individual items were

handled using the last observation carried forward method. Questionnaires missing >10% of the items were not analysed. Intention-to-treat analyses were used unless otherwise specified. Descriptive statistics were used to assess response; Mann-Whitney U test and Wilcoxon signed rank test were used for statistical comparisons.

Role of the funding source

The study was investigator initiated, conceived and designed by the Groningen Mastocytosis Centre and was performed and monitored in collaboration with an independent trial coordination center (TCC, Groningen, The Netherlands). Novartis (Novartis Pharma, Basel, Switzerland) funded the study and provided study drugs. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Patients

Starting June 2012, 248 ISM and SSM patients were screened on symptom severity using the MSAF. Out of the 168 that returned filled out questionnaires, 55 patients met the symptom severity inclusion criterion and were contacted in order of geographic distance to the treatment facility. Between September 2013 and August 2015, twenty ISM patients were included. The patient selection and accrual process is further detailed in Figure 1 and the baseline characteristics of those included are displayed in Table 1. Briefly, the mean age of included was patients was 49 ± 12 years old, there was an almost even male-female proportion (45-55%) and all but five patients exhibited UP (75%). During the trial three patients dropped out due to adverse events, all related to nausea, before week 12.

Efficacy: symptom severity

The primary efficacy endpoint of MSAF measured symptom severity at week 12 showed a statistical significant median 35% ($P < 0.01$; IQR: 16% - 56%) reduction in symptom severity, resulting in an improvement in symptoms for 75% (n=15) of the patients. Symptom severity scores further improved to an average 38% reduction at week 24 (Figure 2). In addition (not depicted in Figure 2), the

frequency of flushing decreased from a median of 5 flushes per week at baseline to 1 flush per week after 24 weeks of treatment. Anaphylactic-like mastocytosis “attacks” were present in 3 patients at baseline, for one of these patients the monthly occurrence dropped from 60 to 23, strongly affecting the ability to perform basic daily activities. In the remaining two patients these attacks stopped completely, coming down from 20 and 3 attacks per month previously. The strongest improvement in chronic mediator release symptoms was seen in the symptoms fatigue and musculoskeletal pain, as evidenced by a median 4 point and 3.5 point difference in score on a 0-10 scale after 24 weeks of treatment. Conversely, there was a median 0.5 point increase in reported nausea and vomiting symptoms after 24 weeks. The symptom specific effect of midostaurin is further illustrated in Figure 3.

Efficacy: quality of life

The secondary efficacy endpoint of MQLQ measured disease specific quality of life indicated a statistical significant median 29% (P< 0.001, IQR 16% - 47%) improvement after 24 weeks of treatment. The strongest improvement of 39% was found in the domain fatigue. This was accompanied by an average 27% improvement in the SF36 measured general health related quality of life across all scales, with a near normalization of median scores on the role limitations due to physical health. All the changes per domain of the quality of life measurement tools are displayed in Figure 4.

Table 1. Patient characteristics

Patients	**n,**	**20**
Age	Years	49 ± 12
	Range	23-71
Female	n, %	11 (55%)
Mast cell load parameters		
Tryptase	µg/l	34 (24 – 41)
Methylhistamine	µm/mol cr.	344 (171 – 391)
Methylimidazole acedic acid	mm/mol cr.	4.5 (3.4 – 5.9)
Urticaria Pigmentosa	n, %	15 (75%)
Hepatosplenomegaly	n, %	3 (15%)
Bone marrow mast cell infiltration		
Biopsy	% mast cells	4.5 (2.0 – 7.5)
Aspirate	% mast cells	1.5 (1.0 – 3.0)

Data are given as mean ± SD, or median (IQR);

Figure 1. Patient accrual and trial profile

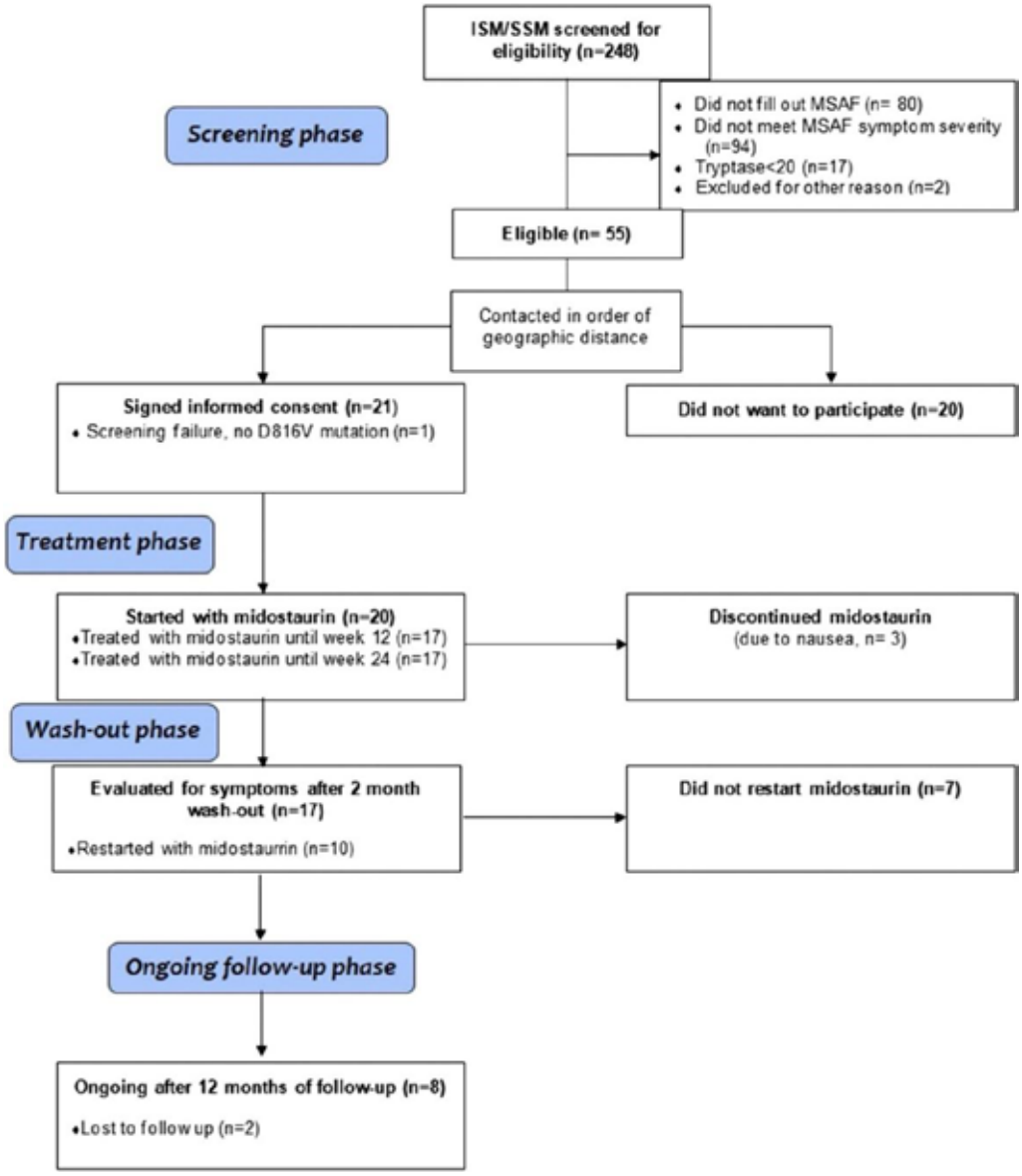


Figure 2: Percentage change in mastocytosis symptom assessment form (MSAF) measured symptom severity compared to baseline.

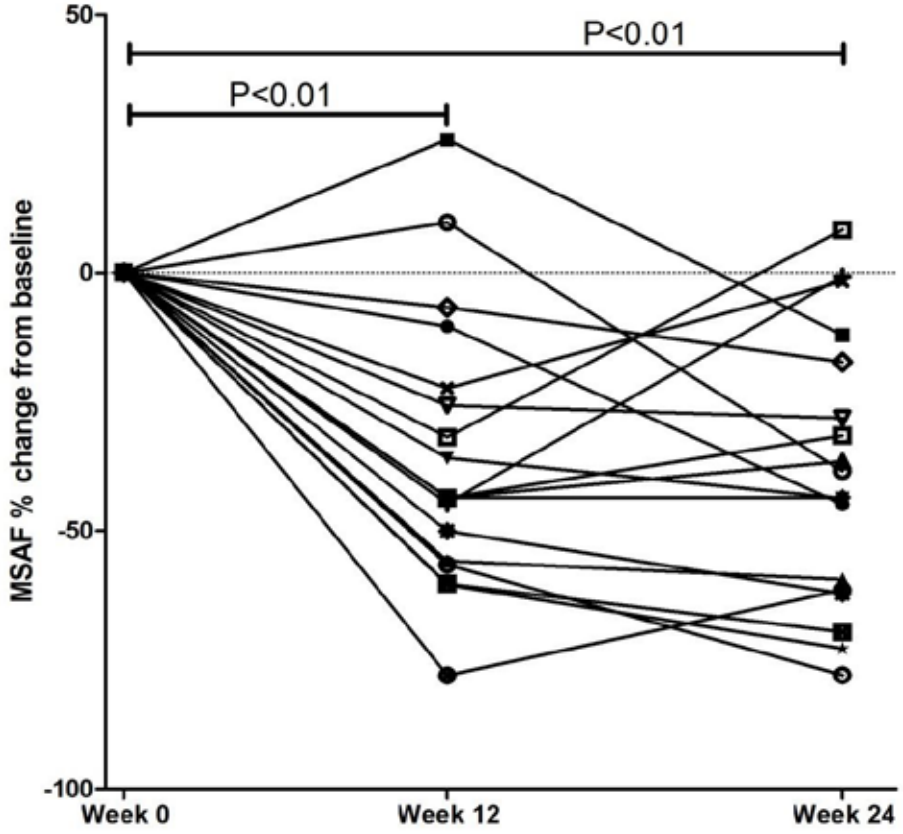
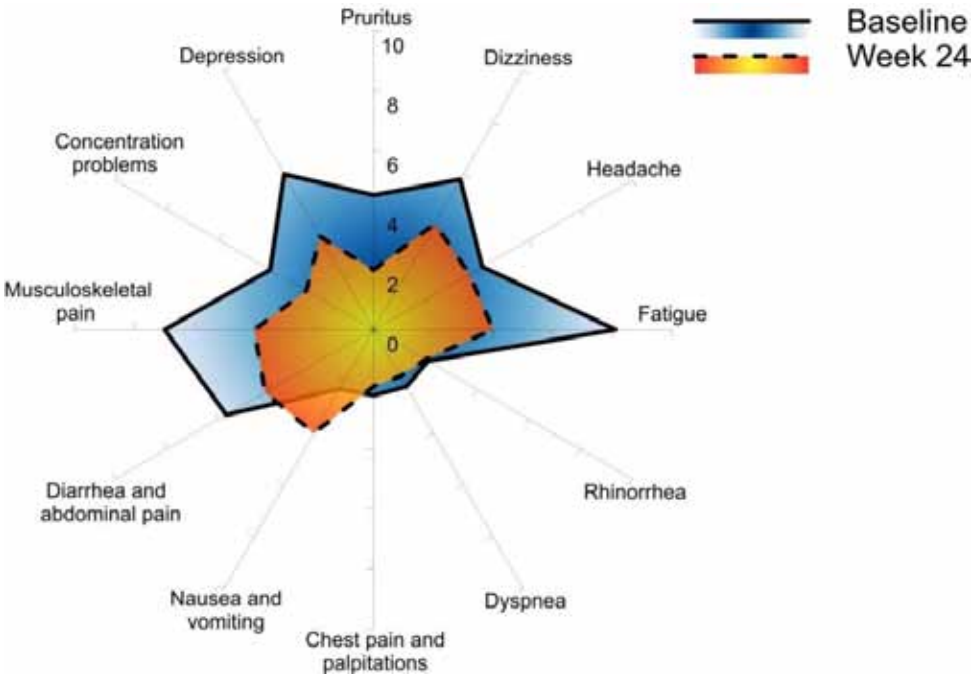


Figure 3: Symptom severity as measured by the mastocytosis symptom assessment form (MSAF) before and after 24 weeks of treatment with midostaurin, the higher the score, the more severe the symptoms.



Biochemical and mast cell infiltration response

After 24 weeks, a reduction of mast cell infiltration, as denoted by a sharp decrease in all mast cell load markers was found in 80% (n=16) of included patients. (Online supplementary Figure 1). Already after 4 weeks all 19 still included patients showed a statistically significant reduction in tryptase levels (from 36.0 to 15.5 ug/l, P< 0.001) that remained stably reduced for all but 1 patient throughout the study (Figure 4). The increase in tryptase seen in the one patient followed an adverse event with associated dosage reduction of midostaurin.

A similar rebound effect was observed in most patients during the 2 month wash-out period. At the end of the study, 8 out of 16 histologically assessable bone marrow biopsies showed a reduction in the percentage of mast cells (from median 7.5% to 4.0%), 2 an

increase and 6 no change. Urticaria pigmentosa improved in 12 (80%) of the 15 patients with skin symptoms, resulting in a 40% reduction in median SCORMA score with the strongest effect seen in the intensity of lesions. (Online supplementary Figure 1)

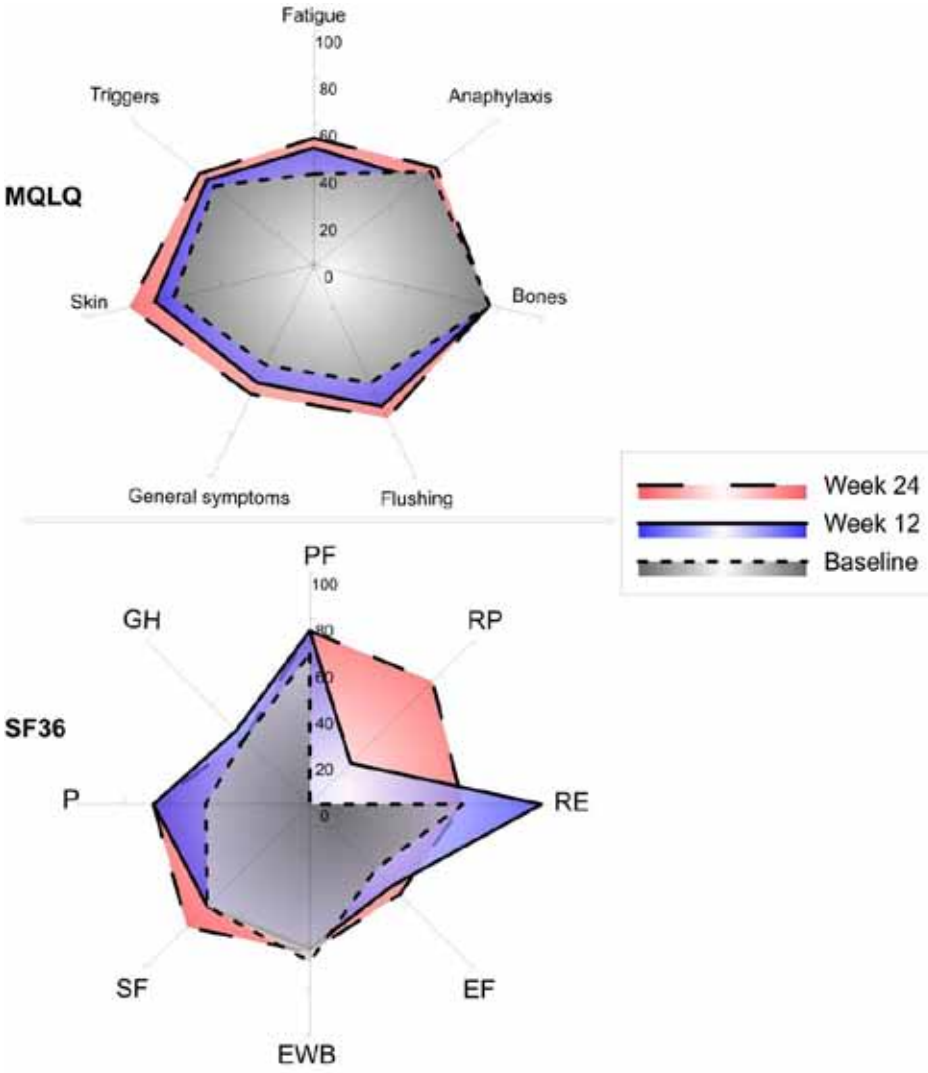
Safety and tolerability

Midostaurin was well tolerated; the most common adverse events were nausea (n=16, 80%), headache (n=10, 50%) diarrhea (n=7, 35%), all grade 1-2. Midostaurin-related nausea responded well to 5-HT3 receptor antagonist anti-emetic medication, but was necessary until the end of the study for all but 6 patients. In 3 female patients nausea was uncontrolled by anti-emetics (CTC grade 2) and these patients dropped out of the study. There was one SAE, anaphylaxis during lunch with collapse not objectified with tryptase, deemed to be probably not treatment related and two additional other grade 3-4 adverse events (syncope and elevated ALT). Notably, there were no CTC grade >1 hematological adverse events. The frequencies of grade 2 AEs are shown in Table 2.

Follow-up

According to protocol, all patients stopped midostaurin at week 24. Next, a 2 month wash-out period gave the opportunity to document duration of response. It appeared that most patients experienced a rapid relapse of symptoms, accompanied by an increase in tryptase levels as well (Figure 4). Ten patients restarted midostaurin at twice 100 mg and all showed an improvement of symptoms once more, accompanied by a reduction in tryptase in all but two patients (Figure 4). It is too early to present more data on longer follow-up, which moreover was not part of this protocol.

Figure 4: Median scoring per domain of the disease specific Mastocytosis Quality of Life Questionaire (MQLQ) and the general Short Form Health Survey 36 (SF36) related quality of life, a higher score indicates less burden.



Online supplementary Figure 1: Response in mast cell infiltration markers after 24 weeks of Midostaurin

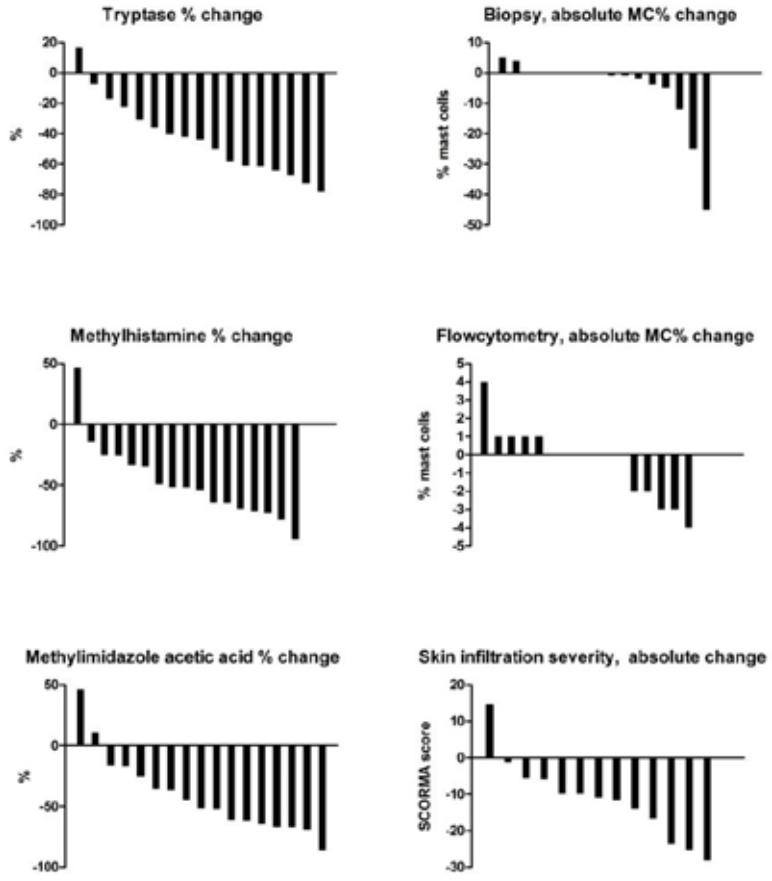
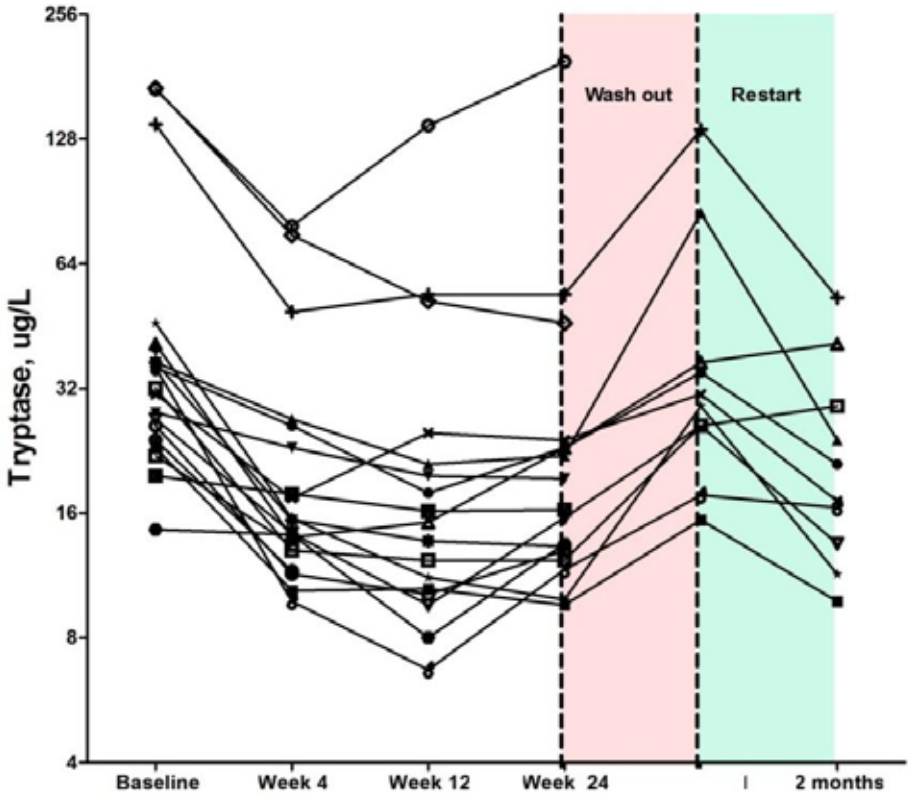


Table 2. Common adverse events, occurring in >10% of patients or CTC grade >2.

Adverse event	CTC grade 1-2	CTC Grade 3
Nausea	16 (80%)	0
Headache	10 (50%)	0
Diarrhea	7 (35%)	0
Elevated transaminases	7 (35%)	1 (5%)
Fatigue	6 (30%)	0
Urinary tract infection	3 (15%)	0
Dizziness	3 (15%)	0
Flu like symptoms	3 (15%)	0
Anemia	3 (15%)	0
Abdominal pain	2 (10%)	0
Arthralgia	2 (10%)	0
Vomiting	2 (10%)	0
Anaphylaxis	0	1 (5%)
Syncope	0	1 (5%)

Figure 4: Serum tryptase reduction during Midostaurin treatment.



Discussion

In this first trial to investigate the use of midostaurin in ISM patients, we found this drug to be effective in symptom and mast cell infiltration-reduction in the large majority of patients. Notably, the responses were fast and seen in traditionally refractory symptoms, such as fatigue, UP and musculoskeletal pain. The only symptom that did not react and even worsened was nausea, but we assume that this did not reflect disease activity, but was a well-known side effect of midostaurin. Due to the non-randomized nature of this trial the contribution of a placebo-effect to symptom reduction can't be ruled out. However, the strong biochemical response suggestive of mast cell load reduction supports the notion that the observed clinical effect was due to mast cell targeting. Notably, reductions in serum tryptase and the urinary histamine metabolites were more pronounced compared to the modest reduction in bone marrow and cutaneous mast cell infiltration. A possible explanation is that the early inhibiting effects of midostaurin on mast cell mediator synthesis and release are stronger than the anti-proliferative effects that will need more time than the 24 weeks of this trial.[16] A mast cell mediator release inhibiting effect is further supported by the fast rebound effect in symptoms and tryptase levels after dosage reduction and during the wash-out phase. This suggests that the dose of twice 100 mg seems necessary, and moreover, that a duration of 24 weeks is not enough to stabilize the disease. This fast rebound of signs and symptoms is disappointing, but is a previously noted characteristic of tyrosine kinase inhibitors.[25] Nevertheless, observations in CML patients treated with a Kit targeting tyrosine kinase inhibitor suggests that mast cell depletion occurs after 1 year of treatment.[26] Consequently, we hope that prolonged administration of midostaurin will enable some dose reduction.

Patient selection for this trial was strict with only patients with severe refractory symptoms and serum tryptase > 20 ug/l accepted to maximize the possibility of finding a clinical or biochemical effect. To illustrate the relative rarity of this patient category, of the 168 patients that filled out the screening questionnaire 94 did not have symptoms severe enough for inclusion and an additional 17 had insufficiently high tryptase levels (Figure 1). As such, the trial population is distinctly different from the average ISM patient. Nevertheless, we feel that the midostaurin might be more broadly

applicable than suggested by these numbers and recommend future trials to broaden the inclusion criteria. One caveat related to our strict patient selection is the possibility of regression to the mean of symptoms. However, all trial patients had their symptoms scored at least twice before the study at start – during pre-screening and at entry. A post hoc analysis comparing symptom severity between the screening phase and the start of the trial did not find a significant difference in symptom severity over these 6+ months. Despite side effects, notably nausea, most patients favored continuation of the drug. As we used symptoms as primary endpoint, obviously any future phase III trial should include a placebo control arm.

In conclusion, we find midostaurin to be an effective, fast acting, safe and reasonably well tolerated treatment modality for ISM patients suffering from severe mediator release symptoms or skin infiltration.

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